CSWAB

Citizens for Safe Water Around Badger
E12629 Weigand's Bay South - Merrimac, WI 53561
Phone (608) 643-3124 - Fax (608) 643-0005
Email: info@cswab.org - Website: www.cswab.org

February 23, 2011

Michael Baes
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1515 Clay St., 16th floor
Oakland, California 94612
mbaes@oehha.ca.gov

SUBMITTED BY ELECTRONIC MAIL

RE: Support for Revised California Public Health Goal of 1 ppb for Perchlorate

Dear Mr. Baes,

We are writing to support the draft public health goal (PHG) of 1 part per billion (ppb) for perchlorate in drinking water proposed by your agency. The proposed goal will revise the existing PHG of 6 ppb for perchlorate based on new data concerning environmental exposure, possible effects of perchlorate, and further consideration of infants as a susceptible population.

Perchlorate is an oxidizer in solid propellants for rockets, missiles, fireworks and explosives that can disrupt the uptake of iodide in the thyroid, potentially interfering with thyroid function and negatively affecting fetal and infant brain development and growth.

Late last year, the State of Wisconsin proposed new rules for previously-unregulated munitions contaminants including perchlorate. Wisconsin's enforceable groundwater standard of 1 ppb for perchlorate became law in January 2011.

Our organization played an important role in reducing the initially-proposed perchlorate standard from 7 to 1 ppb. CSWAB submitted hundreds of pages of public testimony supporting a more protective standard. Toxicologists with the Wisconsin Bureau of Public Health reviewed our submittals and agreed that the lower threshold was necessary to protect several population subgroups, such as breast-fed babies, that may be affected by very low levels in food or water.

Attached to this and two following e-mails are copies of documents from this public rule-making process that we hope will be helpful to California in setting an equally protective standard.

Thank you for your time and consideration of this information.

Sincerely,

Laura Olah
Executive Director

Form 1100-001
(R 12/09)

NATURAL RESOURCES BOARD AGENDA ITEM

Item No. 3.A.1

SUBJECT: Adoption of Board order DG-24-09, revisions to ch. NR 140, Wis. Adm. Code, relating to groundwater quality standards

FOR: AUGUST 2010 **BOARD MEETING**

TO BE PRESENTED BY: Michael D. Lemcke - Chief, Groundwater Section

SUMMARY:

Amendments are proposed to ch. NR 140 to establish new state groundwater quality standards for 15 substances of public health concern and to revise existing groundwater quality standards for 15 additional substances of public health concern. Of the 15 proposed revised groundwater standards, 9 are proposed to be less restrictive than their current standards.

At the April, 2010 Natural Resources Board meeting the Board passed a motion to table Board Order DG-24-09 until, at the latest, the August 2010 Board meeting. At the Board's direction, the Department solicited additional information related to the proposed groundwater standards for aluminum and, based on a review of this additional information, the Department has revised its recommendation for a ch. NR 140 aluminum preventive action limit.

The Department has not changed its other recommendations for new and revised ch. NR 140 groundwater quality standards.

RECOMMENDATION: Adoption of Board Order DG-24-09, revisions to ch. NR 140 relating to groundwater quality standards

LIST OF ATTACHED MATERIALS:

No	☐	Fiscal Estimate Required	Yes	☑	Attached
No	☑	Environmental Assessment or Impact Statement Required	Yes	☐	Attached
No	☐	Background Memo	Yes	☑	Attached

APPROVED:

Bureau Director, — Date 7/13/2010

Administrator, — Date 7/22/10

Secretary, Matt Frank — Date 7-29-10

cc: Laurie J. Ross - AD/8
Jill Jonas - DG/5
Mike Lemcke - DG/5
Judy Ohm - LS/8
Paul Neumann - MB/8
Linda Haddix - LS/8

CORRESPONDENCE/MEMORANDUM

State of Wisconsin

DATE: **July 14, 2010** FILE REF: NR 140

TO: **Members, Natural Resources Board**

FROM: **Matthew J. Frank, Secretary**

SUBJECT: **Recommendation for adoption of proposed amendments to Wis. Adm. Code Chapter NR 140, Groundwater Quality**

Wisconsin state groundwater quality standards are established by the Department of Natural Resources (Department) for substances of public health or welfare concern that are detected in, or have a reasonable probability of entering the groundwater resources of the state. The Department is proposing amendments to ch. NR 140 to add new state groundwater standards for 15 substances of public health concern and to revise existing groundwater standards for 15 substances of public health concern.

At the April 2010 Natural Resources Board (NRB) meeting the Department recommended Board adoption of the proposed amendments to ch. NR 140. Following a discussion of the proposed aluminum groundwater quality standards the Board requested that the Department review information related to those proposed groundwater quality standards and return with recommendations for any changes to the proposed standards by, at the latest, the August, 2010 NRB meeting.

The Department held a meeting on May 20, 2010 with representatives of the Wisconsin Energies Corporation - We Energies subsidiary to listen to their concerns related to the proposed groundwater standards for aluminum. At this meeting We Energies presented a written summary of their concerns with the proposed standards (Attachment 4). We Energies concerns focus on the methodology used by the Wisconsin Department of Health Services (DHS) to develop their recommendations for aluminum groundwater quality standards.

We Energies comments included toxicity values established for aluminum by national and international organizations and a discussion of DHS' development of their recommendation for an aluminum NR 140 enforcement standard (ES) of 200 parts per billion (ppb). Comments were provided related to the animal toxicity study used by DHS to develop their recommendation, and on the uncertainty factors used by DHS in its calculation of a recommended standard. We Energies also supplied information related to carcinogenicity evaluations conducted for aluminum and recommended that a ch. NR 140 aluminum ES be established at 5,000 ppb, and a ch. NR 140 preventive action limit (PAL) for aluminum be established at 20% of this ES value.

The Department requested that DHS staff review the comments and information submitted by We Energies and provide a response to the issues raised. DHS staff reviewed the aluminum information document submitted by We Energies [prepared by Lisa Bradley (AECOM) and Robert Paulson (We Energies)] and provided a written response (Attachment 5) to the Department.

On June 3, 2010 a second meeting/conference call was held with We Energies at which DHS presented their responses to We Energies concerns related to DHS development of proposed aluminum groundwater standards. In their response, DHS stated that they have conducted a comprehensive review of the toxicology literature for aluminum and that they do not support increasing the proposed aluminum ES (of

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200 ppb) to 5,000 ppb - 37,000 ppb, as proposed by We Energies' consultant. DHS pointed out that, in their development of recommended aluminum standards, they used standard toxicological risk assessment methodology, used a lowest observable effect level (LOEL) from a valid and relevant scientific study and, incorporated standard risk assessment uncertainty factors into their calculations. While DHS believes there is a strong weight of evidence supporting use of a PAL established at 10% of the recommended ES value (a "10% PAL"), it does recognize that a scientific case can also be made for a "20% PAL" and, therefore, would support a PAL set at either 10% or 20% of the proposed ES value for aluminum.

The Department has confirmed, based on an evaluation of Waste and Materials Management Program regulations, that it does not appear that the state groundwater quality standards proposed for aluminum would affect landfill monitoring programs, or current approved beneficial reuses of coal combustion byproducts (Attachment 6). It is the Department's understanding that We Energies is not aware that any of their sites would have an issue with the proposed aluminum groundwater quality values. In addition to the discussion of standards development, DHS offered to provide the results of private water supply well testing, conducted by County Health Departments (fee-exempt well testing program), which show that background levels of aluminum in Wisconsin groundwater are relatively low (Attachment 7).

In conclusion, based on meetings with We Energies and reevaluation of relevant information, with input from DHS, the Department is proposing to keep the existing proposed aluminum groundwater quality ES value of 200 ppb. Furthermore, based on the information provided by DHS in its *Response to Comments from WE Energies* document and, considering that a scientific case can be made for a non-carcinogen based PAL groundwater standard for aluminum, the Department is proposing a PAL of 40 ppb, 20% of the proposed ES for aluminum (see proposed Rule Order, page 7, Table 1).

1. Why rule is being proposed

Wisconsin state groundwater quality standards are established by the Department of Natural Resources for substances of public health or welfare concern that are detected in, or have a reasonable probability of entering the groundwater resources of the state.

These groundwater quality standards are established in Wisconsin Administrative Code Chapter NR 140, Groundwater Quality. Amendments are being proposed to ch. NR 140 to:

1) add new state groundwater quality standards for 15 substances of public health concern to s. NR 140.10, Wis. Adm. Code.

2) revise existing s. NR 140.10, Wis. Adm. Code, groundwater quality standards, for 15 substances of public health concern.

3) make minor revisions and additions to update s. NR 140.10, Wis. Adm. Code, Table 1 and Appendix I to Table 1.

Chapter NR 140 was adopted by the Natural Resources Board in 1985 to comply with Wisconsin Statute Chapter 160. Chapter 160, Stats., was created in May of 1984, as part of 1983 Wisconsin Act 410, and requires the Department of Natural Resources to develop groundwater quality standards for substances detected in, or having a reasonable probability of entering the groundwater resources of the state.

Chapter NR 140 establishes state groundwater quality standards at two levels, preventive action limit (PAL) and enforcement standard (ES). In accordance with ch. 160, Stats., ES groundwater quality standards for substances of public health concern are established based on recommendations received from the Department of Health Services (DHS). PAL groundwater quality standards for substances of public health concern are set at either 20% of the concentration of the established ES, or at 10% of the concentration of the established ES if the substance has carcinogenic, mutagenic or teratogenic properties, or interactive effects.

Wisconsin groundwater quality standards are used by state regulatory agencies to develop clean up goals at contaminated sites, to establish design and management criteria for regulated activities and to ensure that regulated facility practices do not endanger state drinking water supplies.

The Department is required to consult with other state agencies, and to consider individual petitions submitted by members of the public, in identifying substances for possible groundwater quality standard setting. State regulatory agencies provided the Department information on the occurrence of substances without standards detected in groundwater, and members of the public requested that the Department review recent groundwater monitoring information related to additional chemicals currently without standards.

DHS staff reviewed existing regulatory and toxicological information for identified substances of potential health concern and developed recommendations for state groundwater quality standards. In accordance with ch. 160, Stats., the Department is proposing rules establishing the DHS recommendations as groundwater quality standards in ch. NR 140.

2. Summary of the rule

Amendments to Chapter NR 140 are being proposed to add new state groundwater quality standards for 15 substances, as indicated below:

	Proposed Standards (ug/L - except as noted)	
Substance	**ES**	**PAL**
1,4-Dioxane (p-dioxane)	**3**	**0.3**
Acetochlor	**7**	**0.7**
Acetochlor ethane sulfonic acid + oxanilic acid (Acetochlor-ESA + Acetochlor-OXA)	**230**	**46**
Aluminum	**200**	**40**
Ammonia (as N)	**9.7 mg/L**	**0.97 mg/L**
Chlorodifluoromethane (HCFC-22)	**7 mg/L**	**0.7 mg/L**
Chlorpyrifos	**2**	**0.4**
Dimethenamid/Dimethenamid-P	**50**	**5**
Dinitrotoluene, Total Residues	**0.05**	**0.005**
Ethyl Ether (Diethyl Ether)	**1000**	**100**
Manganese	**300**	**60**
Metolachlor ethane sulfonic acid + oxanilic acid (Metolachlor-ESA + Metolachlor-OXA)	**1.3 mg/L**	**0.26 mg/L**
Perchlorate	**1**	**0.1**
Propazine	**10**	**2**
Tertiary Butyl Alcohol (TBA)	**12**	**1.2**

Note, after review of comments and new information received during the rulemaking public comment period, DHS revised their original standards recommendations for three substances: acetochlor, aluminum and perchlorate. The recommendation for acetochlor standards was revised, from an ES of 1 ppb and PAL of 0.1 ppb, to an ES of 7 ppb and PAL of 0.7 ppb. The recommendation for aluminum standards was revised, from an ES of 170 ppb and PAL of 17 ppb, to an ES of 200 ppb and PAL of 20 ppb. The recommendation for perchlorate standards was revised, from an ES of 7 ppb and PAL of 0.7 ppb, to an ES of 1 ppb and PAL of 0.1 ppb. After the April 2010 NRB meeting the Department revised the proposed aluminum groundwater quality PAL standard from 20 ppb to 40 ppb (20% of the proposed aluminum ES value). This change was based on information provided by DHS in its May 25, 2010 *Response to Comments from WE Energies* document.

Amendments to Chapter NR 140 are being proposed to revise existing state groundwater quality standards for 15 substances as indicated below:

	Current Standards (ug/L - except as noted)		**Proposed Standards (ug/L - except as noted)**	
Substance	**ES**	**PAL**	**ES**	**PAL**
1,3-Dichlorobenzene	**1250**	**125**	**600**	**120**
1,3 Dichloropropene (cis/trans)	**0.2**	**0.02**	**0.4**	**0.04**
Acetone	**1000**	**200**	**9 mg/L**	**1.8 mg/L**
Boron	**960**	**190**	**1000**	**200**
Carbaryl	**960**	**192**	**40**	**4**
Chloromethane	**3**	**0.3**	**30**	**3**
Dibutyl phthalate	**100**	**20**	**1000**	**100**
Ethylene Glycol	**7 mg/L**	**700**	**14 mg/L**	**2.8 mg/L**
Methyl ethyl ketone (MEK)	**460**	**90**	**4 mg/L**	**0.8 mg/L**
Metolachlor	**15**	**1.5**	**100**	**10**
Metribuzin	**250**	**50**	**70**	**14**
Phenol	**6 mg/L**	**1.2 mg/L**	**2 mg/L**	**0.4 mg/L**
Prometon	**90**	**18**	**100**	**20**
Toluene	**1000**	**200**	**800**	**160**
Xylene	**10 mg/L**	**1 mg/L**	**2 mg/L**	**0.4 mg/L**

Amendments to ch. NR 140 are also being proposed to make minor revisions and additions to ch. NR 140 Table 1 and Appendix I, as indicated below:

- Replacing current "Chromium" in ch. NR 140 Table 1 with "Chromium (total)" to clarify that ch. NR 140 standards apply to total chromium (combination of chromium III and chromium VI).
- Replacing current "Cyanide" term in ch. NR 140 Table 1 with "Cyanide, free" to clarify that ch. NR 140 standards apply to "free cyanide" (HCN, CN^- and metal-cyanide complexes that are easily dissociated into free cyanide ions).
- Changing "Metolachlor" in ch. NR 140 Table 1 to "Metolachlor/s-Metolachlor" to clarify that ch. NR 140 standards apply to both Metolachlor (CAS RN 51218-45-2) and its stereo isomer, s-Metolachlor (CAS RN 87392-12-9).

- Revising units for field specific conductance in s. NR 140.20 Table 3 from micromhos/cm (micromhos per centimeter) to microSiemens/cm (microSiemens per centimeter or µS/cm).
- Revising s. NR 140.28(5)(c)6 note to add "for discharges, as defined by s. 283.01(4), Stats" language related to the need for a wastewater discharge permit.
- Adding CAS RN of 142363-53-9 for Alachlor-ESA to Appendix I to Table 1.
- Changing existing Appendix I to Table 1 CAS RN for Asbestos from 12001-29-5 (chrysotile asbestos) to 1332-21-4 (asbestos, all forms).
- Adding "Chromium (total)", with CAS RN of 7440-47-3, to ch NR 140 Appendix I to table 1.
- Adding CAS RN of 542-75-6 for cis/trans 1,3 Dichloropropene (mixed isomers) to ch. NR 140 Appendix I to Table 1.
- Changing existing Appendix I to Table 1 CAS RN for Fluoride from 16984-48-8 to 7681-49-4.
- Adding 1,1,1,2-PCA synonym for 1,1,1,2 tetrachloroethane to ch. NR 140 Appendix I to table 1.
- Adding 1,1,2,2-PCA synonym for 1,1,2,2 tetrachloroethane to ch. NR 140 Appendix I to table 1.
- Adding 1,1,1-TCA synonym for 1,1,1 trichloroethane to ch. NR 140 Appendix I to table 1.

3. How proposal affects existing policy

The proposed amendments continue the existing policy of protecting Wisconsin's groundwater by utilizing the procedures in ch. 160, Stats., to establish new state groundwater quality standards for 15 substances. These new groundwater quality standards would be added to the present ch. NR 140 groundwater standards. There are currently standards for 131 substances of public health and welfare concern. Existing state groundwater standards for 15 substances would be revised. The addition of new standards, and revision of existing standards, does not affect the evaluation and response procedures in ch. NR 140 used by regulatory programs when standards are attained or exceeded.

4. Hearing Synopsis

At the October 2009 Natural Resources Board meeting the Board authorized the Department to hold public hearings and solicit comments on proposed amendments to ch. NR 140. The Department held five public hearings, Dec. 11, 2009 through Dec. 16, 2009, and accepted written comments through Dec. 30, 2009. A total of 16 people attended the hearings and presented oral and written comments. The ch. NR 140 public hearings, conducted by staff from the Bureaus of Drinking Water & Groundwater and Legal Services, were as follows:

Dec. 11, 2009 in Madison, WI: 5 people attended, 4 hearing appearance slips were submitted (1 "As interest may appear", 3 "In support", and 1 slip not marked), 1 oral comment was made and 1 written comment was submitted.

Dec. 14, 2009 in Baraboo, WI: 5 people attended, 3 hearing appearance slips were submitted (1 "As interest may appear", 1 "In support" and 1 "In opposition"), 2 oral comments were made and 1 written comment was submitted.

Dec. 15, 2009 in Eau Claire, WI: 2 people attended. No hearing appearance slips were submitted and no oral or written comments were received at this hearing.

Dec. 15, 2009 in Stevens Point, WI: 3 people attended, 2 hearing appearance slips were submitted (2 "In support"), 2 oral comments were made and 2 written comments were submitted.

Dec. 16, 2009 in Oshkosh, WI: 1 person attended and signed a hearing appearance slip, "As interest may appear". No oral or written comments were received at this hearing.

5. Summary of Public Comments

During the public comment period the Department received comments both in support of, and in opposition to, the proposed amendments to ch. NR 140. Comments on proposed code clarification language and information related to toxicity risk assessments were also received. In general, comments were received that:

- support establishing health based standards for manganese and encourage reevaluation of these standards, as new research results on health impacts become available;

- recommend re-review of the available toxicity information for dinitrotoluenes, or deferral of standards until additional toxicity assessment studies are completed; suggest laboratory analytical methods for DNT isomers are not currently low enough to allow an evaluation of compliance with the proposed standards to be made;

- support regulation of the six dinitrotoluene isomers as a single entity, and an enforcement standard set at the same level as the health advisory level established by the WI DHS;

- support the regulation of perchlorate, pointing out that there are several population subgroups that may be affected by very low levels in food or water, and recommend establishing a lower, "more protective", enforcement standard;

- note that there is a more recent (Jan. 2007) EPA cancer risk assessment available for acetochlor and recommend that the proposed groundwater quality standards be recalculated;

- oppose the proposed combined standard for the two acetochlor degradation products (ESA and OXA) since the "mode of action" of these chemicals is unknown and thyroid hormone effects on test animals are not the same for both substances;

- request federal reference and risk exposure levels for aluminum be reviewed, aluminum toxicity studies used to develop standards be re-evaluated and the total uncertainty factor used to calculate the enforcement standard be reconsidered;

- note that there are agricultural chemicals, applied to relatively large percentages of potato and corn crop acres, that currently do not have state groundwater standards, and therefore a more proactive, "precautionary" approach to groundwater protection in Wisconsin, and consideration of health threats posed by mixtures of pesticides and metabolites, and residues and nitrate nitrogen is needed.

A separate Response to Public Comments **(Attachment 1)** document provides detailed responses to comments received. The Department of Health Services has also provided responses **(Attachment 2)** to comments and information received related to toxicity assessment studies and their development of new standards. Based on comments and information submitted during the public comment period DHS has revised their recommendations for acetochlor, aluminum and perchlorate groundwater quality standards **(Attachment 3)**.

6. Environmental Analysis

Section NR 150.03, Wis. Adm. Code, (Environmental Analysis and Review Procedures for Department Actions) describes the appropriate categories for various proposed Departmental actions. The Department has determined that this rule proposal is a Type III action. Type III actions normally do not have the potential to cause significant environmental effects, normally do not significantly affect energy usage and normally do not involve unresolved conflicts in the use of available resources. This rule proposal is not expected to cause any of these effects. In accordance with s. 150.20, Wis. Adm. Code, Type III actions do not require an environmental assessment (EA) or environmental impact statement (EIS).

7. Small Business Regulatory Flexibility Analysis

The Department does not believe that the proposed rule will have a significant economic impact on a substantial number of small businesses. The compliance and reporting requirements in ch. NR 140 are not changed by the proposed amendments. If a groundwater quality standard is exceeded, the owner or operator of a facility, practice or activity, including any small business, must report the violation to the appropriate regulatory agency. There would be 15 new substances for which a facility may have to monitor and report exceedances and 15 additional substances with revised standards. Of the 15 revised standards, 9 are proposed to be less restrictive than their current standard.

Chapter 160, Stats., requires establishment of both design and performance standards. Individual state agency regulatory programs establish design and operational standards in their specific program rules. Performance standards (groundwater quality standards) are contained in ch. NR 140. Chapter 160, Stats., does not allow for less stringent schedules, deadlines or reporting requirements, or for exemptions to remedial action, when a groundwater quality standard is attained or exceeded, based on the size of the business causing the contamination.

There would be adverse impacts on public health, welfare, safety and the environment if small businesses were not required to meet regulatory reporting requirements and implement remedial responses. The more quickly contamination can be evaluated and responses initiated, the less likely that public health safety and welfare will be adversely affected. If small businesses were exempt from these requirements, groundwater contamination would continue unabated at least until the Department could appropriate sufficient resources to undertake this work. The delay, or possibility that nothing would be done, would lead to adverse impacts on public health, welfare, safety and the environment.

The type of small businesses that are typically impacted by ch. NR 140 include dry cleaners, small manufacturers, agricultural cooperatives, farmers, underground storage tank owners, small solid waste disposal facilities, small wastewater treatment operations, as well as others. In effect, any small business that has a permitted or unpermitted discharge of a substance exceeding the health or welfare groundwater quality standards listed in ch. NR 140 is responsible for responding to the release consistent with the requirements of ch. NR 140.

There will be 15 additional new groundwater quality standards, and 15 revised standards, which would be used as design and compliance standards, and for clean-up standards in the event of a spill or unpermitted discharge. If remedial action or other response is necessary, the individual programs which regulate the

facility, practice or activity would determine the appropriate level of clean-up required. As the cost of remedial options varies, the cost of remediation of groundwater contamination for small businesses will vary, depending on the complexity of the site and contamination at the facility, practice or activity, and federal and state laws that are being used to guide the remedial action.

The majority of the substances for which new groundwater quality standards are proposed have already been detected in groundwater at one or more sites in Wisconsin. The adoption of design, compliance and clean-up standards for these substances may aid small businesses in a number of ways. The standards will provide specifications for facility and activity design purposes, inform whether a substance detected in groundwater does or does not exceed a standard and, if it does, let a small business know when the clean-up efforts are finished based on standards being met. When substances are detected in groundwater for which a standard does not exist in ch. NR 140, the Department may require clean-up of the groundwater "to the extent practicable" which may be overly conservative depending upon the actual toxicity of the substance detected.

Attachments:

Attachment 1	RESPONSE TO PUBLIC COMMENTS
Attachment 2	Memo from the Wisconsin Dept. of Health Services (dated Feb. 10, 2010) with responses to comments on their groundwater quality standard recommendations
Attachment 3	February 2010 Wisconsin Dept. of Health Services *Scientific Support Documentation for Cycle 9, Revisions of NR 140.10, Groundwater Enforcement Standard & Preventive Action Limit Recommendations*
Attachment 4	We Energies - *Summary of Concerns with WDHS ES/PAL for Aluminum*
Attachment 5	WI Dept. of Health Services – May 25, 2010 *DHS Response to Comments from WE Energies*
Attachment 6	July 8, 2010 Memo from Ed Lynch, DNR Waste and Materials Management Program, to Mike Lemcke, DNR Drinking Water & Groundwater Program, assessment of potential impacts of new aluminum groundwater standards on Environmental Monitoring for Landfills and Beneficial Use of Industrial Byproducts
Attachment 7	County Health Department fee-exempt well testing program - summary of metals sampling results 2007 - 2009

Attachment 1

RESPONSE TO PUBLIC COMMENTS
March, 10, 2010

Revisions to ch. NR 140, Wis. Adm. Code, to amend NR 140.10 Table 1 and Appendix 1, relating to groundwater quality standards

Natural Resources Board Order No. DG-24-09

Introduction

In October of 2009, the Natural Resources Board authorized the Department to hold pubic hearings and solicit comments on proposed revisions to ch. NR 140, "Groundwater Quality". The proposed rule package included establishing new state groundwater quality standards for 15 substances and revising existing state groundwater quality standards for 15 additional substances. In addition, minor revisions and additions were proposed to update and clarify rule language.

Five public hearings were held in December of 2009. A total of 16 people attended these hearings. Two marked hearing appearance slips "As interest may appear", 6 marked hearing appearance slips "In support" of the proposed rule revisions and 1 marked their hearing appearance slip "In opposition" to the proposed rule revisions. 5 oral statements were made at the hearings and 4 written comments were submitted.

Written comments on the proposed rule revisions were accepted through Dec. 30, 2009. Approximately 152 letters, postcards, e-mails and information documents were received by the Department during the rule public comment period.

The Response to Public Comments document is organized in two sections. Section I covers comments received at the public hearings and submitted during the rule comment period. Section II addresses comments received from the Wisconsin Legislative Council Rules Clearinghouse.

Comments related to the interpretation of toxicologic studies and the risk assessment methodology used by the WI Dept. of Health Services (DHS) to develop their recommendations for new and revised state groundwater quality standards have been responded to by DHS staff. These responses are included in a DHS memo, dated Feb. 10, 2010 (Attachment 2). Revised DHS recommendations for groundwater quality standards are included in the DHS (Feb. 2010) *Scientific Support Documentation for Cycle 9, Revisions of NR 140.10, Groundwater Enforcement Standard & Preventive Action Limit Recommendations* document (Attachment 3).

I. Oral and written comments received by the Department on proposed rule revisions

The following acronyms and abbreviations are used to identify commenting organizations in this section:

WE	We Energies (Wisconsin Electric Power Co. and Wisconsin Gas Co.)
DA	Dept. of the Army (Office of Regional Environmental and Government Affairs -Northern)
CSWAB	Citizens for Safe Water Around Badger
ARP	Acetochlor Registration Partnership (Dow AgroSciences, LLC and Monsanto Co.)
PC	Portage County - Planning and Zoning Department
TA	Test America, Inc.

1. **Comment:** Recommended that the Department re-review the available toxicity information for dinitrotoluenes and conduct an independent peer review of this toxicity evaluation, and recommended that the Department defer developing standards for "dinitrotoluene, total residues" groundwater quality standards until after the U. S. Army Public Health Command completes their provisional dinitrotoluene toxicity assessment studies. (DA)

   Response: This information has been reviewed and the proposed standards remain unchanged. The DHS addresses specific technical comments in their Response to Comments document (Attachment 2), see response 3.

2. **Comment:** Laboratory analytical methods for dinitrotoluene isomers are not currently low enough to allow an evaluation of compliance with the proposed standards to be made. (DA)

   Response: Note that s. NR 140.16(2) requires a laboratory to utilize an analytical methodology that produces the lowest available limits of detection, and that s. NR 140.14(3), provides guidance for dealing with situations where groundwater quality standards are equal to, or less than, laboratory limits of quantitation. The DHS addresses this in its Response to Comments document (Attachment 2), see response 3.

3. **Comment:** Multiple comments supporting regulation of the six dinitrotoluene isomers as a single entity, and a groundwater ch. NR 140 enforcement standard set at the same level as the health advisory level for total residues of dinitrotoluene established by the WI DHS. (CSWAB & others)

   Response: The proposed standards regulate the six isomers of dinitrotoluenes as a single entity. The DHS addresses this in its Response to Comments document (Attachment 2), see response 4.

4. **Comment:** Multiple comments made recommending establishment of a lower, "more protective", enforcement standard for perchlorate than proposed in the rule amendments because there are several subgroups, such as pregnant women, people with low iodine intake and those who consume food with iodine uptake blockers, that may be affected by very low levels of perchlorate in food and water. (CSWAB & others)

   Response: The proposed standards have been lowered. The DHS addresses this in its Response to Comments document (Attachment 2), see response 4.

5. **Comment:** Oppose the proposed acetochlor groundwater quality standards as there is a more recent EPA cancer risk assessment (Jan. 2007) available than the one used by DHS to develop the proposed standards. Recommend recalculating the proposed acetochlor groundwater quality standards using the more recent acetochlor cancer risk assessment. (ARP)

   Response: This information has been reviewed and a less stringent standard is proposed. The DHS addresses this in its Response to Comments document (Attachment 2), see response 1.

6. **Comment:** Recommendation made to develop individual standards for each of the two acetochlor degradation products, acetochlor-ethane sulfonic acid (acetochlor-ESA) and acetochlor-oxanilic acid (acetochlor-OXA), as the "mode of action" of these chemicals is

unknown, and because the thyroid hormone effect on test animals is not the same for both substances. Recommendation made to use an uncertainty factor consistent with federal guidance when developing these standards. (ARP)

Response: This information has been reviewed and the proposed standards remain unchanged. The DHS addresses this in its Response to Comments document (Attachment 2), see response 1.

7. **Comment:** Recommendation made to review three potentially relevant federal regulatory levels for aluminum during ch. NR 140 groundwater standards development. These regulatory levels are: US EPA tap water Regional Screening Level (RSL) for aluminum of 37 mg/L (37,000 ppb), US EPA Superfund Program Provisional Peer Reviewed Toxicity Value (PPRTV) for aluminum of 1 mg/kg/day, and Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Level (MRL) for aluminum of 1 mg/kg/day. (WE)

   Response: This information has been reviewed and a less stringent standard is proposed. The DHS addresses this in its Response to Comments document (Attachment 2), see response 2.

8. **Comment:** Recommendation made to re-evaluate the results of the 2005 Yousef et al. rabbit study, used to develop the DHS recommended aluminum standards and to reconsider the total uncertainty factor used in the calculation of the proposed aluminum groundwater enforcement standard. (WE)

   Response: This information has been reviewed and a less stringent standard is proposed. The DHS addresses this in its Response to Comments document (Attachment 2), see response 2.

9. **Comment:** Individual commenter noted that there are agricultural chemicals, applied to relatively large percentages of potato and corn crop acres, that currently do not have state groundwater quality standards. Suggestion made to utilize a more proactive, "precautionary" approach to groundwater protection in Wisconsin.

   Response: The WI Dept. of Agriculture, Trade & Consumer Protection (DATCP) periodically conducts surveys evaluating the occurrence of agricultural chemicals in groundwater. The Department will forward comments related to agricultural chemicals applied to Wisconsin crops to DATCP for possible inclusion in future surveys.

10. **Comment:** Need to consider the health threats posed by mixtures of pesticides and pesticide metabolites, and by pesticide residues and nitrate nitrogen. (PC)

    Response: This information has been reviewed and, in part, is included in the existing process. The DHS addresses this in its Response to Comments document (Attachment 2), see response 5.

11. **Comment:** Need to clarify, in ch. NR 140, what analytical methods could be used as acceptable measures of "free cyanide" in groundwater. (WE & TA).

    Response: A note has been added to s. NR 140.10, Table 1 clarifying what laboratory analytical methods are acceptable for "free cyanide".

II. Wisconsin Legislative Council Rules Clearinghouse report comments

One comment was received from the Legislative Council Rules Clearinghouse on Clearinghouse Rule CR09-102 "Form, Style and Placement in Administrative Code":

Comment: Provide a definition for the symbol μS, proposed to be used for field specific conductance, or keep current "micromho" units term.

Response: The μS symbol was replaced in the proposed code amendments with the term "microSiemens".

Attachment 2

Cycle 9 Groundwater Standard Revisions

Response to Comments

Prepared by Lynda Knobeloch, Ph.D., Senior Toxicologist
Wisconsin Department of Health Services
February 10, 2010

1. Acetochlor Registration Partnership (ARP)

The Acetochlor Registration Partnership (ARP) provided new information regarding EPA's re-assessment of acetochlor. In 2007, the EPA withdrew the cancer slope factor for acetochlor, changing its classification from "probable" to "suggestive" and recommended a threshold approach to risk assessment. The ARP also recommended revising the proposed standards for the ESA and OXA metabolites of acetochlor. Their justification for revision included, in part, current federal risk assessment guidelines which do not allow uncertainty factors to exceed 3,000. ARP also argued that these metabolites should be regulated separately explaining that the toxicity profiles are not 'virtually the same" as stated in the supporting document because one caused thyroid hormone levels to increase, while the other was associated with lower hormone levels.

Response: Following review of the January 3, 2007 report prepared by the EPA's Cancer Assessment Review Committee, DHS has updated the support document for acetochlor and revised the proposed ES from 1 µg/L to 7 µg/L. The newly proposed standard was developed using the federal reference dose with an additional uncertainty factor of 10 to protect against possible oncogenic effects. The proposed PAL has been adjusted to 0.7 µg/L.

With regard to comments regarding the uncertainty factors used to develop the proposed standard for acetochlor metabolites, Wisconsin state statute Chapter 160.13.2(b3) lists ten factors to be considered in establishing an uncertainty factor. EPA's reference dose for acetochlor was developed considering only one of these items – inter and intra-species

variability. We have included two additional uncertainty factors of 10 each to account for the use of a subchronic study and to account for data gaps in the toxicological database. These factors are consistent with Chapter 160's directive to consider the quality and quantity of data relevant to establishing an acceptable daily intake level, but could also be justified under the directive to consider the importance to full health of the most sensitive target organs or body systems affected by the substance, or by the directive to consider potential interactions with other environmental chemicals. It should be noted that while federal risk assessments no longer utilize uncertainty factors above 3,000, EPA routinely applies a relative source contribution of 20% to chemicals in drinking water. When EPA combines an uncertainty factor of 3,000 with the 20% RSC to develop a drinking water health advisory, they are applying an overall safety factor of 15,000 which exceeds the uncertainty factor used in our Cycle 9 proposal. At this time, DHS is not proposing any changes in the proposed enforcement standards or preventive action limits for these metabolites.

2. WE Energies

WE Energies commented on the proposed ES for aluminum citing EPA Region 9's screening level of 37 mg/L for aluminum in tap water and the Agency for Toxic Substances and Disease Registry's (ATSDR) minimal risk level of 1 mg/kg/day for aluminum.

Response: We have not used these values in the development of a groundwater protection ES. It is our understanding that screening levels used by regional EPA offices are not official federal numbers as they are not published in the Federal Register or in IRIS and are not subjected to approval by EPA's central office or peer reviewed. ATSDR's minimal risk level of 1 mg/kg/day provides a guideline for total dietary and drinking water intake and was considered in our development of a safe level in groundwater, but was not used for our calculation since it was developed to consider ingestion from foods as well as water. The most useful federal guideline for drinking water identified in DHS' review was the US Food and Drug Administration's standard of 200 μg/L for commercially-sold bottled water. The World Health Organization has also established a standard of 200 μg/L for aluminum in drinking water.

We thank WE Energies for their comments and have amended the support document for aluminum to include information they have provided. The proposed ES has been rounded up from 170 to 200 μg/L to be consistent with the FDA and WHO guidelines for aluminum in drinking water.

3. US Department of Defense

The US DOD provided comments on the proposed standard for dinitrotoluene isomers. In its comments, the DOD argued that the toxicity database for minor isomers of DNT, as reviewed in our background document, does not support a combined standard and that analytical methods for DNT isomers cannot demonstrate compliance with the proposed standard. They recommended deferment of adoption of an ES until the US Army Public Health Command completes an assessment of the mutagenicity of DNT. The commenter cited two studies conducted by the Midwest Research Institute during the 1970s and supported by the US Army Medical Research and Development Command as primary studies that should have been included in our support document. While data from these studies have been published in secondary sources, the primary sources are available only from a DOD website. We were able to locate the December 8, 1978 progress report prepared by Ellis et al. which was referenced in the DOD comments and have added information from that report to our support document.

The commenter has provided the following technical comments:

The oral LD50 for 3,4 DNT should be 807 mg/kg, not 177 mg/kg.

Response: We appreciate this correction. Table 1 has been amended to list LD_{50}s in female rats as reported by Rickert et al. 1984. While these are not always the lowest LD_{50}s, the selection of a single species and single sex is intended to allow comparison of the toxicity of these isomers.

The underlying science does not support the development of a combined standard for DNT isomers.

Response: While data for the minor isomers is too limited for independent risk assessments, existing data indicates that they are similar in toxicity to the 2,4- and 2,6-isomers and that some effects of exposure are likely to be additive. On page 31 of their Dec 8, 1978 progress report submitted to the US Army, Ellis et al. concluded, "The acute oral toxicities of all the nitrotoluenes tested are generally similar... 3,5-DNT is the most toxic...All these (sic) nitrotoluenes were fairly well absorbed and widely distributed by rats. They were concentrated in the liver and kidneys...Ames tests of various munitions found that TNM, TNT, 2,4-DNT, 2,5-DNT and 1,2-DNG were potential mutagens active at 10 to 30 μg/plate. The other nitrotoluenes tested (2,3-DNT, 2,6-DNT, 3,4-DNT and 3,5-DNT) were weak mutagens." On page 28 of this report, the authors summarize the Ames tests results stating, "Many recent studies have shown that, in general, nitroaromatics exhibit a high degree of mutagenic activity in the Salmonella microsome plate test. . . In light of these considerations, it appears that TNT and the six DNT isomers should be considered as potentially mutagenic and possibly carcinogenic."

Our review of available literature on these isomers suggests that the chronic toxicities of DNT isomers are also likely similar although the toxicological databases are incomplete for the minor isomers. In the absence of a complete toxicological database for all six isomers, the most practical approach to ensure protection of public health is to regulate these chemicals, which have a common production source and are often found together in groundwater, as a group.

Purified 2,4-DNT and all of the minor isomers had no detectable initiating activity. The minor isomers had no detectable hepatocarcinogenic initiating activity.

Response: The literature is inconsistent regarding this issue. While Leonard et al. reported this finding, a 1979 report by Ellis et al. found that mice and rats fed a diet containing 98% pure 2,4-DNT had higher levels of liver (rats) and kidney (mice) tumors. In its review of these studies, the European Organization for Economic Cooperation and Development (OECD) provided the following, "The pure 2,4-DNT isomer induced the same tumor spectrum in long-term feeding studies in rats as was shown for the technical grade isomer mixture. Additionally, tumors of the renal tubular epithelium were observed in male mice after chronic 2,4-DNT feeding."

The minor isomers do not contribute to the carcinogenicity of Technical Grade DNT in an additive manner.

Response: We have been unable to locate any scientific studies that address the carcinogenic additivity of DNT isomers. While we do not have data from long-term feeding studies for the minor isomers, their structural similarity to the 2,4- and 2,6-isomers and their acute toxicity and mutagenicity profiles support an assumption of additivity.

DNT in groundwater cannot be accurately and reliably measured at levels proposed as standards and preventive action limits.

Response: Since analytical precision varies from lab to lab and tends to improve over time, it is not considered in our development of groundwater protection standards. According to Table 2 of the comments submitted by DOD which shows method quantitation limits (MQLs) and method detection limits (MDLs) for DNT isomers at the Badger Army Ammunition Facility in Baraboo, only 2,6- and 3,4-DNT have MQLs that exceed the proposed ES and all of the isomers have MDLs of <0.05 µg/L suggesting that laboratories can detect these substances if they exceed the proposed enforcement standard. While MDLs for some isomers exceed the proposed preventive action limit, detection of these substances would be considered an exceedance of this secondary standard.

4. Laura Olah, Executive Director, Citizens for Safe Water around Badger

DNR's proposal to regulate DNT in drinking water is vital to the community around Badger Army Ammunitions Plant and to millions of Wisconsin adults, children and infants who rely on groundwater as a source of drinking water.

Response: We appreciate the support of Ms. Olah and other members of this group for our efforts in ensuring the safety of Wisconsin's groundwater resource.

We support the proposed regulation of perchlorate and recommend that the proposed standard be revised from 7 µg/L to 1 µg/L – a level that is consistent with

recommendations from the NRDC, Environmental Working Group and many others. The proposed enforcement standard would put breast-fed infants, bottle-fed infants and young children at risk of having daily exposures that are near or even exceed the EPA reference dose considered to be a safe daily intake.

Response: Following review of additional materials submitted by this commenter, we have applied an additional uncertainty factor to ensure protection against long-term exposure to perchlorate, which has been detected in many foods as well as in surface and groundwater throughout the United States and is considered a possible human carcinogen.

5. Raymond Schmidt, Water Quality Specialist, Portage County Planning and Zoning Department

I am pleased to see that additional health-based standards are being proposed by pesticides and metabolites that are found in Wisconsin's groundwater. I encourage the state to develop methods for evaluating the health threats posed by mixtures of pesticides, metabolites and nitrate.

Response: We appreciate this comment. We encourage the use of hazard indices to assess the potability of water that contains more than one contaminant. While this approach does not address potential synergistic effects, it provides an additional measure of safety when multiple contaminants are detected and should be used to assess the need to replace severely contaminated water supplies.

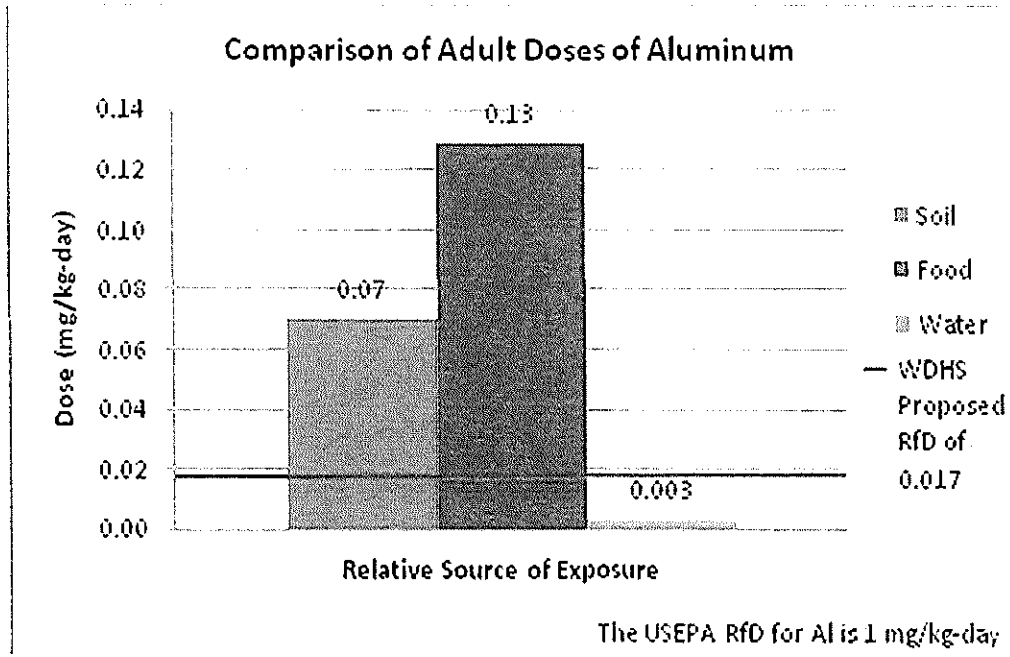
Attachment 4

Summary of Concerns with WDHS ES/PAL for Aluminum

Prepared by: Lisa J.N. Bradley, Ph.D., DABT
and
Robert Paulson – We Energies

Aluminum in the Natural Environment

- As the third most common element on Earth, aluminum (Al) is ubiquitous in the environment.
- It can be found in our food, water, and consumer products.
- The U.S. Geological Survey reports that background levels of Al in soils in Wisconsin range between 2 – 4.9% by weight, which is equivalent to 20,000 – 49,000 mg/kg.
- Naturally occurring Al levels in groundwater in Wisconsin generally range up to 0.1 mg/L (ATSDR, 2008). GRN data query produced results from No Detect to 334 mg/L.
- Based on standard regulatory assumptions (i.e. ,receptor's body weight, incidental soil ingestion rate, water ingestion rate, etc.), predicted exposure for an adult receptor based on incidental ingestion of Al through soil, dietary items, and water is as follows:
  - Exposure dose from soil: **0.03 to 0.07 mg/kg-d**
  - Exposure dose from food: **0.1 to 0.13 mg/kg-d**
  - Exposure dose from water: **0.0003 mg/kg-d**



Exposure to Al in water is a small and even negligible contribution to total exposure to Al in the natural environment.

Diet, however, contributes greatly to the amount of Al that we are exposed to on a daily basis. In fact, if the Al content of the laboratory diet is not considered and accounted for in bioassay studies, it must be assumed that the exposure levels have been <u>underestimated</u> (USEPA, 2006).

Availability of Toxicity Values for Aluminum

- **USEPA (IRIS)** – The IRIS database is a primary source of toxicity values. There are no toxicity values for Al on IRIS.
- **USEPA (PPRTV)**– USEPA has developed a Provisional Peer-Reviewed Toxicity Value (PPRTV) for Al of **1 mg/kg-day** (1 milligram of aluminum per kilogram of body weight per day), which is a daily level that is likely to be without an appreciable risk of deleterious effects during a lifetime of exposure. This value serves as the basis for the USEPA Regional Screening Level (RSL) for tap water of 37,000 ug/L. (LOAEL = 100 mg/kg-day; UF = 100)
- **ATSDR** – the Agency for Toxic Substances and Disease Registry (ATSDR) of the US Department of Health & Human Services has developed a Minimal Risk Level (MRL) for Al of **1 mg/kg-day**, which is a level that is an estimate of the daily human exposure to a substance that is likely to be without appreciable risk of adverse health effects. (LOAEL = 100 mg/kg-day; UF = 100)

Drinking Water Levels for Aluminum

- **USEPA Office of Water** - USEPA has not developed a health-based standard or Maximum Contaminant Level (MCL) for Al. However, it has published a secondary MCL (SMCL) of **200 ug/L**. The SMCL is not health based, but is designed to prevent unpleasant taste, odor, and unusual color. This SMCL is set at a level much lower than those that may be harmful to humans.
- **FDA** - The Food and Drug Administration (FDA) has a bottled water criterion of **200 ug/L** that is based on the USEPA SMCL. Thus, it too is based on prevention of unpleasant taste, odor, and unusual color, and is not based on human health effects.
- **WHO** – The World Health Organization (WHO) established a level of **200 ug/L** to address the use of Al containing compounds that remove solids from drinking water . The level was set based on practicality to achieve, and to minimize color or turbidity that may occur in the treated water at higher levels.
- **USEPA** – USEPA has a Regional Screening Level (RSL) table that provides health-based screening levels for several environmental media including tap water. The human health-based tap water RSL is **37,000 ug/L**.

WDHS Derived Draft Standard for Al

- **WDHS** – The Wisconsin Department of Health Services (WDHS) has proposed a toxicity value for Al of **0.017 mg/kg-day** for use in the development of NR 140 standards. This value is 59-fold lower than peer reviewed values developed independently by two federal agencies (ATSDR and EPA).
- The resulting draft enforcement standard (ES) for aluminum is 170 ug/L, rounded to **200 ug/L**. This level is similar to some other available drinking water levels, none of which are health-risk based.
- The WDHS-derived toxicity value is based on a single study yielding results not replicated by other studies or other species.
- The selection of the study did not consider several important factors:
  - The baseline Al content of the lab animal diet was not reported in the study
  - Only one treatment level was used rather than multiple treatment levels which are needed to develop a dose-response relationship
  - Only a small number of animals were used per treatment group (n=6)
  - The effects were reversed by the inclusion of Vitamin C in the treatment
- WDHS applied three levels of uncertainty factors, each at maximum levels, for a total uncertainty factor of 1,000.

6

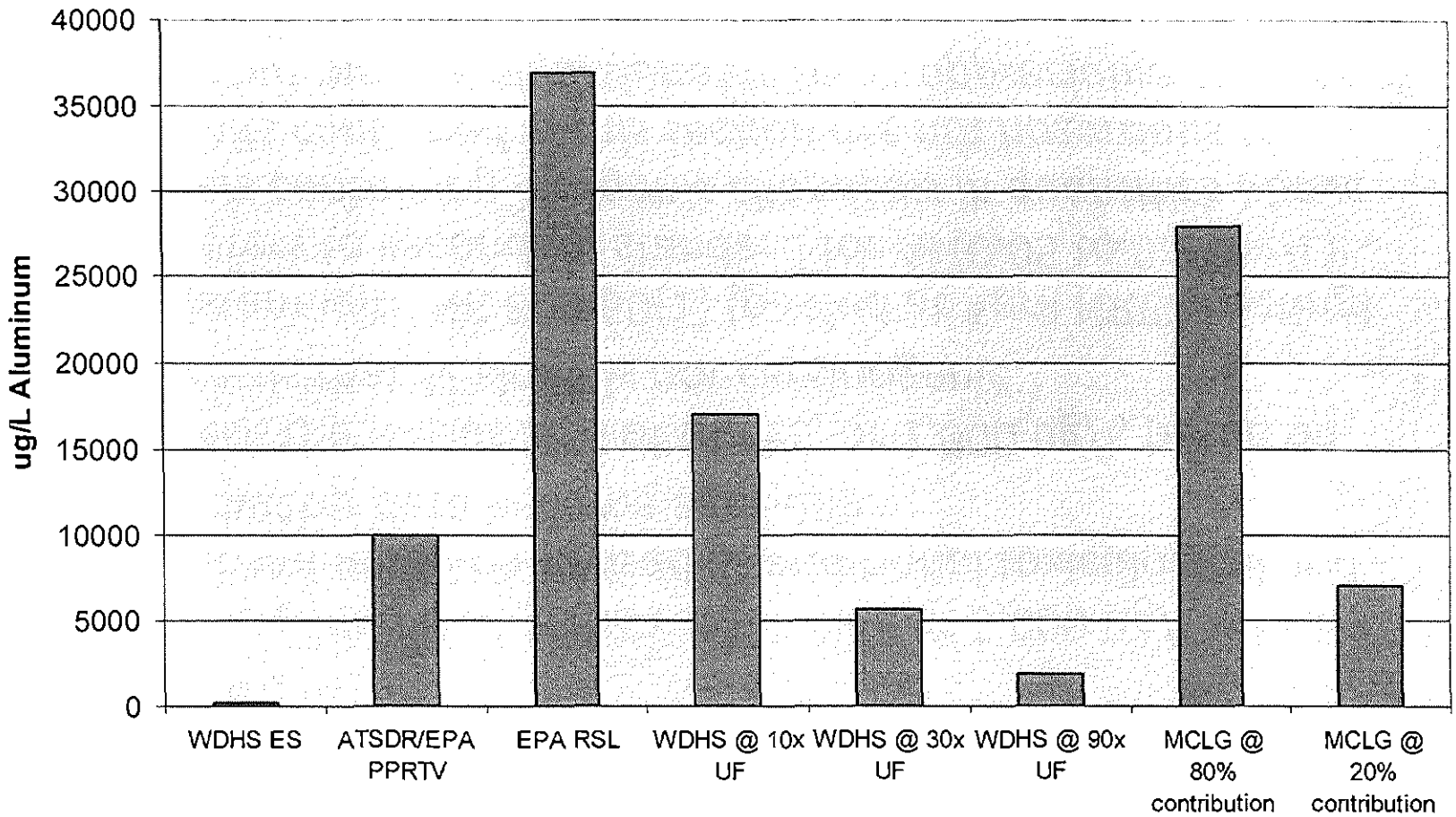
Summary

- In the context of peer-reviewed literature and in the context of the natural environment, the WDHS toxicity derivation for Al seems unrealistically low.
- Health-based reviews of Al from both US federal sources and from the literature have converged on the conclusion that Al has not been shown to be carcinogenic in animals and is not expected to be carcinogenic in humans.
- There is also consensus that due to the high background exposure to Al in the diet, studies that do not quantitatively account for Al exposure in the lab diet cannot be used quantitatively.
- The derivation is inconsistent with the requirements for ADI derivation set out in s. 160.13(2)(b)3.a-j. Specifically:
  - a. **The quality and quantity of data relevant to establishing an acceptable daily intake**
    - the study used is the only such study identified in the literature and, thus, the results have not been independently replicated
    - the study used did not account for the baseline Al content of the lab animal diet
    - Only six (6) animals were exposed
  - c. **The amount of interspecies and intraspecies variations** – WDHS has applied the maximum uncertainty factor for these potential variations (1,000), where those used by federal agencies are much lower (100) and applied to a higher point of departure (a LOAEL of 100 mg/kg-day).
  - d. **The dose-response curve** – WDHS has used a study that evaluated only 1 exposure level for aluminum, and there are no other similar studies in the literature, therefore, a dose-response relationship cannot be defined for aluminum for this endpoint.
  - f. **The potential interactions of the substance** – the study used by WDHS demonstrated that the effects observed in the Al treated animals was fully reversible by exposure to Vitamin C (ascorbic acid).

Alternatives

- Use EPA RSL
- Use ATSDR and EPA PPRTV RfD
- Use the WDHS study derivation, but apply realistic uncertainty factors
- Applying a MCLG derivation process using US EPA/ATSDR RfD
- Pull Al criteria from current NR 140 revision

Alternative Aluminum ES



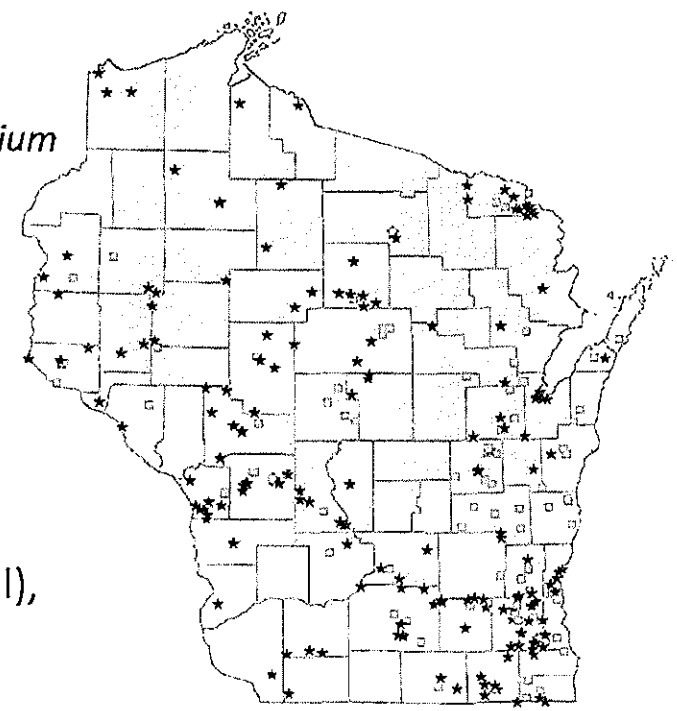
Path Forward

- Recommended that ES be established at 5,000 µg/L which can subsequently be revised as additional toxicological and groundwater data become available.
- Establish the PAL at 20% of the ES, or 1,000 ug/l, based on consensus that Al alone is not carcinogenic.
- Consistent with NR 809.60(1) (passed at April NRB meeting) that refers to secondary standard for Al (0.05 to 0.2 mg/L): *"Waters containing inorganic chemicals in quantities above the limits contained in this section are not hazardous to health but may be objectionable to an appreciable number of persons."*

10

Consequences of PAL Derivation

- PAL proposed at 10% of ES for carcinogenic substance consistent with NR 140.10.
- Other peer reviewed conclusions that also considered Schroder & Mitchener (1975) studies cited by WDHS:
  - ATSDR (2008) carcinogenicity evaluation states *"The available data do not indicate that aluminum is a potential carcinogen. It has not been shown to be carcinogenic in epidemiological studies in humans, nor in animal studies using inhalation, oral, and other exposure routes."*
  - Krewski et al. (2007), cited by WDHS, concluded: *"Overall, experimental animal studies have failed to demonstrate carcinogenicity attributable solely to aluminium compounds (for reviews, see ATSDR, 1999; .....)*
- GRN data query produced 199 potable wells and 313 non-potable wells that exceeded proposed PAL.
- When PAL for a <u>carcinogenic</u> substance is exceeded, NR 140.24 requires the Department to take action regardless of background concentration.
- Significant effort for well owners (private and municipal), the regulated community, and WDNR staff.



Attachment 5

Jim Doyle
Governor

Karen E. Timberlake
Secretary

State of Wisconsin
Department of Health Services

DIVISION OF PUBLIC HEALTH

1 WEST WILSON STREET
P O BOX 2659
MADISON WI 53701-2659

608-266-1251
FAX: 608-267-2832
TTY: 888-701-1253
dhs.wisconsin.gov

Response to Comments from WE Energies

Prepared by Lynda Knobeloch, Ph.D.
Senior Toxicologist
Wisconsin Department of Health Services
May 25, 2010

The document prepared by Lisa Bradley, on behalf of WE Energies, focused on several key points including background aluminum levels in Wisconsin soil and water; human exposure from food and soil; a summary of available risk assessments and toxicity values; the carcinogenicity of aluminum; and the methods we have used to derive a groundwater enforcement standard and preventive action limit for aluminum.

1) Regarding background aluminum levels and human intake, Dr. Bradley provided the following summary:

> Aluminum levels in Wisconsin soil range between 2 and 4.9% by weight.
>
> Naturally-occurring aluminum in groundwater in Wisconsin generally ranges up to 0.1 mg/L.
>
> The average U.S. adult ingests approximately 7 to 9 mg aluminum per day in foods.
>
> A 15-kg child's exposure to aluminum from soil ranges from 0.27 to 0.65 mg/kg/day.
>
> Exposure to aluminum in water is a small and even negligible contribution to total exposure in the natural environment.

DHS agrees that most aluminum exposure is likely to come from foods. Antacids and buffered aspirin are other important sources for people who use these products. Naturally-occurring aluminum levels in Wisconsin's groundwater are quite low and are a minor source of exposure. This would not be the case, however, for someone whose water was contaminated with 5 mg or more aluminum per liter. Assuming daily ingestion of two liters of water per day by an adult, this water would likely be the primary source of exposure and would more than double total daily intake. It is important to realize that aluminum exists in hundreds of different chemical forms and that its bioavailability varies widely. Aluminum silicates found in soil pass through the gastrointestinal tract with very little absorption. Ligand-bound forms of aluminum present in many foods also have low absorption rates following ingestion. However, free aluminum ions from aluminum salts such as gluconates, citrates and lactates are more likely to be absorbed and pose a risk of accumulation and toxicity. We are concerned that dissolved forms of

aluminum that leach to groundwater may be more bioavailable than forms found in food and soil and could pose a greater exposure hazard.

2) Dr. Bradley cited several federal numbers as potentially useful in the development of a health-based groundwater standard. These include the US EPA Provisional Peer-Reviewed Toxicity Value (PPRTV) and ATSDR's Minimal Risk Level (MRL) for aluminum. Both of these values are set at 1 mg/kg/day for total aluminum intake. Dr. Bradley also mentioned a reference dose and drinking water equivalent level for aluminum. However, our review found that EPA has not developed either of these parameters.

The PPRTV and MRL for aluminum are not specific to exposure from water. DHS has concluded that these values cannot be used to develop a health-based groundwater protection standard without modification to consider the bioavailability and total intake from all sources. Although a reference dose and drinking water equivalent level are not available for aluminum, in their 2007 report to EPA, titled *Human Health Risk Assessment for Aluminium, Aluminium Oxide, and Aluminium Hydroxide*, Krewski et al. determined that the most sensitive endpoints were on reproductive and neurological function and concluded that a level of 100 ppb in drinking water was likely protective against these effects.

3) Dr. Bradley expressed concern that a single study was used to develop the groundwater enforcement standard for aluminum. While DHS conducted a comprehensive review of the toxicity literature for aluminum, the calculation of a numerical standard is traditionally based on a a NOEL or LOEL from a single study that is deemed scientifically valid and relevant to human health.

4) Regarding the carcinogenic potential of aluminum, Dr. Bradley pointed out that occupational studies of aluminum workers were confounded by concurrent exposure to other constituents that are more likely to be carcinogenic than aluminum. She went on to state that animal studies have failed to demonstrate a carcinogenic effect of aluminum.

DHS based the 10% PAL on the International Agency for Research on Cancer's classification of aluminum production as a known human carcinogen and on animal studies conducted by Schroeder and Mitchner which found a carcinogenic effect of aluminum in drinking water fed to rats and mice. While DHS recognizes that the IARC classification is for aluminum production and could be confounded by other workplace exposures, the peer-reviewed publications by Schroeder and Mitchner remain unchallenged. In 2002 Morton et al. also reported on the carcinogenicity of aluminum (Toxicol Pathol. 2002). These researchers found higher rates of preneoplastic and neoplastic renal lesions in Eker rats given IP injections of 2 mg Al per kg per day three times a week over a period of 4 to 6 months. Other recent studies have found genetic toxicity and epigenetic effects of aluminum suggesting the potential for aluminum to increase tumor development. While we believe there is a strong weight of evidence supporting use of a 10% preventive action limit, we recognize that a scientific case can also be made for a 20% preventive action limit. Therefore, DHS would support either a 10% or a 20% preventive action limit for aluminum.

5) WE Energies' comments included proposals to use a lower uncertainty factor to derive a groundwater standard. DHS opposes modification of the uncertainty factors which are standard to our risk assessment methods and necessary to ensure protection of vulnerable individuals.

6) Dr. Bradley recommended that Wisconsin's groundwater standard be set in the range between 5,000 and 35,000 µg/L. DHS does not support increasing the proposed enforcement

standard since there is no evidence that long-term consumption of aluminum-contaminated water is safe and considerable evidence to the contrary. An incident that occurred in Camelford England in which the drinking water supply was accidentally contaminated with aluminum at levels between 100 and 500 mg/L for several days is a case in point. Village residents experienced immediate symptoms of nausea, vomiting and diarrhea. A 10-year follow-up assessment of 55 exposed adults found evidence of long-term brain damage. A post-mortem examination of a Camelford resident who died after developing severe dementia at the age of 58, 15 years after the aluminum exposure, revealed a rare form of sporadic, early-onset β amyloid angiopathy in the cerebral cortex. High concentrations of aluminum were found in the affected regions of her brain (23 ug/g dry wt; normal 0-2 ug/g) suggesting that her illness and death were a direct result of her exposure to aluminum. Findings from this cohort suggest a long-term, delayed or progressive effect of acute aluminum intoxication on brain function.

7) DHS is also concerned regarding the bioavailability of aluminum in water. While aluminum silicates found in soil and ligand-bound forms found in some foods tend to pass through the gastrointestinal tract with little uptake into the blood stream, water soluble salts are more readily absorbed. Absorption is enhanced by low pH foods such as orange or grapefruit juice. Human uptake also varies depending on age, genetics, and health status.

DHS appreciates this opportunity to respond to the comments prepared by Dr. Bradley. However, we continue to support a groundwater enforcement standard of 200 µg/L and 10% or 20% preventive action limit for aluminum.

Attachment 6

State of Wisconsin

CORRESPONDENCE/MEMORANDUM

DATE: July 8, 2010

TO: Michael Lemcke – DG/5

FROM: Edward Lynch – WA/5

SUBJECT: Propose NR 140 Aluminum Standard

This memo was prepared following a conference call on June 3, 2010 between WE Energies representatives and representatives of the Wisconsin Departments of Health Services and Natural Resources. The DNR's Drinking and Groundwater program is proposing the establishment of groundwater standards for aluminum (Al) in Ch. NR 140, Wis. Admin. Code – Groundwater Quality. The proposed NR 140 enforcement standard (ES) for aluminum is 200 parts per billion (ppb) and the proposed preventive action level (PAL) is 20 ppb. This proposed rule was brought to the April 2010 Natural Resources Board (NRB).

At the April NRB meeting, WE Energies expressed concern regarding the potential effects the proposed Al standards would have on the DNR's Waste and Materials Management (WMM) program in the following areas:

- Ch. NR 507, Wis. Admin. Code – Environmental Monitoring for Landfills
- Ch. NR 538, Wis. Admin. Code – Beneficial Use of Industrial Byproducts

The WMM program initially requested the establishment of the Al standards as a result of high Al concentrations in groundwater resulting from alum sludge disposal at a few select industrial disposal sites. This was done to enable the DNR to require that landfill operators address high Al exceedances resulting from alum disposal. In one situation in northeastern Wisconsin, a private well located down-gradient of an alum landfill was reported to have discolored water which led to sampling. DNR staff sampling revealed concentrations of 1,100 and 1,920 ug/l (ppb). At another alum disposal site in central Wisconsin, Al concentrations have been in the 40,000 to 60,000 ppb range and have been as high as 155,000 ppb as recently as October, 2009.

<u>Relationship between ch. NR 140, Wis. Admin. Code and monitoring at landfills</u>. Ch. NR 507, Wis. Admin. Code (Environmental Monitoring for Landfills) identifies parameters to be monitored in groundwater at municipal solid waste landfills and landfills accepting waste other than municipal solid waste (i.e., paper mill sludge, fly or bottom ash, foundry waste, etc). Al monitoring is not a requirement in any of the tables in the appendices to Ch. NR 507, Wis. Admin. Code. At this time, the WMM program does not plan to amend Ch. NR 507, Wis. Admin. Code to add Al. When necessary, such as in the case of landfills accepting alum sludge for disposal, the WMM program can require Al monitoring through the initial approval or subsequent plan modification to a landfill's monitoring plan.

The WMM program does not plan to modify plan approvals for utility landfills to require Al monitoring of the groundwater unless there is some evidence that Al be could elevated or potentially causing a groundwater problem. There are two reasons WMM does not plan to add Al. First, other parameters such as alkalinity, boron, sulfate, conductivity, pH, and hardness provide adequate monitoring for landfills managing ash. This parameter list can be updated on a case by case basis as was done with molybdenum at a few ash sites. Second, the WMM has data from Al in groundwater collected in the vicinity of a utility landfill in southeast Wisconsin. Of the 40 test results from adjacent wells, the highest

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concentration of Al was 25 ug/l (ppb) and Al was not detected in 19 (about 1/2) of them. In other words, investigations at former landfill sites are driven by parameters other than Al.

The WMM program does not believe it is necessary to adopt for groundwater monitoring at landfills for all the parameters set forth in ch. NR 140, Wis. Admin. Code. Of the 131 substances currently in ch. NR 140, Wis. Admin. Code, ch. NR 507, Wis. Admin. Code identifies only a very small subset to be included as part of a landfill detection monitoring program. When necessary, WMM has the authority to add parameters at a particular site as part of a plan modification. S. NR 507.18 Wis. Admin. Code covers baseline groundwater quality sampling and s. NR 507.18(1) Wis. Admin. Code allows the department to require additional parameters based on the waste types and waste characteristics accepted at the landfill. S. NR 507.19 Wis. Admin. Code covers detection groundwater monitoring which requires owners or operators of solid waste landfills to implement a detection groundwater monitoring program in accordance with their approved plan of operation. In EPA's proposed rule on management of coal combustion residuals, EPA is not proposing Al monitoring of their baseline groundwater monitoring program under their subtitle D proposal (information the EPA proposal follows).

Ch. NR 140, Wis. Admin. Code and beneficial use of industrial byproducts. Ch. NR 538, Wis. Admin. Code – Beneficial use of industrial byproducts. DNR promulgated NR 538, Wis. Admin Code in 1998 "*...to allow and encourage to the maximum extent possible, consistent with the protection of public health and the environment and good engineering practices, the beneficial use of industrial byproducts in a nuisance-free manner. The department encourages the beneficial use of industrial byproducts in order to preserve resources, conserve energy, and reduce or eliminate the need to dispose of industrial byproducts in landfills*". WE Energies has been in the forefront in finding and developing markets for coal combustion byproducts. These efforts have led to utilization of large volumes of their coal combustion byproducts which in turn has saved landfill space and reduced disposal costs. Coal combustion byproducts (bottom ash, fly ash and flue gas desulfurization ash) take the place of virgin materials in products such as cement manufacturing, drywall manufacturing, brick manufacturing and in WE's Gypsoil soil amendment and are also used as geo-technical fill and as concrete aggregate replacement materials. The WMM program would like to see these beneficial use efforts continue.

WMM only uses Al as a value in Appendix 1 to identify category 1 byproducts. In NR 538, Wis. Admin. Code, Appendix 1, Table 1A, the Al standard is 1.5 mg/l (ppm) Al using ASTM water leach test (for coal ash). This Al standard has been in existence since the rule was promulgated in 1998 and does not seem to have limited WE Energies coal byproduct utilization as they have successfully developed beneficial uses for coal ash byproducts. Byproducts from sources other than those listed in Appendix 1, Table 2 (which includes coal ash) do not monitor for Al unless directed by the department. We have not required Al monitoring for coal ash byproducts beyond what is required in the code nor is it our intention to modify those requirements without going through the code revision process.

S. NR 538.10 (1) Wis. Admin. Code allows for the beneficial uses of industrial byproducts as raw materials for manufacturing of a product in which the measurable leaching, emissions or decomposition characteristics of the industrial byproduct are substantially eliminated. These include cement, lightweight aggregate, concrete, and wallboard. We Energies manages a significant amount of its ash byproduct via manufacturing of these products. WMM encourages the continuation of this practice and we have no plans to limit this use due to Al content of the byproducts.

WE Energies bottom ash is typically Category 2 material and the fly ash is typically Category 4. Category 1 materials have the fewest use restrictions and most flexibility in use. Beneficial uses of industrial byproducts include use as raw materials, as supplemental fuels providing energy through

controlled burning, daily cover or internal structures at landfills, confined or unconfined geotechnical fill material such as transportation embankments or side walls, as un-bonded or bonded surface course material, or as winter weather road abrasive. Category 1 materials are the only industrial byproducts that can be placed below the water table or in standing water.

As a point of clarification, at the April NRB meeting, I indicated there are separation distances between ground water and industrial byproducts such coal ash material when used in road construction. This is true for the use of category 2 and higher byproducts which I assumed we were talking about during our discussion since the Al standard has been around for over 10 years already and not posed a problem.

Other than for Category 1 identification, WMM has no other Al standards in ch. NR 538, Wis. Admin. Code and has no plans to add Al to any of the other category designations. WMM does not see a need for further monitoring of Al in coal ash. In the future, when WMM has time and resources to revise NR 538, Wis. Admin. Code, we would plan to have a technical advisory committee and would invite utility participation.

Proposed Federal Legislation concerning coal combustion byproducts. An important caveat concerning the management of coal combustion byproducts is the recently proposed federal rules for management of these materials. These proposed rules may have a significant effect on management of coal combustion byproducts. These first ever federal rules on coal combustion byproducts include language that could result in coal combustion byproducts being regulated under subtitle C (typically hazardous waste) of the federal Resource Conservation and Recovery Act (RCRA) or subtitle D (typically solid waste) of RCRA. EPA is proposing these rules to ensure the safe management of combustion coal residuals that are disposed in surface impoundments and landfills as well as when beneficially used. EPA believes that additional coal ash specific federal regulations are necessary to protect human health and the environment. This is the first time national rules have been issued specifically to manage coal ash disposal. In their subtitle D proposal, EPA does not include Al monitoring as part of the initial site detection monitoring program. The EPA rule proposal includes Al only in the assessment monitoring program when a statistically significant increase over background is detected.

On May 4, 2010, EPA released their pre-publication version of this rule and amended it on May 18, to make corrections. On June 21, 2010, EPA published the proposed rules in the Federal Register to officially begin the federal comment period. DNR plans comment on this federal proposal.

Please let me know if you have questions.

Ce: Ann Coakley – WA/5
Kate Cooper & Jack Connely – WA/5
Phil Fauble – WA/5

Attachment 7

Summary of Metal Test Results, 2007-2009

	Health Advisory	Max	Mean	No. High	No. Tests
	ug/L	ug/l	ug/L		
AL	170	2,210	19.13	32	3,560
AS	10	1,929	8.06	153	3,560
CA	N/A	1,965	51.78	NA	3,560
CD	5	1,947	6.22	24	3,560
CO	40	1,280	1.62	0	3,554
CR	100	17	0.44	0	3,554
CU	1300	8,600	45.20	16	3,554
FE	300	66	0.48	731	3,532
MG	NA	2,975	32.23	NA	3,532
MN	300	3,540	56.87	141	3,531
NI	100	2,790	3.73	18	3,531
PB	15	803	1.91	61	3,532
SR	4,000	32,500	365.26	3	354
V	30	114	1.25	18	3,531
ZN	5,000	6,720	92.44	5	3,531

Wisconsin Department of Administration
Division of Executive Budget and Finance
DOA-2048 (R10/2000)

Fiscal Estimate — 2009 Session

		LRB Number	Amendment Number if Applicable
☒ Original	☐ Updated		
☐ Corrected	☐ Supplemental	Bill Number	Administrative Rule Number DG-24-09

Subject

Amendments to ch. NR 140, Wis. Adm. Code (Groundwater Quality)

Fiscal Effect

State: ☒ No State Fiscal Effect
☐ Indeterminate

Check columns below only if bill makes a direct appropriation or affects a sum sufficient appropriation.

☐ Increase Existing Appropriation ☐ Increase Existing Revenues
☐ Decrease Existing Appropriation ☐ Decrease Existing Revenues
☐ Create New Appropriation

☐ Increase Costs — May be possible to absorb within agency's budget. ☐ Yes ☐ No
☐ Decrease Costs

Local: ☒ No Local Government Costs
☐ Indeterminate

1. ☐ Increase Costs ☐ Permissive ☐ Mandatory
2. ☐ Decrease Costs ☐ Permissive ☐ Mandatory
3. ☐ Increase Revenues ☐ Permissive ☐ Mandatory
4. ☐ Decrease Revenues ☐ Permissive ☐ Mandatory
5. Types of Local Governmental Units Affected: ☐ Towns ☐ Villages ☐ Cities ☐ Counties ☐ Others ____ ☐ School Districts ☐ WTCS Districts

Fund Sources Affected
☐ GPR ☐ FED ☐ PRO ☐ PRS ☐ SEG ☐ SEG-S

Affected Chapter 20 Appropriations

Assumptions Used in Arriving at Fiscal Estimate

SUMMARY OF RULE - Chapter NR 140, Wis. Adm. Code, establishes Wisconsin state groundwater quality standards and creates a framework for implementing those standards in compliance with Wis. Stat. Ch. 160. These proposed amendments to NR 140 add a new enforcement standard (ES) and preventive action limit (PAL) for 15 substances, and revise existing ESs and PALs for an additional 15 substances. In accordance with Wis. Stat. Ch. 160, these proposed amendments to NR 140 groundwater quality standards are based on recommendations from the Wisconsin Department of Health Services.

Chapter NR 140 currently contains groundwater standards for 123 substances of public health concern, 8 substances of public welfare concern and 15 indicator parameters. The proposed new and revised standards would apply to all regulated facilities, practices and activities which may impact groundwater quality. Regulated facilities, practices and activities, which are sources of the substances for which groundwater standards are proposed, are, for the most part, likely sources of substances for which groundwater standards already exist. Consequently, there should be few cases where the proposed standards would be exceeded where existing standards are not currently being exceeded. Thus, the Department does not anticipate significant additional costs to the regulated community associated with these new and revised NR 140 standards. Also, any additional monitoring costs to the regulated community should be minimal, and the workload of state regulatory agencies should not change substantially.

FISCAL IMPACT - Although additional monitoring costs may be imposed upon the state or local government entities that are within the regulated community, the extent of such monitoring and any costs associated with it--while too speculative to quantify at this time--are not expected to be significant. Further, any increased monitoring costs associated with the setting of an ES and PAL for new substances and the lowering of the existing ES and PAL for other substances may be offset by cost savings associated with the relaxing of ESs and PALs for other compounds. Thus, on balance, the Department believes it is unlikely that there will be additional costs to state and local governments resulting from adopting these groundwater standards.

Long-Range Fiscal Implications

Prepared By:	Telephone No.	Agency
Joe Polasek	266-2794	Department of Natural Resources
Authorized Signature	Telephone No.	Date (mm/dd/ccyy)
	266-2794	03-10-10

Fiscal Estimate — 2009 Session

Page 2 Assumptions Narrative Continued

LRB Number	Amendment Number if Applicable
Bill Number	Administrative Rule Number DG-24-09

Assumptions Used in Arriving at Fiscal Estimate – Continued

Wisconsin Department of Administration
Division of Executive Budget and Finance
DOA-2047 (R10/2000)

Fiscal Estimate Worksheet — 2009 Session

Detailed Estimate of Annual Fiscal Effect

☒ Original	☐ Updated	LRB Number	Amendment Number if Applicable
☐ Corrected	☐ Supplemental	Bill Number	Administrative Rule Number DG-24-09

Subject

Amendments to ch. NR 140, Wis. Adm. Code (Groundwater Quality)

One-time Costs or Revenue Impacts for State and/or Local Government (do not include in annualized fiscal effect):

None

Annualized Costs:	Annualized Fiscal Impact on State Funds from:	
A. State Costs by Category	Increased Costs	Decreased Costs
State Operations — Salaries and Fringes	$	$ -
(FTE Position Changes)	(FTE)	(- FTE)
State Operations — Other Costs		-
Local Assistance		-
Aids to Individuals or Organizations		-
Total State Costs by Category	$	$ -
B. State Costs by Source of Funds	Increased Costs	Decreased Costs
GPR	$	$ -
FED		-
PRO/PRS		-
SEG/SEG-S		-
State Revenues — Complete this only when proposal will increase or decrease state revenues (e.g., tax increase, decrease in license fee, etc.)	Increased Revenue	Decreased Revenue
GPR Taxes	$	$ -
GPR Earned		-
FED		-
PRO/PRS		-
SEG/SEG-S		-
Total State Revenues	$	$ -

Net Annualized Fiscal Impact

	State	Local
Net Change in Costs	$	$
Net Change in Revenues	$	$

Prepared By:	Telephone No.	Agency
Joe Polasek	266-2794	Department of Natural Resources
Authorized Signature	Telephone No.	Date (mm/dd/ccyy)
Joe Polasek	266-2794	03-10-10

ORDER OF THE STATE OF WISCONSIN
NATURAL RESOURCES BOARD
AMENDING RULES

The Wisconsin Natural Resources Board proposes an order to amend s. NR 140.10 Table 1 and Appendix 1, relating to groundwater quality standards	**DG-24-09**

Analysis Prepared by the Department of Natural Resources

1. Statutes interpreted: In promulgating this rule, ss. 281.12(1), 281.15, 281.19(1) and 299.11, Stats., and ch. 160, Stats., have been interpreted as authorizing the department to modify and create rules relating to development of numerical groundwater quality standards.

2. Statutory authority: Sections 281.12(1), 281.15, 281.19(1) and 299.11, Stats., and ch. 160, Stats.

3. Explanation of agency authority to promulgate the proposed rules under the statutory authority: Section 281.12(1), Stats., grants the Department the authority to carry out planning, management and regulatory programs necessary to protect, maintain and improve the quality and management of the waters of the state, ground and surface, public and private. Section 281.15, Stats., states that the Department shall promulgate rules setting standards of water quality, applicable to the waters of the state, that protect the public interest, including the protection of public health and welfare, and the present and prospective future use of such waters for public and private water systems. Section 281.19(1), Stats., grants the Department the authority to issue general orders and adopt rules applicable throughout the state for the construction, installation, use and operation of practicable and available systems, methods and means for preventing and abating pollution of the waters of the state.

Chapter 160, Stats., establishes an administrative process for developing numerical state groundwater quality standards to be used as criteria for the protection of public health and welfare by all state groundwater regulatory programs. Chapter 160, Stats., directs the Department to use this administrative process to establish numeric groundwater quality standards for substances of public health or welfare concern, found in, or having a reasonable probability of being detected in, the groundwater resources of the state.

In accordance with ch. 160, Stats., the reliability of sampling data is to be considered when determining the range of responses that a regulatory agency may take, or require, to address attainment or exceedance of a state groundwater quality standard at an applicable "point of standards application". Section 299.11, Stats., authorizes the Department, in conjunction with the Department of Agriculture Trade and Consumer protection, to establish uniform minimum criteria for laboratories certified to conduct water analysis testing, and to establish accepted methodologies to be followed in conducting tests and sampling protocols and documentation procedures to be followed when collecting water samples for testing.

4. Related statute or rule: Chapter 280, Stats., authorizes the Department to prescribe, publish and enforce minimum standards and rules to be pursued in the obtaining of pure drinking water for human consumption. Chapter NR 809, Wis. Adm. Code, establishes minimum state drinking water standards for the protection of public health, safety and welfare. This administrative code contains numeric water quality protection standards applicable to public water supply systems in Wisconsin. Wisconsin state

drinking water standards, applicable to public drinking water systems, have not yet been established for: 1,4-Dioxane, Acetochlor, Acetochlor ethane sulfonic acid (ESA) + oxanilic acid (OXA), Ammonia (as N), Chlorodifluoromethane, Chlorpyrifos, Dimethenamid/Dimethenamid-P, Dinitrotoluene Total Residues, Ethyl Ether, Metolachlor ethane sulfonic acid (ESA) + oxanilic acid (OXA), Perchlorate, Propazine or Tertiary Butyl Alcohol. Secondary Standards, established for aesthetic quality, have been promulgated in s. NR 809.60, Wis. Adm. Code, for Aluminum and Manganese. These ch. NR 809 Secondary Standards are 50 to 200 parts per billion (ppb) for aluminum, and 50 ppb for manganese. Note, units are parts per billion (ppb), 1 ppb is equivalent to 1 microgram per liter (ug/L).

5. Plain language analysis of the proposed rule: Chapter 160, Stats., requires the Department to develop numerical groundwater quality standards, consisting of enforcement standards and preventive action limits. Chapter NR 140, Wis. Adm. Code, establishes groundwater standards and creates a framework for implementation of the standards by the Department. These proposed amendments to ch. NR 140 would add new state groundwater quality standards for 15 substances and revise existing standards for another 15 substances. In accordance with ch. 160, Stats., amendments to ch. NR 140 groundwater quality standards are based on recommendations from the Department of Health Services.

New public health related groundwater quality standards are proposed for: 1,4-Dioxane, Acetochlor, Acetochlor - ESA + OXA, Aluminum, Ammonia, Chlorodifluoromethane, Chlorpyrifos, Dimethenamid/Dimethenamid-P, Dinitrotoluenes, Ethyl Ether, Manganese, Metolachlor - ESA + OXA, Perchlorate, Propazine and Tertiary Butyl Alcohol.

Revised public health related groundwater quality standards are proposed for: 1,3-Dichlorobenzene, 1,3-Dichloropropene, Acetone, Boron, Carbaryl, Chloromethane, Dibutyl Phthalate, Ethylene Glycol, Methyl Ethyl Ketone, Metolachlor, Metribuzin, Phenol, Prometon, Toluene and Xylene.

Minor revisions, to clarify rule language and update rule reference information, are also proposed to ch. NR 140. These revisions include:

- Replacing current "Chromium" in ch. NR 140 Table 1 with "Chromium (total)" to clarify that ch. NR 140 standards apply to total chromium (combination of chromium III and chromium VI).
- Replacing current "Cyanide" term in ch. NR 140 Table 1 with "Cyanide, free" to clarify that ch. NR 140 standards apply to "free cyanide" (HCN, CN^- and metal-cyanide complexes that are easily dissociated into free cyanide ions). Footnote added to Table 1 stating that "Cyanide, free" refers to the simple cyanides (HCN, CN^-) and /or readily dissociable metal-cyanide complexes, and that free cyanide is regulatorily equivalent to cyanide quantified by approved analytical methods for "amenable cyanide" or "available cyanide".
- Changing "Metolachlor" in ch. NR 140 Table 1 to "Metolachlor/s-Metolachlor" to clarify that ch. NR 140 standards apply to both Metolachlor (CAS RN 51218-45-2) and its stereo isomer, s-Metolachlor (CAS RN 87392-12-9).
- Revising units for field specific conductance in s. NR 140.20 Table 3 from micromhos/cm (micromhos per centimeter) to microSiemens/cm (microSiemens per centimeter or µS/cm).
- Revising s. NR 140.28(5)(c)6 note to add "for discharges, as defined by s. 283.01(4), Stats" language related to the need for a wastewater discharge permit.
- Adding CAS RN of 142363-53-9 for Alachlor-ESA to Appendix I to Table 1.
- Changing existing Appendix I to Table 1 CAS RN for Asbestos from 12001-29-5 (chrysotile asbestos) to 1332-21-4 (asbestos, all forms).
- Adding "Chromium (total)", with CAS RN of 7440-47-3, to ch. NR 140 Appendix I to table 1.
- Adding CAS RN of 542-75-6 for cis/trans 1,3 Dichloropropene (mixed isomers) to ch. NR 140 Appendix I to Table 1.
- Changing existing Appendix I to Table 1 CAS RN for Fluoride from 16984-48-8 to 7681-49-4.

- Adding 1,1,1,2-PCA synonym for 1,1,1,2 tetrachloroethane to ch. NR 140 Appendix I to table 1.
- Adding 1,1,2,2-PCA synonym for 1,1,2,2 tetrachloroethane to ch. NR 140 Appendix I to table 1.
- Adding 1,1,1-TCA synonym for 1,1,1 trichloroethane to ch. NR 140 Appendix I to table 1.

6. Summary of and preliminary comparison with any existing or proposed federal regulation: The United States Environmental Protection Agency (US EPA) establishes health based drinking water maximum contaminant levels (MCLs), cancer risk levels and health advisories (HAs). Federal drinking water MCLs are established based on scientific risk assessments and, in some cases, economic and technological considerations. Cancer risk levels are established as the concentration of a chemical in drinking water that corresponds to a specific excess estimated lifetime cancer risk. Federal lifetime health advisories (LHAs) are developed based on an established health risk acceptable daily intake (ADI) level or reference dose (RfD). An ADI or RfD is the daily oral exposure to a chemical that is likely to be without an appreciable risk over a lifetime.

No federal drinking water MCLs have yet been established for any of the substances for which new Wisconsin state groundwater quality standards are proposed. Federal 1 in 1,000,000 drinking water cancer risk levels have been established at 3 ppb for 1,4-Dioxane and at 0.05 ppb for DNT (mixture of 2,4-/2,6-DNT). US EPA LHAs have been established at 2 ppb for Chlorpyrifos, at 300 ppb for Manganese and at 10 ppb for Propazine. The US EPA has also developed an "Interim Drinking Water Health Advisory" of 15 ppb for Perchlorate. RfDs have been established by EPA for: Dimethenamid at 0.05 mg/kg-day, Ethyl Ether at 0.2 mg/kg-day and Perchlorate at 0.0007 mg/kg-day. A Reference Concentration (RfC) for Chronic Inhalation Exposure of 50 mg/m^3 has been established by EPA for Chlorodifluoromethane.

US EPA Contaminant Candidate List (CCL): The Contaminant Candidate List (CCL) is the US EPA's list of unregulated contaminants which may require national drinking water regulation in the future. The current list is designated Contaminant Candidate List 3 (CCL 3). Substances on EPA's CCL 3 include: 1,4-Dioxane, Acetochlor, Acetochlor ethansulfonic acid (Acetochlor-ESA), Acetochlor oxanillic acid (Acetochlor-OXA), HCFC-22 (Chlorodifluoromethane), Metolachlor ethansulfonic acid (Metolachlor-ESA), Metolachlor oxanillic acid (Metolachlor-OXA), and Perchlorate.

7. Comparison of similar rules in adjacent states (Minnesota, Iowa, Illinois and Michigan): The proposed amendments to ch. NR 140, Wis. Adm. Code, would add new state numeric groundwater quality standards for 15 substances: 1,4-Dioxane, Acetochlor, Acetochlor ESA + OXA, Aluminum, Ammonia (as N), Chlorodifluoromethane, Chlorpyrifos, Dimethenamid/Dimethenamid-P, Dinitrotoluenes (Total Residues), Ethyl Ether, Manganese, Metolachlor ESA + OXA, Perchlorate, Propazine and Tertiary Butyl Alcohol. The groundwater quality standards contained in ch. NR 140 are used in Wisconsin by state regulatory agencies as state groundwater protection standards. These standards are used as contamination site cleanup levels, design and management criteria for regulated activities and as minimum public health and welfare protection standards for contaminants in groundwater.

The states surrounding Wisconsin: Minnesota, Michigan, Illinois and Iowa, also use groundwater protection values/levels/standards in their regulation of practices and activities that might impact the quality of groundwater resources. Three of the states surrounding Wisconsin have promulgated individual state groundwater protection standards and one utilizes established federal standards (federal drinking water maximum contaminant levels, lifetime health advisory levels and established cancer risk levels) as their state groundwater protection standards.

Groundwater protection quality values/levels/standards are usually developed based on health risk assessments. States are often required to follow state specific health risk assessment methodology when

establishing groundwater protection quality standards. States may use state specific health risk assessments; factors and methodology in calculating and developing their groundwater protection standards. This use of different health risk assessment factors and methodologies has lead to the establishment of different state groundwater protection values/levels/standards for the same substance. For example, the health based groundwater protection quality standard for manganese used by the states surrounding Wisconsin varies by state - the standard used in Minnesota is 300 ppb, the standard used in Michigan is 860 ppb, Illinois uses 150 ppb and the standard used in Iowa is 300 ppb, the federal Lifetime Health Advisory level.

The state of Minnesota has established state groundwater protection "Health Risk Limits" (HRLs) under Minnesota Statutes Section 103H.201. The State of Minnesota has established HRLs for Acetochlor at 9 ppb and for Ethyl Ether at 1,000 ppb. The Minnesota Department of Health has also calculated "Health Based Values" (HBVs) for some groundwater contaminants. Minnesota HBVs are not standards that have been promulgated by rule but are calculated concentrations that may be used as advisory levels by Minnesota state groundwater and environmental protection programs. The State of Minnesota has established HBVs for: Metolachlor-ESA at 800 ppb, Metolachlor-OXA at 800 ppb, Acetochlor-ESA at 300 ppb and Acetochlor-OXA at 100 ppb. The Minnesota Department of Health also issues Risk Assessment Advice (RAA) levels for some groundwater contaminants. Minnesota Department of Health RAAs are advisory concentrations developed to assist Minnesota agencies in evaluating potential health risks to humans from exposures to a chemical. Generally, RAAs contain greater uncertainty than HRLs and HBVs because the information available to develop them is more limited. The State of Minnesota has established a RAA for Manganese at 300 ppb.

The state of Michigan has established state groundwater protection quality standards. Michigan "Drinking Water Criteria and Risk Based Screening Levels (RBSLs)" are Michigan state groundwater protection standards authorized in accordance with Michigan's Natural Resources and Environmental Protection Act, 1994 PA 451 (NREPA). The State of Michigan has established a Drinking Water Criteria/RBSL for: 1,4-Dioxane at 85 ppb, Manganese at 860 ppb, Aluminum at 300 ppb, Propazine at 200 ppb, Chlorpyrifos at 22 ppb, Ethyl Ether at 3,700 ppb and Tertiary Butyl Alcohol at 3,900 ppb. The State of Michigan also has established a Drinking Water Criteria/RBSL for "all potential sources of nitrate-nitrogen", including ammonia nitrogen, in groundwater drinking water supplies at 10,000 ppb.

The state of Illinois has established state groundwater quality standards for "potable resource groundwater". Illinois Groundwater Quality Standards are state groundwater protection standards promulgated in 35 Ill. Adm. Code 620, environmental protection regulations. Illinois state "Groundwater Quality Standards for Class I: Potable Resource Groundwater" have been established for Manganese at 150 ppb. The state of Illinois also has established "Groundwater Cleanup Objectives" in 8 Ill. Adm. Code 259. Illinois Groundwater Cleanup Objectives include both Illinois state Groundwater Quality Standards and Human Threshold Toxicant Advisory Concentrations (HTTACs). Illinois has established state Groundwater Cleanup Objectives for Class I, Potable Resource Groundwater: at 21 ppb for Chlorpyrifos, at 2 ppb for Acetochlor and at 10,000 ppb for Ammonia. The Illinois Acetochlor groundwater cleanup objective value was established in accordance with the Acetochlor Registration Agreement monitoring program. The state groundwater cleanup objective for Ammonia was developed based on the US EPA's 30,000 ppb Lifetime Health Advisory level for ammonia in drinking water.

The state of Iowa has not established specific state groundwater protection standards. In accordance with Iowa Environmental Protection Regulations 567 IAC Chapter 133, Iowa uses established federal EPA lifetime health advisory levels, "negligible risk levels" (NRLs) for carcinogens, the estimate of one additional cancer case per million people over a lifetime of exposure, and federal drinking water maximum contaminant levels (MCLs) as "Action Levels" in their regulation of practices and activities that may adversely impact groundwater quality. As noted in section 6 above, federal lifetime health

advisory levels have been established at 2 ppb for Chlorpyrifos, at 300 ppb for Manganese and at 10 ppb for Propazine. Federal 1 in 1,000,000 drinking water cancer risk levels have been established at 3 ppb for 1,4-Dioxane and at 0.05 ppb for DNT (mixture of 2,4-/2,6-DNT).

8. Summary of the factual data and analytical methodologies that the agency used in support of the proposed rule and how any related findings support the regulatory approach chosen for the proposed rule: In accordance with s. 160. 07, Stats., the Department is required, for substances of public health concern, to propose rules establishing recommendations from the Department of Health Services (DHS) as state groundwater quality enforcement standards. In accordance with s. 160.15, Stats., the Department is required to establish by rule a preventive action limit for each substance for which an enforcement standard is established.

The DHS has provided the Department, in a document titled *Scientific Support Documentation for Cycle 9 Revisions of NR 140.10 Groundwater Enforcement Standard & Preventive Action Limit Recommendations* (Revised February 2010), its recommendations for new state public health related groundwater quality standards for 15 substances: 1,4-Dioxane, Acetochlor, Acetochlor ESA + OXA, Aluminum, Ammonia (as N), Chlorodifluoromethane, Chlorpyrifos, Dimethenamid/Dimethenamid-P, Dinitrotoluenes, Ethyl Ether, Manganese, Metolachlor ESA + OXA, Perchlorate, Propazine and Tertiary Butyl Alcohol. DHS has also provided recommendations for revisions to existing public health related state groundwater quality standards for 15 additional substances: 1,3-Dichlorobenzene, 1,3-Dichloropropene, Acetone, Boron, Carbaryl, Chloromethane, Dibutyl Phthalate, Ethylene Glycol, Methyl Ethyl Ketone, Metolachlor, Metribuzin, Phenol, Prometon, Toluene and Xylene.

The Department is proposing rules establishing the DHS enforcement standard recommendations as ch. NR 140, Wis. Adm. Code, state groundwater quality enforcement standards. The Department is also proposing rules establishing ch. NR 140, Wis. Adm. Code, state groundwater quality preventive action limits in accordance with s. 160.15(1), Stats.

9. Any analysis and supporting documentation that the agency used in support of the agency's determination of the rule's effect on small business under s. 227.114, Stats., or that was used when the agency prepared an economic impact report: In its determination of the effect of this proposed rule on small businesses, the Department used analysis and supporting documentation that included information from the United States Department of Agriculture - National Agricultural Statistics Service (NASS), the University of Wisconsin (UW) - Department of Agronomy and the Wisconsin Department of Agriculture Trade and Consumer Protection (DATCP). Information used from the United States Department of Agriculture NASS included agricultural chemical usage reports from 2001 - 2007, and the NASS Agricultural Chemical Use Database. Information used from the UW Department of Agronomy included the UW Extension 2008 Herbicide price list and the UW Extension Corn and Soybean Herbicide Chart. Information from DATCP included data from DATCP's *Agricultural Chemicals in Wisconsin Groundwater - Final Report March 2008* document and results from the agency's groundwater monitoring and pesticide registration databases.

10. Effects on small business, including how the rule will be enforced: The Department has determined that this rule order will not have a significant economic impact on small businesses. Chapter NR 140, Wis. Adm. Code, currently contains groundwater standards for 123 substances of public health concern, 8 substances of public welfare concern and 15 indicator parameters. The proposed groundwater standard revisions would apply to all regulated facilities, practices and activities which may impact groundwater quality.

The enforcement of Wisconsin state groundwater quality standards is done by state regulatory agencies through their groundwater protection programs. State regulatory agencies, in exercising their statutory

powers and duties, establish groundwater protection regulations that assure that regulated facilities and activities will not cause state groundwater quality standards to be exceeded. A state regulatory agency may establish specific design and management criteria to ensure that regulated facilities and activities will not cause the concentration of a substance in groundwater, affected by the facilities or activities, to exceed state groundwater quality enforcement standards or preventive action limits at an applicable "point of standards application" location.

Regulated facilities, practices and activities, which are sources of the substances for which new and revised groundwater standards are proposed are, for the most part, likely sources of substances for which other groundwater standards already exist. Consequently, there will likely be few cases where the proposed standards will be exceeded where existing standards are not currently being exceeded. Additional monitoring costs may be imposed upon regulated facilities, practices and activities, but the extent of such monitoring and any costs associated with it, while too speculative to quantify at this time, are not expected to be significant.

The proposed revisions to state groundwater quality standards include new and revised standards for some pesticides and pesticide degradation products found in Wisconsin groundwater. New proposed groundwater quality standards include standards for the insecticide chlorpyrifos, the herbicides acetochlor, dimethenamid and propazine, and the herbicide degradation products acetochlor ethane sulfonic acid and oxanilic acid, and metolachlor ethane sulfonic acid and oxanilic acid.

The insecticide active ingredient chlorpyrifos is used on corn crops to control rootworm, and on soybean crops to control aphids and spider mites. There are currently 32 insecticide products registered in Wisconsin that contain the active ingredient chlorpyrifos. Chlorpyrifos has been reported as detected in groundwater at 2% of DATCP Agricultural Chemical Cleanup Program sites. In a DATCP 2007 statewide survey of agricultural chemicals in Wisconsin groundwater, no chlorpyrifos was reported detected in 398 private water supply wells sampled.

Acetochlor and dimethenamid/dimethenamid-P are herbicides that have been used in Wisconsin to control weeds in corn and soybeans. There are currently 46 herbicide products registered in Wisconsin that contain the active ingredient acetochlor or dimethenamid/dimethenamid-P. Acetochlor has been reported as detected in groundwater at 25% of DATCP Agricultural Chemical Cleanup Program sites and dimethenamid/dimethenamid-P has been reported as detected at 27% of those sites. In DATCP's 2007 statewide survey of agricultural chemicals in Wisconsin groundwater, no "parent" acetochlor or dimethenamid/dimethenamid-P were reported as detected in 398 private water supply wells sampled. Metabolite degradation products of these herbicides were, however, detected in some of the sampled wells.

Propazine is a herbicide used for weed control on sorghum, umbelliferous crops (carrots, parsley etc.) and greenhouse ornamentals. It is also a contaminant of the herbicide atrazine, which is used in Wisconsin on corn. There are currently no herbicide products registered in Wisconsin that contain the active ingredient propazine. Propazine has been reported as detected in groundwater at 22% of DATCP Agricultural Chemical Cleanup Program sites.

The acetochlor ethane sulfonic acid and oxanilic acid (acetochlor ESA & OXA) degradation products of acetochlor have been found in Wisconsin groundwater. In DATCP's 2007 statewide survey of agricultural chemicals in Wisconsin groundwater, acetochlor ESA & OXA were reported as detected in 16 private water supply wells and 3 private water supply wells respectively, of 398 wells sampled. The highest levels of acetochlor ESA & OXA reported in the DATCP study were 2.32 ppb and 4.36 ppb respectively. The highest levels reported in the DATCP groundwater monitoring database for private water supply wells are 9.52 ppb for acetochlor-ESA and 4.36 ppb for acetochlor-OXA.

In the DATCP's 2007 statewide survey of agricultural chemicals in Wisconsin groundwater, metolachlor ESA & OXA were reported as detected in 106 private water supply wells and 18 private water supply wells respectively, of 398 wells sampled. The highest levels of metolachlor ESA & OXA reported in the DATCP study were 6.54 ppb and 1.37 ppb respectively. The highest levels reported in the DATCP groundwater monitoring database for private water supply wells are 31.2 ppb for metolachlor-ESA and 22.8 ppb for metolachlor-OXA.

As it appears that the occurrence of the pesticides chlorpyrifos, acetochlor, dimethenamid/dimethenamid-P and propazine in Wisconsin groundwater is limited to DATCP Agricultural Chemical Cleanup Program sites, and as the pesticide metabolite degradation products acetochlor ESA & OXA and metolachlor ESA & OXA have been detected statewide at levels relatively low compared to proposed state groundwater quality standards for those substances, and as comparably priced alternative herbicide products appear to be available to state farmers, the Department has determined that any management practice restrictions placed on the pesticides chlorpyrifos, acetochlor, dimethenamid/dimethenamid-P and propazine to limit their impact on Wisconsin groundwater, or on acetochlor or metolachlor to limit the impact of their ESA or OXA metabolite degradation products on groundwater, are unlikely to have a significant economic impact on corn or soybean growers in Wisconsin.

11. Agency Contact Person: Mike Lemcke, Wisconsin Dept. of Natural Resources, Bureau of Drinking Water & Groundwater, 101 S. Webster St., Madison, WI, 73707-7921; (608) 266-2104; michael.lemcke@wisconsin.gov.

SECTION 1. NR 140.10, Table 1 is amended to read:

Table 1
Public Health Groundwater Quality Standards

Substance[1]	Enforcement Standard (micrograms per liter - except as noted)	Preventive Action Limit (micrograms per liter - except as noted)
Acetochlor	7	0.7
Acetochlor ethane sulfonic acid + oxanilic acid (Acetochlor - ESA + OXA)	230	46
Acetone	~~1000~~ 9 mg/l	~~200~~ 1.8 mg/l
Alachlor	2	0.2
Alachlor ethane sulfonic acid ~~(Alachlor-~~ (Alachlor – ESA)	20	4
Aldicarb	10	2
Aluminum	200	40
Ammonia (as N)	9.7 mg/l	0.97 mg/l
Antimony	6	1.2
Anthracene	3000	600
Arsenic	10	1
Asbestos	7 million fibers per liter (MFL)	0.7 MFL
Atrazine, total chlorinated residues	3[2]	0.3[2]
Bacteria, Total Coliform	0[3]	0[3]
Barium	2 milligrams/liter (mg/l)	0.4 mg/l
Bentazon	300	60
Benzene	5	0.5
Benzo(b)fluoranthene	0.2	0.02
Benzo(a)pyrene	0.2	0.02
Beryllium	4	0.4

Boron	~~960~~ 1000	~~190~~ 200
Bromodichloromethane	0.6	0.06
Bromoform	4.4	0.44
Bromomethane	10	1
Butylate	400	80
Cadmium	5	0.5
Carbaryl	~~960~~ 40	~~192~~ 4
Carbofuran	40	8
Carbon disulfide	1000	200
Carbon tetrachloride	5	0.5
Chloramben	150	30
Chlordane	2	0.2
Chlorodifluoromethane	7 mg/l	0.7 mg/l
Chloroethane	400	80
Chloroform	6	0.6
Chlorpyrifos	2	0.4
Chloromethane	~~3~~ 30	~~0.3~~ 3
Chromium (total)	100	10
Chrysene	0.2	0.02
Cobalt	40	8
Copper	1300	130
Cyanazine	1	0.1
Cyanide, free[4]	200	40
Dacthal	70	14
1,2–Dibromoethane (EDB)	0.05	0.005
Dibromochloromethane	60	6
1,2–Dibromo–3–chloropropane (DBCP)	0.2	0.02
Dibutyl phthalate	~~100~~ 1000	~~20~~ 100
Dicamba	300	60
1,2–Dichlorobenzene	600	60
1,3–Dichlorobenzene	~~1250~~ 600	~~125~~ 120
1,4–Dichlorobenzene	75	15
Dichlorodifluoromethane	1000	200
1,1–Dichloroethane	850	85
1,2–Dichloroethane	5	0.5
1,1–Dichloroethylene	7	0.7
1,2–Dichloroethylene (cis)	70	7
1,2–Dichloroethylene (trans)	100	20
2,4–Dichlorophenoxyacetic Acid (2,4–D)	70	7
1,2–Dichloropropane	5	0.5
1,3–Dichloropropene (cis/trans)	~~0.2~~ 0.4	~~0.02~~ 0.04
Di (2–ethylhexyl) phthalate	6	0.6
Dimethenamid/Dimethenamid-P	50	5
Dimethoate	2	0.4
2,4–Dinitrotoluene	0.05	0.005
2,6–Dinitrotoluene	0.05	0.005
Dinitrotoluene, Total Residues[5]	0.05	0.005
Dinoseb	7	1.4
1,4–Dioxane	3	0.3
Dioxin (2, 3, 7, 8–TCDD)	0.00003	0.000003
Endrin	2	0.4
EPTC	250	50
Ethylbenzene	700	140
Ethyl ether	1000	100
Ethylene glycol	~~7 mg/l~~ 14 mg/l	~~0.7 mg/l~~ 2.8 mg/l
Fluoranthene	400	80
Fluorene	400	80
Fluoride	4 mg/l	0.8 mg/l
Fluorotrichloromethane	3490	698
Formaldehyde	1000	100
Heptachlor	0.4	0.04
Heptachlor epoxide	0.2	0.02

Hexachlorobenzene	1	0.1
N–Hexane	600	120
Hydrogen sulfide	30	6
Lead	15	1.5
Lindane	0.2	0.02
Manganese	300	60
Mercury	2	0.2
Methanol	5000	1000
Methoxychlor	40	4
Methylene chloride	5	0.5
Methyl ethyl ketone (MEK)	~~460~~ 4 mg/l	~~90~~ 0.8 mg/l
Methyl isobutyl ketone (MIBK)	500	50
Methyl tert–butyl ether (MTBE)	60	12
Metolachlor/s-Metolachlor	~~15~~ 100	~~1.5~~ 10
Metolachlor ethane sulfonic acid + oxanilic acid (Metolachlor - ESA + OXA)	1.3 mg/L	0.26 mg/L
Metribuzin	~~250~~ 70	~~50~~ 14
Molybdenum	40	8
Monochlorobenzene	100	20
Naphthalene	100	10
Nickel	100	20
Nitrate (as N)	10 mg/l	2 mg/l
Nitrate + Nitrite (as N)	10 mg/l	2 mg/l
Nitrite (as N)	1 mg/l	0.2 mg/l
N–Nitrosodiphenylamine	7	0.7
Pentachlorophenol (PCP)	1	0.1
Perchlorate	1	0.1
Phenol	~~6 mg/l~~ 2 mg/l	~~1.2 mg/l~~ 0.4 mg/l
Picloram	500	100
Polychlorinated biphenyls (PCBs)	0.03	0.003
Prometon	~~90~~ 100	~~18~~ 20
Propazine	10	2
Pyrene	250	50
Pyridine	10	2
Selenium	50	10
Silver	50	10
Simazine	4 0	.4
Styrene	100	10
Tertiary Butyl Alcohol (TBA)	12	1.2
1,1,1,2–Tetrachloroethane	70	7
1,1,2,2–Tetrachloroethane	0.2	0.02
Tetrachloroethylene	5	0.5
Tetrahydrofuran	50	10
Thallium	2	0.4
Toluene	~~1 mg/l~~ 800	~~0.2 mg/l~~ 160
Toxaphene	3	0.3
1,2,4–Trichlorobenzene	70	14
1,1,1–Trichloroethane	200	40
1,1,2–Trichloroethane	5	0.5
Trichloroethylene (TCE)	5	0.5
2,4,5–Trichlorophenoxy–propionic acid (2,4,5–TP)	50	5
1,2,3–Trichloropropane	60	12
Trifluralin	7.5	0.75
Trimethylbenzenes (1,2,4– and 1,3,5– combined)	480	96
Vanadium	30	6
Vinyl chloride	0.2	0.02
Xylene[2]	~~10 mg/l~~ 2 mg/l	~~1 mg/l~~ 0.4 mg/l

[1] Appendix I contains Chemical Abstract Service (CAS) registry numbers, common synonyms and trade names for most substances listed in Table 1.
[2] Total chlorinated atrazine residues includes parent compound and the following metabolites of health concern: 2–chloro–4–amino–6–isopropylamino–s–triazine

(formerly deethylatrazine), 2-chloro-4-amino-6-ethylamino-s-triazine (formerly deisopropylatrazine) and 2-chloro-4,6-diamino-s-triazine (formerly diaminoatrazine).

[3]Total coliform bacteria may not be present in any 100 ml sample using either the membrane filter (MF) technique, the presence-absence (P-A) coliform test, the minimal medium ONPG-MUG (MMO-MUG) test or not present in any 10 ml portion of the 10-tube multiple tube fermentation (MTF) technique.

[4]"Cyanide, free" refers to the simple cyanides (HCN, CN^-) and /or readily dissociable metal-cyanide complexes. Free cyanide is regulatorily equivalent to cyanide quantified by approved analytical methods for "amenable cyanide" or "available cyanide".

[5]Dinitrotoluene, Total Residues includes the dinitrotoluene (DNT) isomers: 2,3-DNT, 2,4-DNT, 2,5-DNT, 2,6-DNT, 3,4-DNT and 3,5-DNT.

[6]Xylene includes meta-, ortho-, and para-xylene combined. ~~The preventive action limit has been set at a concentration that is intended to address taste and odor concerns associated with this substance.~~

SECTION 2. NR 140.20, Table 3 is amended to read:

Table 3
Methodology for Establishing Preventive Action Limit for Indicator Parameters

Parameter	*Minimum Increase (mg/l)*
Alkalinity	100
Biochemical oxygen demand (BOD_5)	25
Calcium	25
Chemical oxygen demand (COD)	25
Magnesium	25
Nitrogen series	
Ammonia nitrogen	2
Organic nitrogen	2
Total nitrogen	5
Potassium	5
Sodium	10
Field specific conductance	200 ~~micromhos/cm~~ microSiemens/cm
Total dissolved solids (TDS)	200
Total hardness	100
Total organic carbon (TOC)	1
Total organic halogen (TOX)	0.25

SECTION 3. NR 140.28(5)(c)6 note is amended to read:

Note: The issuance of a wastewater discharge permit by the Department is required prior to the infiltration or injection of substances or remedial material into unsaturated soil or groundwater for discharges, as defined by s. 283.01(4), Stats. A wastewater discharge permit establishes the effluent or injection limits for substances or remedial material which may be infiltrated or injected into unsaturated soil or groundwater. A temporary exemption granted under this subsection applies to substances or remedial material which may enter groundwater or may be detected at a point of standards applications; it does not apply to substances or remedial material infiltrated or injected into unsaturated soil.

SECTION 4. Appendix to Table 1 is amended to read:

CHAPTER NR 140
APPENDIX 1 TO TABLE 1
PUBLIC HEALTH GROUNDWATER QUALITY STANDARDS

Substance	**CAS RN[1]**	**Common synonyms/*Tradename*[2]**
Acetochlor	34256-82-1	*Cadence, Degree, Harness, Keystone, Overtime, Volley*
Acetochlor ethane sulfonic acid + oxanilic acid	187022-11-3 (ESA) 184992-44-4 (OXA)	Acetochlor - ESA + OXA
Acetone	67-64-1	*Propanone*
Alachlor	15972-60-8	*Lasso*

Alachlor ethane sulfonic acid ~~(Alachlor-ESA)~~	142363-53-9	Alacblor-ESA, Alachlor Ethane Sulfonate, MON 5775
Aldicarb	116-06-3	*Temik*
Aluminum	7429-90-5	
Ammonia	7664-41-7	
Anthracene	120-12-7	Para-naphthalene
Asbestos	~~12001-29-5~~ 1332-21-4	
Bentazon	25057-89-0	*Basagran*
Benzene	71-43-2	
Benzo(b)fluoranthene	205-99-2	B(b)F,3,4-Benzofluoranthene
Benzo(a)pyrene	50-32-8	BaP, B(a)P
Boron	7440-42-8	
Bromodichloromethane	75-27-4	Dichlorobromomethane, BDCM
Bromoform	75-25-2	Tribromomethane
Bromomethane	74-83-9	Methyl bromide
Butylate	2008-41-5	S-ethyl di-isobutylthiocarbamate, *Sutan+*
Carbaryl	63-25-2	*Sevin*
Carbofuran	1563-66-2	*Furadan*
Carbon disulfide	75-15-0	Carbon bisulfide
Carbon tetrachloride	56-23-5	Tetrachloromethane, Perchloroethane
Chloramben	133-90-4	
Chlordane	57-74-9	
Chlorodifluoromethane	75-45-6	HCFC-22, Freon 22
Chloroethane	75-00-3	Ethyl chloride, Monochloroethane
Chloroform	67-66-3	Trichloromethane
Chlorpyrifos	2921-88-2	*Dursban, Lorsban, Warhawk, Hatchet, Yuma, Whirlwind, Eraser*
Chloromethane	74-87-3	Methyl chloride
Chromium (total)	7440-47-3	
Chrysene	218-01-9	1,2-Benzphenanthrene
Cobalt	7440-48-4	
Cyanazine	21725-46-2	*Bladex* , 2-chloro-4-ethylamino-6-nitriloisopropylamino-s-triazine
Cyanide, free	57-12-5	
Dacthal	1861-32-1	DPCA, Chlorothal, *Dacthalor*, 1,4-benzenedicarboxylic acid
Dibromochloromethane	124-48-1	Chlorodibromomethane, DBCM
1,2-Dibromo-3-chloropropane	96-12-8	DBCP, Dibromochloropropane
1,2-Dibromoethane	106-93-4	EDB, Ethylene dibromide, Dibromoethane
Dibutyl phthalate	84-74-2	DP, Di-*n*-butyl phthalate, *n*-Butyl phthalate
Dicamba	1918-00-9	*Banvel*
1,2-Dichlorobenzene	95-50-1	o-Dichlorobenzene, o-DCB
1,3-Dichlorobenzene	541-73-1	m-Dichlorobenzene, m-DCB
1,4-Dichlorobenzene	106-46-7	p-Dichlorobenzene, p-DCB
Dichlorodifluoromethane	75-71-8	*Freon 12*
1,1,-Dichloroethane	75-34-3	Ethylidine chloride
1,2-Dichloroethane	107-06-2	1,2-DCA, Ethylene dichloride
1,1-Dichloroethylene	75-35-4	1,1-DCE, 1,1-Dichloroethene, Vinylidene chloride
1,2-Dichloroethylene (cis)	156-59-2	cis-Dichloroethylene, 1,2-Dichloroethene (cis)
1,2-Dichloroethylene (trans)	156-60-5	trans-1,2-Dichloroethylene
2,4-Dichlorophenoxyacetic acid	94-75-7	2,4-D
1,2-Dichloropropane	78-87-5	Propylene dichloride
1,3-Dichloropropene (cis/trans)[3]	542-75-6	*Telone,* DCP, Dichloropropylene
Di(2-ethylhexyl) phthalate	117-81-7	DEHP, Bis(2-ethylhexyl) phthalate, 1,2-Benzenedicarboxylic acid, Bis (2-ethyl-hexyl)ester
Dimethenamid/Dimethinamid-P	87674-68-8 163515-14-8 (-P)	*Frontier, Outlook, Propel, Establish, Sortie, Tower*
Dimethoate	60-51-5	
2,4-Dinitrotoluene	121-14-2	2,4-DNT, 1-methyl-2,4-dinitrobenzene

2,6–Dinitrotoluene	606–20–2	2,6–DNT, 2–methyl–1,3–dinitrohenzene
Dinitrotoluene, Total Residues	25321-14-6	Dinitrotoluene, DNT
Dinoseb	88–85–7	2–(1–methylpropyl)–4,6–dinitrophenol
1,4–Dioxane	123-91-1	*p*-Dioxane
Dioxin	1746–01–6	2,3,7,8–TCDD,2,3,7,8–Tetrachlorodibenzo–p–dioxin
Endrin	72–20–8	
EPTC	759–94–4	*Eptam, Eradicane*
Ethylbenzene	100–41–4	Phenylethane, EB
Ethyl ether	60-29-7	Diethyl Etber
Ethylene glycol	107–21–1	
Fluoranthene	206–44–0	Benzo(jk)fluorene
Fluorene	86–73–7	2,3–Benzidine, Diphenylenemethane
Fluoride	~~16984–48–8~~ 7681-49-4	
Fluorotrichloromethane	75–69–4	*Freon11*, Trichlorofluoromethane
Formaldehyde	50–00–0	
Heptachlor	76–44–8	*Velsicol*
Heptachlor epoxide	1024–57–3	
Hexachlorobenzene	118–74–1	Perchlorobenzene, *Granox*
N–Hexane	110–54–3	Hexane, Skellysolve B
Hydrogen sulfide	7783–06–4	Dihydrogen sulfide
Lindane	58–89–9	
Manganese	7439-96-5	
Mercury	7439–97–6	
Methanol	67–56–1	Methyl alcohol, Wood alcohol
Methoxychlor	72–43–5	
Methylene chloride	75–09–2	Dichloromethane, Methylene dichloride
Methyl ethyl ketone	78–93–3	MEK, 2–Butanone
Methyl isobutyl ketone	108–10–1	MIBK, 4–Methyl–2–pentanone, Isopropylacetone, *Hexone*
Methyl tert–butyl ether	1634–04–4	MTBE, 2–Methoxy–2–methyl–propane, tert–Butyl methyl ether
Metolachlor/s-Metolachlor	51218–45–2 87392-12-9 (s-)	*Dual, Bicep, Milocep, Stalwart, Parallel, Prefix, Charger, Brawl, Cinch, Dual Magnum, Boundary*
Metolachlor ethane sulfonic acid + oxanilic acid	171118-09-5 (ESA) 152019-73-3 (OXA)	Metolachlor - ESA + OXA
Metribuzin	21087–64–9	Sencor, Lexone
Molybdenum	7439–98–7	
Monochlorobenzene	108–90–7	Chlorobenzene
Naphthalene	91–20–3	
N–Nitrosodiphenylamine	86–30–6	NDPA
Pentachlorophenol	87–86–5	PCP, Pentachlorohydroxybenzene
Perchlorate	14797-73-0	Perchlorate and perchlorate salts, Perchlorate ion
Phenol	108–95–2	
Picloram	1918–02–1	*Tordon*, 4–amino–3,5,6–trichloropicolinic acid
Polychlorinated biphenyls[4]		PCBs
Prometon	1610–18–0	*Pramitol, Prometone*
Pyrene	129–00–	Benzo(def)phenanthrene
Pyridine	110–86–1	Azabenzene
Simazine	122–34–9	*Princep*, 2–chloro–4,6–diethylamino–s–triazine
Styrene	100–42–5	Ethenylbenzene, Vinylbenzene
Tertiary Butyl Alcohol	75-65-0	TBA
1,1,1,2–Tetrachlorethane	630–20–6	1,1,1,2–TCA, 1,1,1,2-PCA
1,1,2,2,–Tetrachloroethane	79–34–5	1,1,2,2–TCA, 1,1,2,2-PCA
Tetrachloroethylene	127–18–4	Perchloroethylene, PERC, Tetrachloroethene
Tetrahydrofuran	109–99–9	THF
Toluene	108–88–3	Methylbenzene
Toxaphene	8001–35–2	
1,2,4–Trichlorobenzene	120–82–1	

1,1,1–Trichloroethane	71–55–6	Methyl chloroform, 1,1,1-TCA
1,1,2–Trichloroethane	79–00–5	1,1,2–TCA, Vinyl trichloride
Trichloroethylene	79–01–6	TCE, Chloroethene
2,4,5–Trichlorophenoxy–propionic acid	93–72–1	2,4,5–TP,*Silvex*
1,2,3–Trichloropropane	96–18–4	1,2,3–TCP, Glycerol trichlorohyrin
Trifluralin	1582–09–8	*Treflan*
1,2,4–Trimethylbenzene	95–63–6	
1,3,5–Trimethylbenzene	108–67–8	
Vanadium	7440–62–2	
Vinyl chloride	75–01–4	VC, Chloroethene
Xylene[5]		

[1]Chemical Abstracts Service (CAS) registry numbers are unique numbers assigned to a chemical substance. The CAS registry numbers were published by the U.S. Environmental Protection Agency in 40 CFR Part 264, Appendix IV

[2]Common synonyms include those widely used in government regulations, scientific publications, commerce and the general public. A trade name, also known as the proprietary name, is the specific, registered name given by a manufacturer to a product. Trade names are listed in *italics*. Common synonyms and trade names should be cross–referenced with CAS registry number to ensure the correct substance is identified.

[3]This is a combined chemical substance which includes cis 1,3–Dichloropropene (CAS RN 10061–01–5) and trans 1,3–Dichloropropene (CAS RN 10061–02–6).

[4]Polychlorinated biphenyls (CAS RN 1336–36–3); this category contains congener chemicals (same molecular composition, different molecular structure and formula), including constituents of Aroclor–1016 (CAS RN12674–11–2), Aroclor–1221 (CAS RN 11104–28–2), Aroclor–1232 (CAS RN 11141–16–5), Aroclor–1242 (CAS RN 53469–21–9), Aroclor–1248 (CAS RN 12672–29–6), Aroclor–1254 (CAS RN 11097–69–1), and Aroclor–1260 (CAS RN 11096–82–5).

[5]Xylene (CAS RN 1330–20–7) refers to a mixture of three isomers, meta–xylene (CAS RN 108–38–3), ortho–xylene (CAS RN 95–47–6), and para–xylene (CAS RN 106–42–3)

The foregoing rules were approved and adopted by the State of Wisconsin Natural Resources Board on _____.

The rules shall take effect on the first day of the month following publication in the Wisconsin administrative register as provided in s. 227.22(2)(intro.), Stats.

Dated at Madison, Wisconsin _____

STATE OF WISCONSIN
DEPARTMENT OF NATURAL RESOURCES

By _____
Matthew J. Frank, Secretary

(SEAL)

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J Occup Environ Med. 2000 Aug;42(8):777-82.

Ammonium perchlorate contamination of Colorado River drinking water is associated with abnormal thyroid function in newborns in Arizona.

Brechner RJ, Parkhurst GD, Humble WO, Brown MB, Herman WH.

Office of Epidemiology and Statistics, Arizona Department of Health Services, Phoenix, USA. rbrechn@hs.state.az.us

Comment in:

J Occup Environ Med. 2001 Apr;43(4):305-9.
J Occup Environ Med. 2001 Apr;43(4):307-9.
J Occup Environ Med. 2003 Nov;45(11):1131-2.

The Colorado River below Lake Mead, which supplies drinking water for approximately 20,000,000 people, is contaminated by ammonium perchlorate. We identified populations who were exposed and unexposed to perchlorate-contaminated drinking water and compared median newborn thyroid-stimulating hormone (TSH) levels after adjusting for age in days at measurement and for race/ethnicity. Median newborn TSH levels in a city whose drinking water supply was 100% perchlorate-contaminated water from the Colorado River below Lake Mead were significantly higher than those in a city totally supplied with non-perchlorate-contaminated drinking water, even after adjusting for factors known or suspected to elevate newborn TSH levels. This ecological study demonstrates a statistically significant association between perchlorate exposure and newborn TSH levels. It suggests that even low-level perchlorate contamination of drinking water may be associated with adverse health effects in neonates and highlights the need for both further study and control of human low-level perchlorate exposure.

PMID: 10953814 [PubMed - indexed for MEDLINE]

MeSH Terms, Substances

LinkOut - more resources

2005 Salt Lake City Annual Meeting (October 16–19, 2005)
Paper No. 141-4
Presentation Time: 8:50 AM-9:10 AM

PLANTS AS BIOACCUMULATORS OF PERCHLORATE

HARVEY, Gregory J., Environmental Safety and Health Division, United States Air Force, 1801 10th St Bldg 8 Suite 200, Area B, Wright-Patterson AFB, OH 45433, gregory.harvey@wpafb.af.mil, ORRIS, Greta J., USGS, 520 N Park Ave, Tucson, AZ 85719, JACKSON, Andrew, Department of Civil Engineering, Lubbock, TX 79409, and ANDRASKI, Brian, USGS Nevada District, Carson City, NV 89706

Perchlorate can have both natural and anthropogenic origins. Our knowledge of the extent and origin of perchlorate in the environment is incomplete. Early studies conducted for the United States Air Force (USAF) by the United States Environmental Protection Agency (USEPA) and the University of Georgia-Athens showed that a number of different plants under a variety of lab and field conditions can accumulate perchlorate. To test the efficacy of plants as bioindicators of perchlorate, the United States Geological Survey (USGS), USAF, and Texas Tech University obtained leaves and other biomass in remote locations in the southwestern United States and western North Atlantic. Water extraction of this biomass was performed and analyses of the extracts were conducted by IC-MS. Results to date have shown that perchlorate can be detected in several different marine plants from the western North Atlantic, in one specimen from off the coast of Chile, and in dominant xerophytes from the southwestern US. Testing of commercially available species specific kelp meal reveal that Chondrus crispus, Ascophyllum nodosoum, Laminria sp. around New Brunswick and Nova Scotia typically contain 20-80 ppb and Gigartina from the Pacific Ocean off Chile contained less than 10 ppb perchlorate on a dry weight basis. Dominant desert scrub, non-succulent xerophytes from remote locations in the four major deserts of the southwestern US (Chihuahuan, Great Basin, Mojave, and Sonoran) reveal that perchlorate can be found in concentrations ranging from less than 10 parts per billion (ppb) to almost 600 ppb. Limited testing of succulents of the genus Opuntia revealed levels of perchlorate greater than 1 part per million (ppm). Results from long-lived xerophytes such as Larrea tridentate (creosote bush) suggest that xerophytes may be sinks for atmospherically-derived perchlorate. Additional studies are in progress to investigate this possibility.

2005 Salt Lake City Annual Meeting (October 16–19, 2005)
General Information for this Meeting

Session No. 141
Naturally Occurring Perchlorate (and Other Oxyanions) in the Hydrologic Cycle—Origins, Accumulation, Transformations, and Transport
Salt Palace Convention Center: 251 C
8:00 AM-12:00 PM, Tuesday, 18 October 2005

Geological Society of America *Abstracts with Programs*, Vol. 37, No. 7, p. 321

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Mol Cell Endocrinol. 2009 Jan 27;298(1-2):101-14. Epub 2008 Aug 28.

Perchlorate and ethylenethiourea induce different histological and molecular alterations in a non-mammalian vertebrate model of thyroid goitrogenesis.

Opitz R, Schmidt F, Braunbeck T, Wuertz S, Kloas W.

Department of Inland Fisheries, Leibniz-Institute of Freshwater Ecology and Inland Fisheries, Berlin, Germany. r.opitz@igb-berlin.de

Despite evidence for a conserved role of thyroid-stimulating hormone (TSH) in regulating vertebrate thyroid function, molecular data on thyroid responses to TSH are mainly limited to mammalian species. In this study, we examined histological and molecular changes in the thyroid of *Xenopus laevis* tadpoles during a 12-day treatment with 20mg/l perchlorate (PER) and 50mg/l ethylenethiourea (ETU). Inhibition of thyroid hormone (TH) synthesis by PER and ETU was evident from developmental retardation, reduced expression of TH-regulated genes and up-regulation of tshb-A mRNA. Thyroid histopathology revealed goiters with strikingly different follicular morphologies following PER and ETU treatment. Using real-time PCR, we analyzed thyroids sampled on day 12 for differential expression of 60 candidate genes. Further temporal analyses were performed for a subset of 14 genes. Relative to the control, PER and ETU treatment modulated the expression of 51 and 49 transcripts, respectively. Particularly genes related to TH synthesis and protein metabolism were similarly affected by PER and ETU. However, several genes were differentially expressed in PER- and ETU-treated tadpoles. Specifically, goiter formation in the PER treatment was associated with low expression of genes related to DNA replication but high expression of negative growth regulators. Results from this work provide for the first time a characterization of gene expression profiles during goitrogenesis in a non-mammalian vertebrate model. Overall, our data suggest that, in addition to TSH over-stimulation, further mechanisms related to the mode of goitrogen action contribute to the regulation of thyroid gene expression.

PMID: 18801409 [PubMed - indexed for MEDLINE]

Publication Types, MeSH Terms, Substances

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Laura Olah

From: lladd@sprintmail.com
Sent: Tuesday, September 08, 2009 10:48 AM
To: Laura Olah; Utah; aventura@cleanwater.org; Mark Grzan
Subject: Fw: [TheRocketdyneInformationSociety] The Chilean nitrate fertilizer ClO4- "fingerprint"

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Subject: [TheRocketdyneInformationSociety] The Chilean nitrate fertilizer ClO4- "fingerprint"

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1: Environ Sci Technol. 2009 Aug 1;43(15):5619-25.

Atacama perchlorate as an agricultural contaminant in groundwater: isotopic and chronologic evidence from Long Island, New York.

Böhlke JK, Hatzinger PB, Sturchio NC, Gu B, Abbene I, Mroczkowski SJ.
U.S. Geological Survey, 431 National Center, Reston, Virginia 20192, USA.
jkbohlke@usgs.gov

Perchlorate (ClO4-) is a common groundwater constituent with both synthetic and natural sources. A potentially important source of ClO4- is past agricultural application of ClO4(-)-bearing natural NO3- fertilizer imported from the Atacama Desert, Chile, but evidence for this has been largely circumstantial. Here we report ClO4- stable isotope data (delta37Cl, delta18O, and delta17O), along with other supporting chemical and isotopic environmental tracer data, to document groundwater ClO4 contamination sources and history in parts of Long Island, New York. Sampled groundwaters were oxic and ClO4- apparently was not affected by biodegradation within the aquifers. Synthetic ClO4- was indicated by the isotopic method in groundwater near a fireworks disposal site at a former missile base. Atacama ClO4- was indicated in agricultural and urbanizing areas in groundwaters with apparent ages > 20 years. In an agricultural area, ClO4- concentrations and ClO4-/NO3- ratios increased with groundwater age, possibly because of decreasing application rates of Atacama NO3- fertilizers and/or decreasing ClO4- concentrations in Atacama NO3- fertilizers in recent years. Because ClO4-/NO3- ratios of Atacama NO3- fertilizers imported in the past (approximately 2 x 10(-3) mol mol(-1)) were much higher than the CO4-/NO3- ratio of recommended drinking-water limits (7 x 10(-5) mol mol(-1) in New York), ClO4- could exceed drinking-water limits even where NO3- does not, and where Atacama NO3- was only a minor source of N. Groundwater ClO4- with distinctive isotopic composition was a sensitive indicator of past Atacama NO3- fertilizer use on Long Island and may be common in other areas that received NO3- fertilizers from the late 19th century through the 20th

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Perchlorate: Concern About Environmental Exposures, Thyroid Homeostasis, and Developmental Impacts

December 16th, 2009

Dr. Mark Miller, University of California, San Francisco Pediatric Environmental Health Specialty Unit (PEHSU)

Dr. Craig Steinmaus, California Environmental Protection Agency's Office of Environmental Health Hazard Assessment (OEHHA)

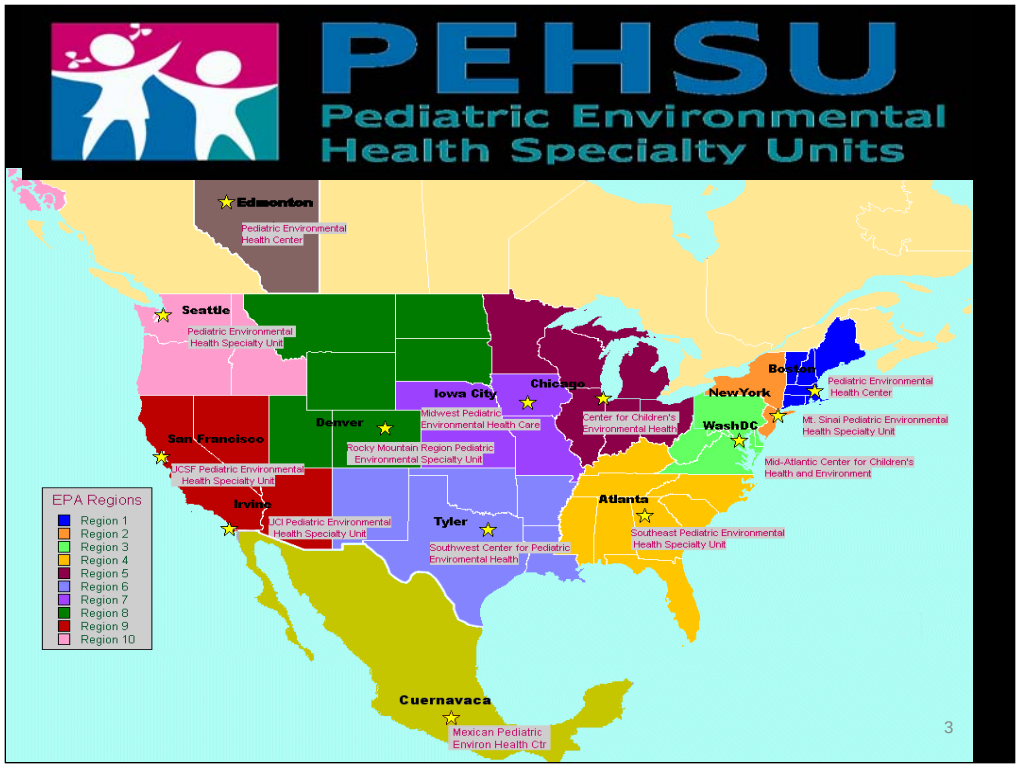
Superfund Research Program

U.S. Department of Health and Human Services
National Institute of Health
National Institute of Environmental Health Services

Perchlorate: Environmental exposures, thyroid homeostasis, and development

Craig Steinmaus MD, MPH
University of California, Berkeley
Office of Environmental Health Hazard Assessment, CA EPA
Mark Miller MD, MPH
Director, Pediatric Environmental Health Specialty Unit, UCSF
Office of Environmental Health Hazard Assessment, CA EPA

2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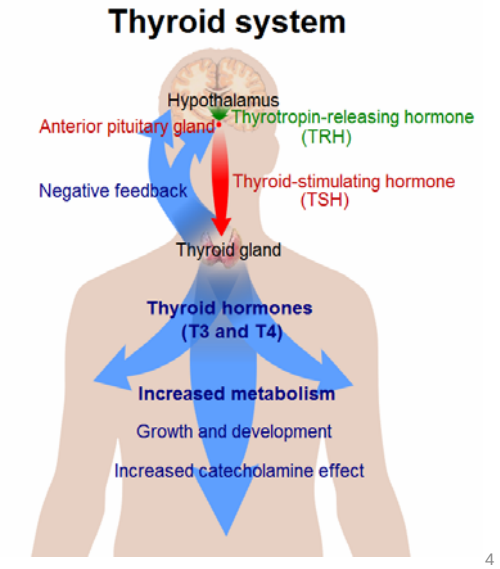
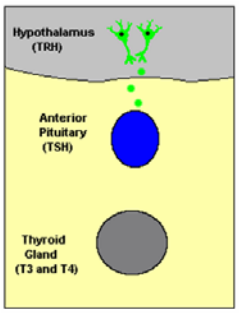
Link between Thyroid and Mental Retardation Recognized for 100 Years

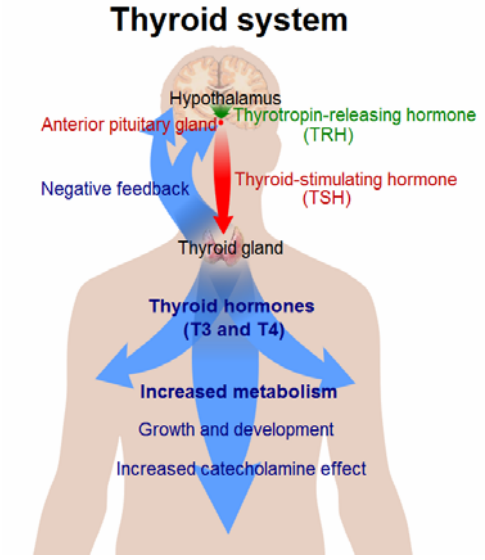


4

Neurons in the hypothalamus secrete thyroid releasing hormone (TRH), which stimulates cells in the anterior pituitary to secrete thyroid-stimulating hormone (TSH).
TSH binds to receptors on epithelial cells in the thyroid gland, stimulating synthesis and secretion of thyroid hormones, which affect probably all cells in the body.
When blood concentrations of thyroid hormones increase above a certain threshold, TRH-secreting neurons in the hypothalamus are inhibited and stop secreting TRH. *This is an example of "negative feedback".*

Link between Thyroid and Mental Retardation Recognized for 100 Years





During first trimester fetus is dependant on maternal thyroid

5

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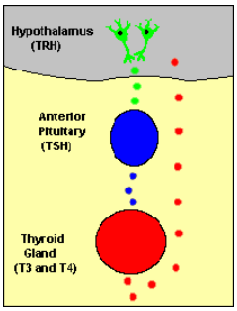

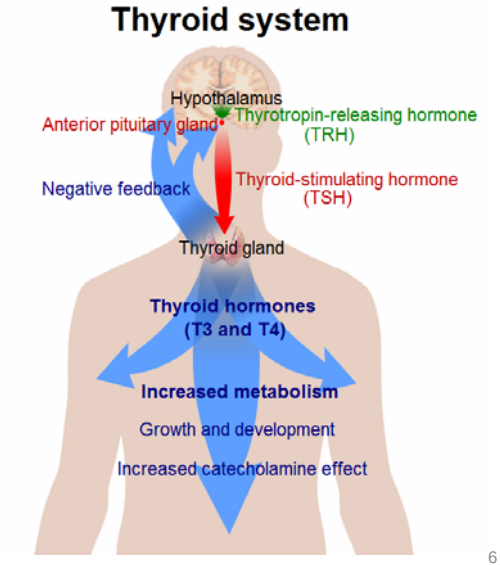

During first trimester fetus is dependant on maternal thyroid

6

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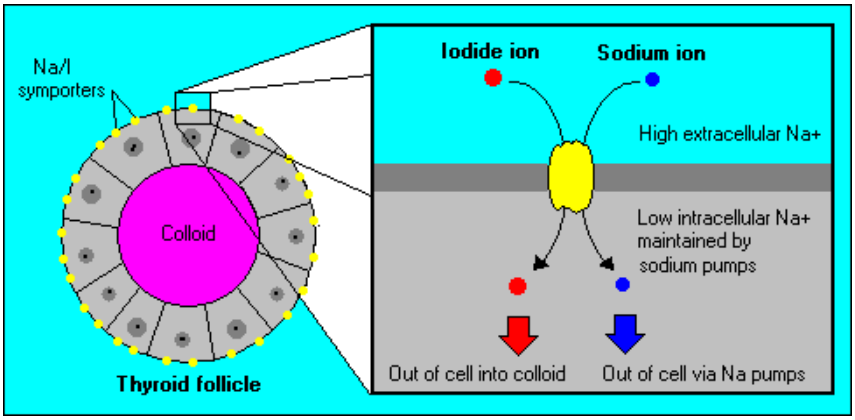
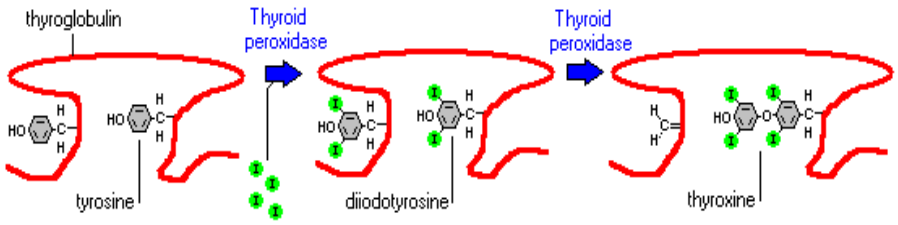
Thyroid gland ability to transport and concentrate iodide from blood is necessary for synthesis of thyroid hormones.
Inhibited by perchlorate, thiocyanate, nitrate.



7

As its name indicates, **the sodium-iodide symporter simultaneously transports both Na^+ and I^- ions** from extracellular fluid (i.e. blood) into the thryoid epithelial cell. This process is an example of secondard active transport. Energy is provided by the electrochemical gradient of sodium across the cell membrane; the low intracellular concentration of sodium is maintained by sodium pumps.
The sodium-iodide symporter is most highly expressed in thyroid epithelial cells. Lower levels of expression can be detected in mammary gland, salivary gland, stomach and colon, but none of these tissues is known to organify iodide. The presence of the symporter in mammary gland leads to secretion of iodine in milk, which is probably important for thyroid function in neonatal animals.
The most important stimulator of symporter gene and protein expression is thyroid-stimulating hormone, similar to what is observed with other important thyroid proteins such as thyroglobulin and thyroid peroxidase.
The ability of the thyroid gland to transport and concentrate iodide from blood is absolutely necessary for the synthesis of thyroid hormones. The key player in this process is the sodium-iodide symporter, an integral membrane protein that resides in the basolateral membrane of thyroid epithelial cells.

Three or Four Iodines are Added to Tyrosine to Make T_3 or T_4



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•**Tyrosines** are provided from a large glycoprotein scaffold called **thyroglobulin**, which is synthesized by thyroid epithelial cells and secreted into the lumen of the follicle - colloid is essentially a pool of thyroglobulin. A molecule of thyroglobulin contains 134 tyrosines, although only a handful of these are actually used to synthesize T4 and T3.

•**Iodine**, or more accurately iodide (I^-), is avidly taken up from blood by thyroid epithelial cells, which have on their outer plasma membrane a sodium-iodide symporter or "*iodine trap*". Once inside the cell, iodide is transported into the lumen of the follicle along with thyroglobulin.

Fabrication of thyroid hormones is conducted by the enzyme thyroid peroxidase, an integral membrane protein present in the apical (colloid-facing) plasma membrane of thyroid epithelial cells. Thyroid peroxidase catalyzes two sequential reactions:

1.Iodination of tyrosines on thyroglobulin (also known as "organification of iodide").

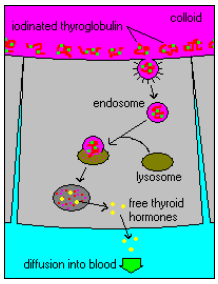
2.Synthesis of thyroxine (or triiodothyronine) from two iodotyrosines.

Through the action of thyroid peroxidase, thyroid hormones accumulate in colloid, on the surface of thyroid epithelial cells. *Remember that hormone is still tied up in molecules of thyroglobulin - the task remaining is to liberate it from the scaffold and secrete free hormone into blood.*

Control of Thyroid Hormone Synthesis and Secretion

- **Thyroid hormone is released into the blood after being excised from the thyroglobulin scaffold**

- **Each of the processes appears to be stimulated by <u>Thyroid Stimulating Hormone</u> from the anterior pituitary gland. Binding of TSH to its receptors on thyroid epithelial cells stimulates synthesis of the iodine transporter, thyroid peroxidase and thyroglobulin.**



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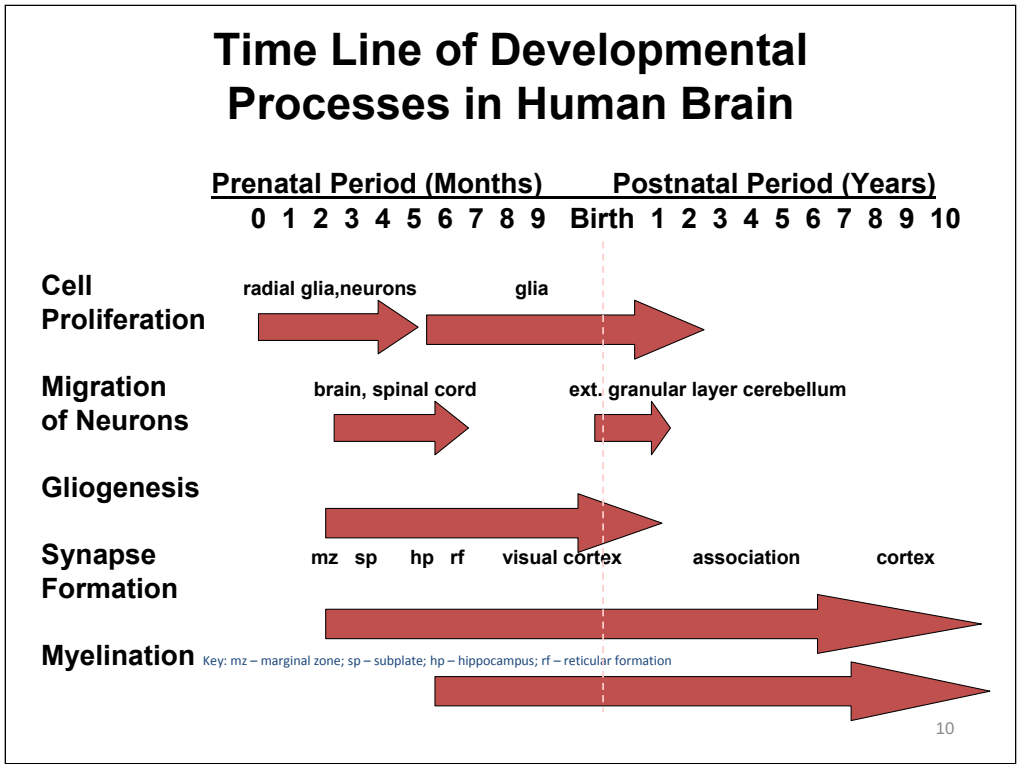

• Brain development involves the production of 1 billion nerve cells and 1 trillion glial, or support, cells. Once produced neurons undergo migration, synaptogenesis, cell loss, and myelination. Pruning of synapses occurs through adolescence. The peak number of synapses is reached in early childhood. Inhibition at one stage can cause alterations throughout the cascade. Various aspects of myelination occur from around 5 months gestation through 10 years of life.

• Compared to other organs, the brain remains vulnerable to developmental disruption over a prolonged period of time, extending from shortly after conception, until well after birth.

• This slide shows how the timing of processes involved in normal brain development vary during fetal life, infancy, childhood, and adolescence. Notice, for example, how cellular migration tends to be compressed into fairly short timeframes compared to cell proliferation, synapse formation or myelination.

• The clinical effect of disruption of the process by a developmental neurotoxic compound depends not only on the size of the dose but also on the timing and duration.

• EXAMPLE: Effects of the developmental neurotoxin, methylmercury, in large populations of people, include mixtures of developmental delays, learning disabilities, attention deficits, seizures, and mental retardation, depending on the size, timing, and duration of exposure.

•EXAMPLE: Thalidomide caused autism in some children only when the exposure occurred between gestational days 20-24. The window of vulnerability to limb development defects is much longer.

Source: Rice D, Barone S. Critical periods of vulnerability for the developing nervous system: evidence from human and animal models. Environ Health Perspect 108 (Suppl 3):511-533, 2000. *With author's permission.*

Specific processes disrupted by neurodevelopmental toxicants

proliferation	radiation, ethanol, mercury, cholinesterase inhibitors, thyroid
migration	radiation, mercury, ethanol, thyroid
differentiation	ethanol, nicotine, mercury, lead, thyroid
synaptogenesis	radiation, ethanol, lead, triethyl tin, parathion, PCBs, thyroid
gliogenesis & myelinization	thyroid, ethanol, lead, thyroid
apoptosis	ethanol, lead, mercury
signaling	ethanol, cholinesterase inhibitors, mercury, lead, PCBs , thyroid

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Toxic substances can interfere with one or several processes necessary for normal brain development. For example, lead can interfere with cell differentiation, synapse formation, myelinization, programmed cell death (apoptosis), and neurotransmitter levels. Similarly, mercury interferes with cell proliferation, migration, programmed cell death, and neurotransmitter levels.

Therefore the size, timing, and duration of exposures will determine which processes are disrupted and how brain function will be impaired.

Sources:
1. Rice D, Barone S. Critical periods of vulnerability for the developing nervous system: evidence from human and animal models. Environ Health Perspect 108 (Suppl 3):511-533, 2000.
2. Olney JW, Farber NB, Wozniak DF, Jevtovic-Todorovic V, Ikonomidou C.
Environmental agents that have the potential to trigger massive apoptotic neurodegeneration in the developing brain.
Environ Health Perspect. 2000 Jun;108 Suppl 3:383-8. Review.

MATERNAL THYROID DEFICIENCY DURING PREGNANCY AND SUBSEQUENT NEUROPSYCHOLOGICAL DEVELOPMENT OF THE CHILD
Haddow et al., 1999 NEJM

- Examined 2nd trimester blood for TSH in 25,216 women
  - 48 had untreated high TSH levels (above 98%)
  - compared to 124 matched controls
- Children at 7-9 years tested intelligence, attention, language, etc.
  - Full scale IQ decreased by 7 points (p 0.005)
  - 19% had scores of 85 or less (p 0.007)

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Even Sub-clinical Thyroid Hormone Levels Appear Harmful

- Being in the lowest 10% of maternal $\mathbf{T_4}$ (Nl. TSH) at 12 weeks gestation resulted in a decrease of 8 IQ points at 2 years
- Additional study confirms finding in infants (NBAS)
- Having antibodies to thyroid during pregnancy increased risk of low T_4 6 fold

Pop, *et al*., Clin Endocrin 2003
Pop, *et al*., Pediatrics 2006

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Neonatal Effects of Maternal Hypothyroxinemia During Early Pregnancy

METHODS. Examined were 108 neonates who were born to mothers with low maternal free thyroid hormone (fT4 concentrations; 10th percentile) at 12 weeks' gestation (case patients) and 96 neonates who were born to women whose fT4 values were between the 50th and 90th percentiles, matched for parity and gravidity (control subjects). Newborn development was assessed at 3 weeks of age using the Neonatal Behavioral Assessment Scale. Maternal thyroid function (fT4 and thyrotropin hormone) was assessed at 12, 24, and 32 weeks' gestation.

RESULTS. Infants of women with hypothyroxinemia at 12 weeks' gestation had significantly lower scores on the Neonatal Behavioral Assessment Scale orientation index compared with subjects. Regression analysis showed that first-trimester maternal fT4 but not maternal TSH or fT4 later in gestation was a significant predictor of orientation scores.

CONCLUSIONS. This study confirms that maternal hypothyroxinemia constitutes a serious risk factor for neurodevelopmental difficulties that can be identified in neonates as young as 3 weeks of age.

Boston women have higher breast milk perchlorate and lower iodine than expected

- Mean BM Iodine =
  - 62mcg/L in smokers
  - 221 mcg/L non-smokers
  - Iodine ranged from 84-224mcg/L in formula
- 4 out of 49 had perchlorate in breast milk greater than 100 mcg/L
  - Infant formulas also contained perchlorate at up to 4.1 mcg/L

•Pearce et al., J Clin Endocrin Metab 2007

14

Breast milk in Boston

- IOM iodine adequate intake 110-130 mcg/d
- Estimated that as many as 47% of nursing women in the study may be providing insufficient iodine
- Median perchlorate 9.1mcg/L

15

Pearce et al., J Clin Endocrin Metab 2007

Perchlorate content formula and estimated dose (perchlorate-free water)

Infant Formula	Iodide (µcg/L)	Perchlorate (µcg/L)	Perchlorate dose (µcg/kg d)
Dairy based formula N=4	70-110	0.24 – 1.8	0.03 – 0.23
Dairy based lactose-free N=2	81/90	0.08/0.43	0.01/0.054
Soy N=4	19-96	0.11 – 0.47	0.015 – 0.06

RfD = 0.7 mcg/kg/d

- Blount and Valentin-Blasini, Thyroid 2007

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Blood Pressure and Lipid Values Change with Thyroid

A

B

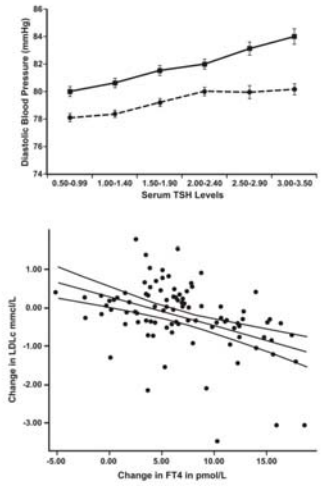

Figure 2

Miller et. al. 2009 Env Health Persp redrawn with permission from Asvold (2007; *A) and from Razvi (2007; B) (Copyrights 2007, The Endocrine Society).*

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Population vs. Individual Impact

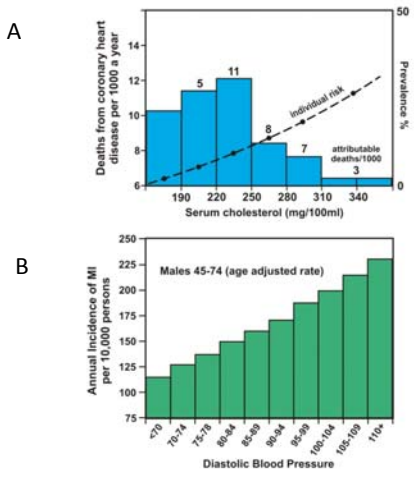
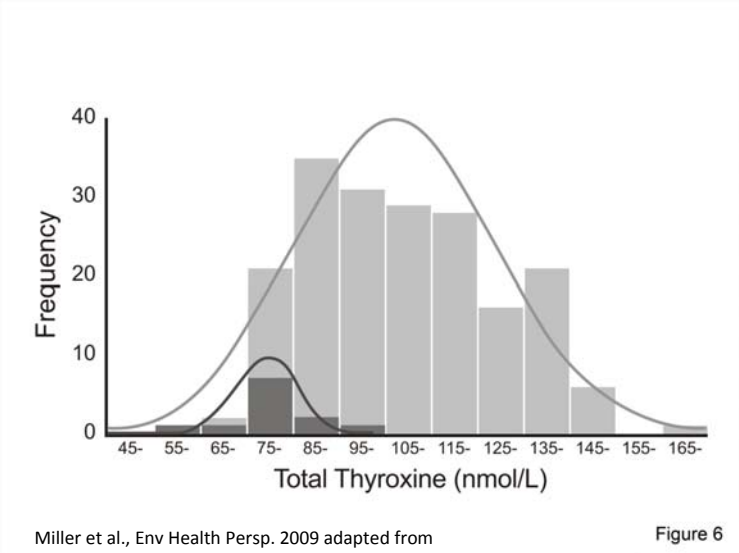


Figure 7

Miller et al., Env Health Persp. 2009 A (adapted from Rose 1981; with permission from the BMJ Publishing Group)
(*B) Death from MI associated with increased diastolic blood pressure in males 45–74 (age-adjusted rate) (adapted U.S. EPA 1985).*

Individual vs. Population Normal Range Thyroid



Miller et al., Env Health Persp. 2009 adapted from
Andersen et al. (2002); copyright 2002, The Endocrine Society

Perchlorate in Foods: US FDA 2005-6 Survey

- Market basket survey each year involving grocery stores and fast food restaurants in four regions in the US, three cities in each region
- Detectable levels of perchlorate found in 213 of the 286 foods assessed

Food item	Ppb
Tomato, raw	78.0
Grapes (red/green), raw	72.7
Shrimp, boiled	55.0
Cantaloupe, raw/frozen	47.2
Watermelon, raw/frozen	42.6
Spinach, fresh/frozen, boiled	40.0
Tortilla, flour	31.8
Apple pie, fresh/frozen	27.5
English muffin, plain, toasted	26.8
Cauliflower, fresh/frozen, boiled	25.9
Cucumber, peeled, raw	25.3
Pork bacon, oven-cooked	25.2
Ham, cured (not canned), baked	17.1
Bagel, plain, toasted	16.8
Potato, french-fried, fast-food	14.5

Public Water Sources in California 2004-9 with Detectable Perchlorate Levels (≥ 4 ppb)

County	No. of Sources	No. of Systems	Peak Conc. (ppb)
Los Angeles	117	33	86
Riverside	68	9	73
San Bernardino	58	15	80
Orange	21	11	11
Tulare	9	6	24
Santa Clara	7	3	7
Kern	5	4	34
Sacramento	4	2	10
San Diego	5	2	8
Madera	2	1	7
San Joaquin	1	1	69
Tehama	1	1	82
San Luis Obispo	1	1	20
Monterey	1	1	7
Sutter	1	1	6
Ventura	1	1	5
TOTAL	297	92	-

CDPH (2009). http://www.cdph.ca.gov/certlic/drinkingwater/pages/Perchlorate.aspx

Medicinal doses: 800 mg/day (aplastic anemia?)

Selected High Dose Studies of Perchlorate and Thyroid Function

Study	Type	Dose	Outcome Assessed	Result
Greer et al, 2002	Clinical dosing	35 mg/d x 2 wk	T4, fT4, T3, TSH	No effect*
Lawrence et al, 2000	Clinical dosing	10 mg/d x 2 wk	T3, T4, TSH	No effect*
Lawrence et al, 2001	Clinical dosing	3 mg/d x 2 wk	T3, T4, TSH, FTI	No effect
Braverman et al, 2006	Clinical dosing	3 mg/d x 6 mo	T4, FTI, TSH	No effect
Gibbs et al, 1998	Occupational	2.5 mg/d#	T3, T4, FTI, TSH	No effect
Lamm et al, 1999	Occupational	1-34 mg/d#	T4, T3, TSH, FTI	No effect
Braverman et al, 2005	Occupational	12 mg/d#	T4, FTI, T3, TSH	No effect
Crump et al, 2000	Environmental	0.2 mg/d#	Child T4 and TSH	No effect
Tellez et al, 2000	Environmental	0.2 mg/d#	Mom/neonate T3, fT4, TSH	No effect
Amatai et al, 2007	Environmental	0.7 mg/d#	Neonatal T4	No effect

* Decreases in radioactive iodine uptake were seen, but no impact on thyroid hormone levels
# Estimated

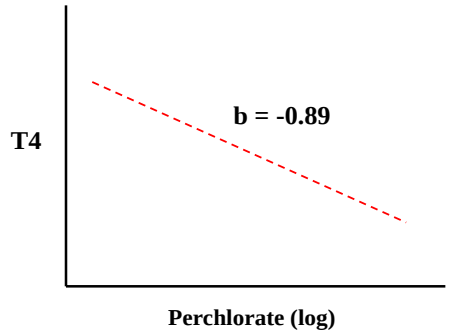
Blount et al. "Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States." Environ Health Perspect 114(12):1865-1871.

- Cross sectional study of urinary perchlorate and serum thyroid hormone levels (T4 and TSH)
- 2299 men and women in NHANES 2001-2
- Detectable perchlorate found in all urine samples tested.
- Mean urinary perchlorate = 2.84 ug/L (intake of about 5 ug/day)
- Excluded people with thyroid disease
- Adjusted for multiple potential confounding variables

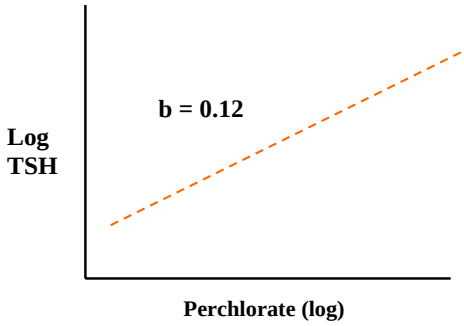
Regression coefficient (b) between perchlorate (log) and thyroid hormones (Blount et al. 2006)

	Total T4	TSH (log)
	b (p-value)	b p-value
Men	No effect	No effect
Women		
Iodine < 100*	-0.89 (p <0.0001)	0.12 (p = 0.001)
Iodine ≥ 100	No effect	0.11 (p = 0.02)

*35% of all women had urinary iodine levels < 100 ug/L



Low iodine women



All women

BIOLOGICAL PLAUSIBILITY OF THE FINDINGS:

- Perchlorate is known (at high doses) to decrease thyroid hormone production, which can increase TSH
- Perchlorate is known to inhibit iodine uptake
- Women have higher rates of thyroid disease than men
- Synergistic effect with thiocyante, another known NIS inhibitor

REMAINING QUESTIONS:

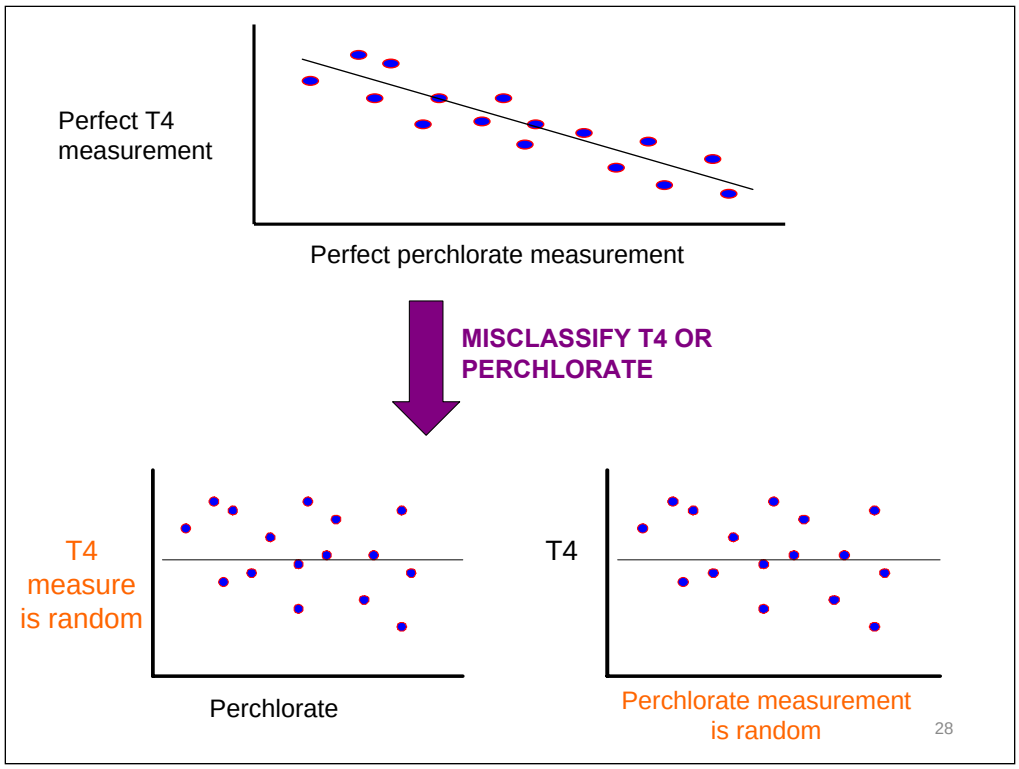
- Exposures in Blount et al. 2006 are very low
- No effect of nitrate, another NIS inhibitor
- Others

Some critiques of Blount et al. 2006

Misclassification of true thyroid status and true long-term perchlorate exposure

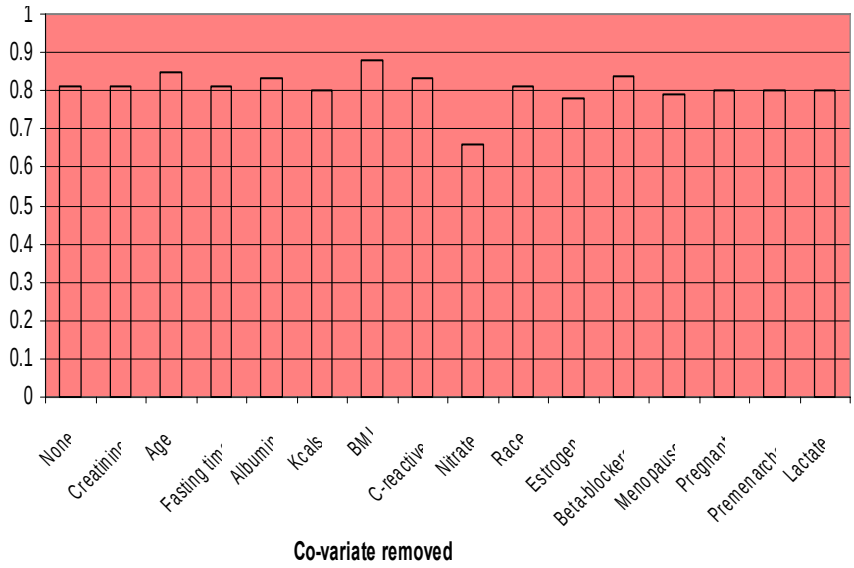
Effects may be due to confounding

Not consistent with other data

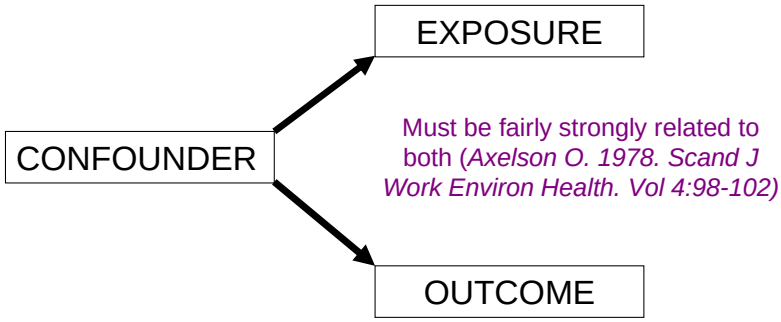

Perfect T4 measurement
Perfect perchlorate measurement
MISCLASSIFY T4 OR PERCHLORATE
T4 measure is random
Perchlorate
T4
Perchlorate measurement is random

Perchlorate-T4 Regression Coefficients (B) After Removing Each Co-variate From the Fully Adjusted Model.

[b]



Why aren't these things causing confounding if we know they are related to thyroid hormone levels?



Must be fairly strongly related to both (*Axelson O. 1978. Scand J Work Environ Health. Vol 4:98-102)*

What about other factors: PCBs?

CONSISTENCY: WHAT ABOUT STUDIES IN OTHER SUSCEPTIBLE GROUPS

Exposure:

Perchlorate in Maternal Residential Drinking Water During Pregnancy

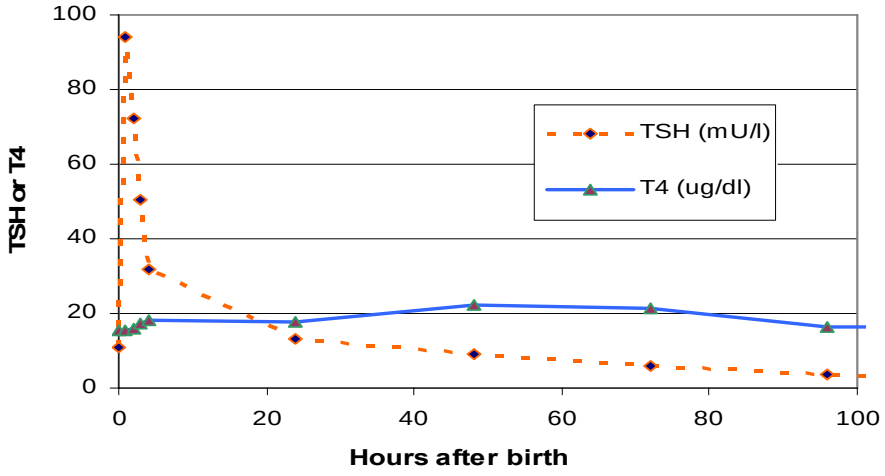
→

Outcome:

Newborn T4 and TSH levels

- Kelsh et al., Buffler et al., Schwartz, Brechner et al., Li et al., Tellez et al.
- Most are "negative"
- Some removed TSH or T4 measurements collected in the first 24 hours after birth**** *Does this reduce the ability to ID effects?*

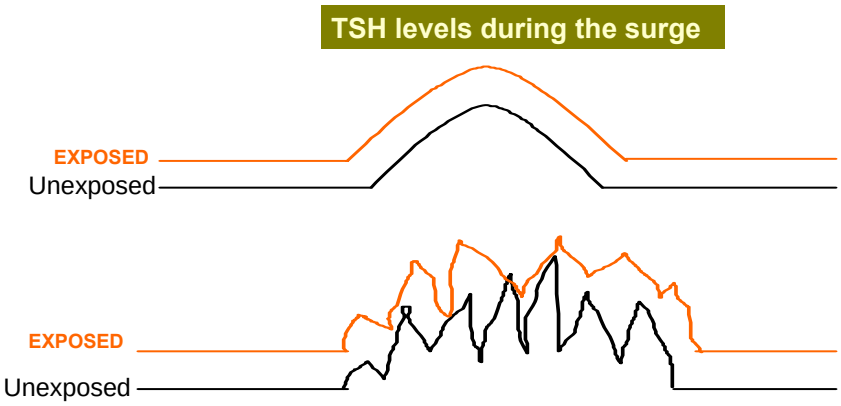
REMOVE MEASUREMENTS IN FIRST 24 HOURS AFTER BIRTH: SURGE IN THYROID HORMONES DURING THIS TIME



Abuid et al. 1973; Cavallo et al. 1980; Fisher and Odell 1969; Sack et al. 1976

1. Lots of "false positives" when determining which children need to be treated for congenital hypothyroidism with thyroid hormone.

2. Increased variability during the surge may make it more difficult to find a true effect



Perchlorate-TSH neonatal study results excluding the first 18-24 hours:

California: Odds ratio for a high TSH = 0.73 (95% CI, 0.40-1.23)

Redlands: Odds ratio for a high TSH = 0.69 (95% CI, 0.27-1.45)

Las Vegas: Mean TSH: Exposed = 12.8 Unexposed = 12.8

Israel*: Mean T4: High exposed = 14.5 Low exposed = 13.98

*Not excluded, but <10% in first 30 hours after birth

Refs: Amatai et al. 2007, Li et al. 2001, Kelsh et al. 2003, Buffler et al. 2006

First 24 hours may be the most relevant

- The half life of perchlorate is short (8 hours)[1]
- The half life of thyroid hormones is very short (a few hours)[2]
- Perchlorate exposure may change at birth: > 50% newborns receive some formula[3]

1. Greer et al. EHP 2002)
2. Fisher and Odell 1969, de Zegher et al 1994, van den Hove et al 1999
3. California 1998 unpublished

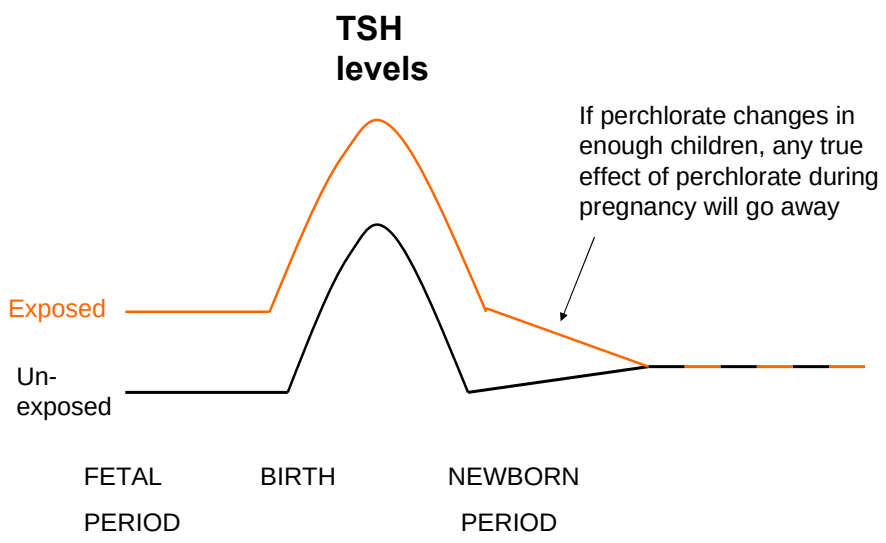
What can happen if exposure changes soon after birth

	FETUS – PREGNANCY	BIRTH	NEWBORN > 24 hrs
Perchlorate > 5 ppb	E E E E E E E E 8 exposed Ave. TSH = 8	→	E U E U U E U E 4 exposed 4 unexposed Ave. TSH = 6
Perchlorate < 5 ppb	U U U U U U U U 8 unexposed Ave. TSH = 4	→	U E U E E U E U 4 exposed 4 unexposed Ave. TSH = 6

Exposure Sources:

Maternal only:
- Water
- Food

Multiple:
- Maternal (breast fed)
- Hospital and bottled
- Formula


TSH
levels
If perchlorate changes in enough children, any true effect of perchlorate during pregnancy will go away
Exposed
Un-
exposed
FETAL
PERIOD
BIRTH
NEWBORN
PERIOD

Selected Results in Using Data from First 24 Hour after Birth

Study	Who	Where	Outcome	Result: exposed vs. unexposed*	Levels
Unpublished	TSH measured ≤ 18 hours	Redlands 1983-97	High TSH	Odds ratio = 1.57	0-9 ppb
Unpublished	TSH measured < 24 hours	California 1998	High TSH	Odds ratio = 1.60	> 5 ppb
Schwartz 2001	All	California 1996	Ave. T4	Difference in T4 = 18.2 mg/dl	> 13 ppb
Brechner et al. 2000	All	Arizona 1994-7	Low T4 Ave TSH	Odds ratio = 1.18 19.9 vs. 13.4 mU/l	4-6 ppb

* $p < 0.05$ for all results

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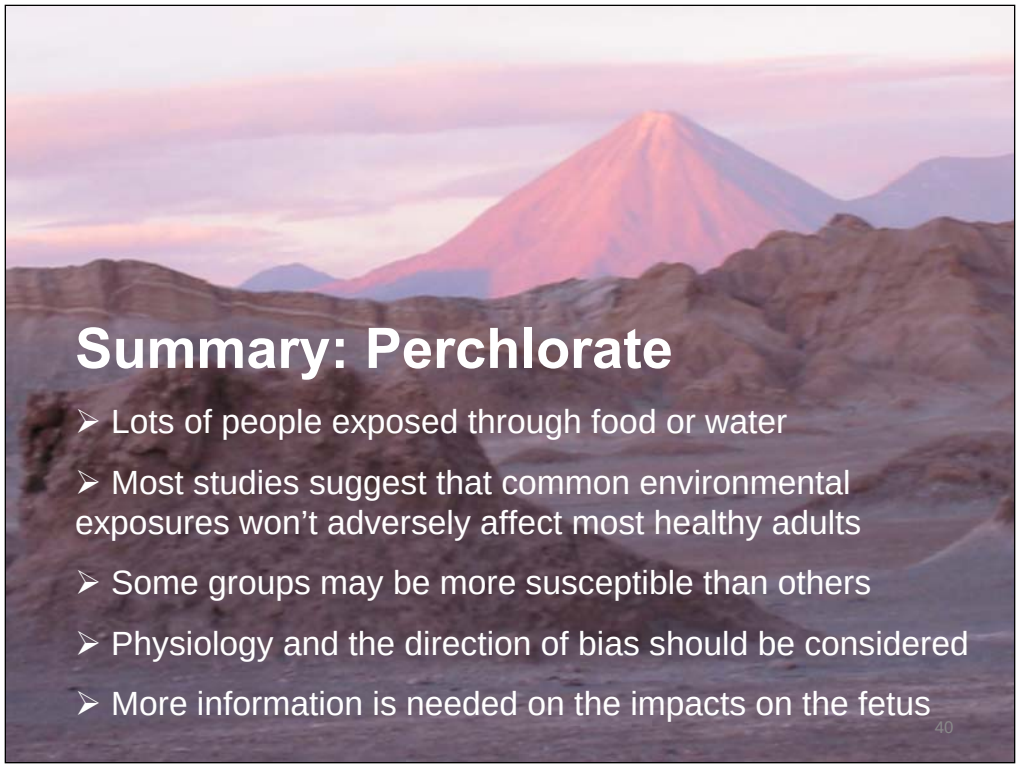
1. Lots of "false positives" when determining which children need to be treated for congenital hypothyroidism with thyroid hormone.

- Determining need for Rx. is not our only goal
- More subtle effects may also be important

2. Increased variability during the surge may make it more difficult to find a true effect

- This causes bias to the null, not towards a false effect


Summary: Perchlorate
➢ Lots of people exposed through food or water
➢ Most studies suggest that common environmental exposures won't adversely affect most healthy adults
➢ Some groups may be more susceptible than others
➢ Physiology and the direction of bias should be considered
➢ More information is needed on the impacts on the fetus
40

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Superfund Research Program

41

ScienceDaily
Your source for the latest research news

Web address:
http://www.sciencedaily.com/releases/2005/02/050222110959.htm

Perchlorate Found In Dairy And Breast Milk Samples From Across The Country

ScienceDaily (Feb. 24, 2005) — In a new study of breast milk and store-bought milk from across the United States , scientists at Texas Tech University found perchlorate in every sample but one. The results suggest that this thyroid-disrupting chemical may be more widespread than previously believed.

The report was published Feb. 22 on the Web site of Environmental Science & Technology, a peer-reviewed journal of the American Chemical Society, the world's largest scientific society.

Perchlorate occurs naturally and is also a primary ingredient in solid rocket fuel. The chemical, which has been showing up in many segments of the environment, can interfere with iodide uptake in the thyroid gland, disrupting adult metabolism and childhood development.

The researchers, led by Professor Purnendu Dasgupta, Ph.D., of the university's department of chemistry and biochemistry, analyzed 47 dairy milk samples purchased randomly from grocery stores in 11 states, and 36 breast milk samples from women recruited at random in 18 states. Every sample of breast milk contained perchlorate, and only one sample of dairy milk contained no detectable levels.

The average perchlorate concentration in breast milk was 10.5 micrograms per liter; the dairy milk average was 2.0 micrograms per liter. No definitive national standard exists, although the U.S. Environmental Protection Agency had suggested a limit of 1.0 micrograms per liter in drinking water.

The researchers also found that high levels of perchlorate correlated with low levels of iodide in breast milk, which can inhibit thyroid function in nursing women—an essential component for proper neural development of the fetus. Although the data are limited, the levels of iodide in this study are sufficiently low to be of concern, according to the researchers. They suggest that the recommended daily intake of iodine for pregnant and nursing women may need to be revised upwards.

The American Chemical Society is a nonprofit organization, chartered by the U.S. Congress, with a multidisciplinary membership of more than 159,000 chemists and chemical engineers. It publishes numerous scientific journals and databases, convenes major research conferences and provides educational, science policy and career programs in chemistry. Its main offices are in Washington, D.C., and Columbus, Ohio.

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American Chemical Society (2005, February 24). Perchlorate Found In Dairy And Breast Milk Samples From Across The Country. *ScienceDaily*. Retrieved December 24, 2009, from http://www.sciencedaily.com/releases/2005/02/050222110959.htm

Note: If no author is given, the source is cited instead.

Impact of Smoking and Thiocyanate on Perchlorate and Thyroid Hormone Associations in the 2001–2002 National Health and Nutrition Examination Survey

Craig Steinmaus, Mark D. Miller, and Robert Howd

Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Oakland, California, USA

Background: Findings from a recent large study suggest that perchlorate at commonly occurring exposure concentrations may decrease thyroid hormone levels in some women. Decreases in thyroid hormone seen with perchlorate exposure could be even greater in people with concomitant exposure to agents such as thiocyanate that may affect the thyroid by mechanisms similar to those of perchlorate.

Objectives and methods: We used data from the National Health and Nutrition Examination Survey to assess the impact of smoking and thiocyanate on the relationship between urinary perchlorate and serum thyroxine (T_4) and thyroid-stimulating hormone (TSH).

Results: In women with urinary iodine levels < 100 µg/L, the association between the logarithm of perchlorate and decreased T_4 was greater in smokers [regression coefficient (β) = –1.66, p = 0.0005] than in nonsmokers (β = –0.54, p = 0.04). In subjects with high, medium, and low cotinine levels, these regression coefficients were –1.47 (p = 0.0002), –0.57 (p = 0.03), and -0.16 (p = 0.59). For high, medium, and low thiocyanate tertiles they were –1.67 (p = 0.0009), –0.68 (p = 0.09), and –0.49 (p = 0.11). Clear interactions between perchlorate and smoking were not seen with TSH or with T_4 in women with urinary iodine levels ≥ 100 µg/L or in men.

Conclusions: These results suggest that thiocyanate in tobacco smoke and perchlorate interact in affecting thyroid function, and this effect can take place at commonly occurring perchlorate exposures. Agents other than tobacco smoke might cause similar interactions, and further research on these agents could help identify people who are particularly susceptible to perchlorate.

Key words: cotinine, interactions, iodine, perchlorate, thiocyanate, thyroid, tobacco smoke. *Environ Health Perspect* 115:1333–1338 (2007). doi:10.1289/ehp.10300 available via *http://dx.doi.org/* [Online 9 July 2007]

Perchlorate has been used by the aerospace industry as an oxidizer in solid rocket propellant, slurry explosives, road flares, and air bag inflation systems. Human environmental exposure can occur through food or water after industrial contamination or from perchlorate that is naturally occurring. In a recent analysis of data from the 2001–2002 National Health and Nutrition Examination Survey (NHANES), detectable levels of perchlorate were found in the urine of all 2,820 U.S. residents assessed (Blount et al. 2006b). Further analysis of the 2001–2002 NHANES data also identified an association between urinary levels of perchlorate and decreased levels of serum thyroxine (T_4) in women with urinary iodine concentrations < 100 µg/L (Blount et al. 2006a). A remarkable feature of this finding is that it was identified at perchlorate concentrations much lower than those linked to thyroid effects in any previous study. In fact, NHANES was designed to provide a nationally representative sample. Thus, the perchlorate exposure levels of the subjects in this study are likely similar to exposures occurring in a large portion of the U.S. population. Another notable feature was the relatively large fraction of women who had urinary iodine levels in the range where these effects were found. That is, 35% of all women ≥ 12 years of age in NHANES 2001–2002 had urinary iodine levels < 100 µg/L.

High doses of perchlorate have been shown to competitively inhibit iodide uptake in the thyroid gland, and perchlorate has been used therapeutically for this effect (Stanbury and Wyngaarden 1952; Wyngaarden et al. 1952). Other agents, including nitrate in food and water and thiocyanate in food or from tobacco smoke, also affect the thyroid by the same mechanism (Braverman et al. 2005; Tonacchera et al. 2004; Wyngaarden et al. 1953). Thiocyanate is a metabolite of cyanide found in tobacco smoke, and increased serum thiocyanate levels are associated with increasing levels of smoking (Foss and Lund-Larsen 1986). Thiocyanate is also found in some foods including cabbage, broccoli, cassava, and rapeseed oil (Foss and Lund-Larsen 1986).

In this investigation, we used data from the 2001–2002 NHANES to assess whether thiocyanate or other substances in tobacco smoke may interact with iodine and low levels of perchlorate in affecting T_4 and thyroid-stimulating hormone (TSH) (National Center for Health Statistics 2002). The purpose of this investigation was to help increase our understanding of the mechanisms of perchlorate toxicity, to evaluate whether associations between perchlorate and thyroid hormones may differ between smokers and nonsmokers (or categories of cotinine and thiocyanate), and to help identify subpopulations that may be more susceptible than others to the thyroid effects of perchlorate. These issues could have tremendous public health significance given the large numbers of people who appear to be exposed to perchlorate and have low iodine intake. The recent finding linking low levels of urinary perchlorate to reduced thyroid function, and the possibility that even minor decrements in thyroid function could affect early-life cognitive development, highlight the potentially serious impact of perchlorate exposure.

Materials and Methods

NHANES is a national survey of health, nutrition, and sociodemographic information involving a complex multistage probability sampling design conducted by the Centers for Disease Control and Prevention's National Center for Health Statistics (2002). In NHANES 2001–2002, levels of perchlorate, cotinine, and thiocyanate were analyzed in a representative one-third subsample of all subjects. For all subjects ≥ 12 years of age, these data were combined with data on levels of serum T_4, serum TSH, smoking status, and other variables that might affect perchlorate–thyroid associations. These included race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, or other, each entered as a dichotomous variable), age (years), iodine status, serum albumin (grams per deciliter), body mass index (BMI) (kilograms per square meter), 24-hr caloric intake (kilocalories per day from 24-hr dietary recall data), pregnancy status (based on urinary pregnancy test results and self-reports),

Address correspondence to C. Steinmaus, Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, 1515 Clay St., 16th Floor, Oakland, CA 94612 USA. Telephone: (510) 504-5395. Fax: (510) 843-5539. E-mail: csteinmaus@oehha.ca.gov

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The authors declare they have no competing financial interests.

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postmenopausal status (based on self-report, time since last period, and presence or absence of other reasons for missed menstruation), premenarche status (self-report), serum c-reactive protein (milligrams per deciliter), hours of fasting before serum collection (self-report), urinary nitrate (micrograms per liter), current lactation (dichotomous based on self-report), and use of medications known to affect the thyroid (e.g., levothyroxine, methimazole, propylthiouracil, beta blockers, and estrogens) (dichotomous based on self-reported use). A description of the possible impacts these variables may have on the relationship between perchlorate and thyroid function has been provided by Blount et al. (2006a).

In NHANES 2001–2002, information on self-reported smoking status was provided in two separate sections, the questionnaire and the medical examination component (MEC). For the study presented here, subjects were divided into four groups: current smokers, recent former smokers, long-term former smokers, and never-smokers. Current smokers were defined as those who reported that they smoked cigarettes at the time of the survey (questionnaire) or reported that they had smoked at least 20 cigarettes in the preceding 30 days (MEC). Never-smokers were defined as those who reported that they had not smoked at least 100 cigarettes in their life (questionnaire) or that they had never tried cigarette smoking (MEC). Recent former smokers were defined as those who quit smoking within 12 months of the survey. Long-term former smokers were defined as those who quit > 12 months before the survey. Because no difference between long-term former smokers and never-smokers was found in the association between T_4 or TSH and perchlorate, these two groups were combined into one group labeled "nonsmokers" for this study. Because the latency of the impact of tobacco smoke on thyroid function is unknown, all recent former smokers were excluded from analyses comparing smokers and nonsmokers. Approximately 10% of the subjects did not provide adequate information to assess smoking status. Few women were regular users of cigars, chewing tobacco, or snuff, and excluding regular users of these products had no impact on the analyses.

The methods used to collect and perform laboratory analyses of perchlorate, iodine, T_4, TSH, cotinine, and thiocyanate, and the quality control procedures involved in NHANES 2001–2002, are described in detail elsewhere (National Center for Health Statistics 2002). Briefly, serum samples collected in 2001 were assayed for TSH using a microparticle immunoassay and for T_4 using a Hitachi 704 chemistry analyzer (Hitachi Chemical Diagnostics, Mountain View, CA). Samples collected in 2002 were assayed for T_4 and TSH using a chemiluminescent immunoassay (Access Immunoassay Systems; Beckman Instruments, Fullerton, CA). Urine samples were analyzed for perchlorate, thiocyanate, and nitrate using ion chromatography tandem mass spectrometry (Blount 2006b). Iodine was analyzed using inductively coupled plasma mass spectrometry (National Center for Health Statistics 2002).

Using data from NHANES 2001–2002, Blount et al. (2006a) identified an association between the logarithm of perchlorate concentration in urine (log perchlorate) and decreased serum T_4 in women with urinary iodine < 100 µg/L ($\beta = -0.89$, $p < 0.0001$), but not in women with higher urinary iodine levels ($\beta = 0.22$, $p = 0.55$). Associations between log perchlorate and increases in the logarithm of serum TSH (log TSH) were also identified, both in women with urinary iodine levels above and below 100 µg/L ($\beta = 0.11$, $p = 0.02$; and $\beta = 0.12$, $p = 0.001$, respectively). The urinary iodine stratification level of 100 µg/L was selected by Blount et al. because the World Health Organization (WHO) has defined populations with median urinary iodine excretion > 100 µg/L as having sufficient intake (WHO 1994). This stratification level was chosen for the analyses presented here for the same reason and so that our results could be compared more directly with those of Blount et al. (2006a)

We assessed serum cotinine in this study because it is a metabolite of nicotine and may be a more accurate indicator of current smoking status than self-reported smoking (Wells et al. 1998). We categorized cotinine concentrations into three levels for this study. Serum cotinine levels > 10 ng/mL were classified as high, whereas levels below the detection level of 0.015 ng/mL were classified as low. All levels between these cutoff points were classified as medium. Using a cutoff of 15 ng/mL to define the high cotinine category had little impact on our results. Thiocyanate categories were based on the sex-specific tertiles.

All statistical analyses were performed with SAS version 9.1 (SAS Institute Inc., Cary, NC) using SAS procedures surveyreg, %sregsub, and surveymeans. The following model was used: T_4 or log TSH = intercept + β_1(log perchlorate) + β_2(log creatinine) + β_3(iodine category) + β_4(iodine category × log perchlorate) + β_5(smoking category) + β_6(smoking category × log perchlorate) + β_n(n = other potential confounding variables). In this model iodine category is defined as < 100 µg/L or not, and smoking category is defined either as current versus nonsmokers or as classes of cotinine or thiocyanate as defined above. The model allows estimates of the effect of smoking category and the interaction of perchlorate with smoking category, after adjustment for creatinine and iodine category. Similarly, estimates of the effect of iodine category and the interaction of iodine category with perchlorate are made after adjustment for creatinine and smoking category. Initially, we performed univariate analyses to assess the relationship between urinary perchlorate, all potential covariates, and serum T_4 and log TSH. We also performed univariate analyses and data plots to identify outliers and to assess distributions. Variables such as urinary perchlorate, urinary creatinine, and serum TSH were log 10-transformed to normalize distributions. In analyses involving surveymeans, urinary perchlorate residuals adjusted for creatinine were calculated using the method described by Willet and Stampfer (1998).

Initial univariate and multivariate analyses showed no clear evidence of interaction among smoking, cotinine, thiocyanate, and urinary perchlorate on serum T_4 or log TSH levels in men or in women with urinary iodine levels > 100 µg/L, so we focus on women with urinary iodine < 100 µg/L. Women who reported a history of thyroid disease or use of thyroid medications were excluded. Two women with very high serum TSH levels (43 and 68 IU/L) and one woman with a very high serum T_4 level (27 µg/dL) were also excluded.

We constructed separate regression models for serum T_4 and log TSH as the dependent variables. Model building followed the general principles presented by Hosmer and Lemeshow (2000). Independent variables that were associated with T_4 or log TSH with $p < 0.20$ were added to and retained in the model that included the log perchlorate and log creatinine. Excluded variables were added back to the model one at a time to assure that they did not have important impacts on the perchlorate regression coefficient.

Results

Of the 11,039 subjects in NHANES 2001–2002, 5,708 were women and 4,137 of these were ≥ 12 years of age. Of these, 1,203 (29%) had data on serum T_4, serum TSH, and urinary perchlorate, iodine, and creatinine. Three of these had extreme values of T_4 or TSH, and 91 reported a history of thyroid disease or use of thyroid medication. Of the remaining women, 385 (35%) had urinary iodine levels < 100 µg/L. Table 1 provides

Table 1. Mean (± SE) levels of perchlorate, iodine, T_4, logTSH, and other variables in smoking and nonsmoking women with urinary iodine < 100 µg/L, 2001–2002 NHANES.

	Current smokers	Nonsmokers
No.	66	260
Perchlorate (µg/L)	2.52 ± 0.55	3.15 ± 0.88
Iodine (µg/L)	51.7 ± 3.7	54.3 ± 2.2
Thiocyanate (µg/L)	4,344 ± 646	813 ± 64
Cotinine (ng/mL)	201.5 ± 15.7	1.1 ± 0.6
T_4 (µg/dL)	8.6 ± 0.2	8.2 ± 0.2
logTSH (µg/dL)	0.12 ± 0.06	0.14 ± 0.03

mean levels of various parameters for smokers and nonsmokers.

Table 2 shows the regression coefficients for the association between serum T_4 and log perchlorate in women with urinary iodine levels < 100 µg/L. The adjusted regression coefficient in all women with low urinary iodine was –0.73 (p = 0.004). The adjusted regression coefficients between T_4 and log perchlorate in current smokers and nonsmokers were –1.66 (p = 0.0005) and –0.54 (p = 0.04), respectively. The regression coefficient for the product term including log perchlorate and smoking category was 1.12 (p = 0.008), consistent with a biologic interaction. Regression coefficients between T_4 and log perchlorate were higher in women with serum cotinine levels > 10 ng/mL than in women with cotinine levels below the detection limit, and higher in women with thiocyanate levels in the upper tertile than in women with levels in the lower tertile. We observed only small differences between the adjusted and unadjusted regression coefficients in most analyses. The differences in T_4–log perchlorate regression coefficients seen between smoking categories changed only slightly when different iodine cutoff points were used. For example, using a cut-off point of 75 µg/L and 125 µg/L, the T_4–log perchlorate regression coefficients for smokers and nonsmokers were –1.58 and –0.48, and –1.42 and –0.33, respectively. No clear associations between urinary perchlorate and T_4 or interactions with smoking, cotinine, or thiocyanate were found in men, or in women with urinary iodine levels ≥ 100 µg/L (data not shown).

Table 2 shows the regression coefficients for the association between log TSH and log perchlorate in women with urinary iodine levels < 100 µg/L. In all women in this group, the regression coefficient was 0.13 (p = 0.02). The corresponding coefficients in current smokers and nonsmokers were 0.13 (p = 0.23) and 0.11 (p = 0.009). Consistent differences in the regression coefficients between urinary perchlorate and serum TSH were not seen across subgroups of serum cotinine or thiocyanate.

The associations between T_4 and smoking, thiocyanate, and cotinine, independent of urinary perchlorate, were assessed in women with urinary iodine < 100 µg/L. In univariate analyses, no associations were found between the logarithm of serum cotinine and serum T_4 or log TSH (for T_4: n = 382, β = 0.03, p = 0.73; for log TSH: n = 382, β = –0.02, p = 0.26). In analyses adjusted for creatinine, no statistically significant associations were found between log thiocyanate and T_4 or log TSH (for T_4: n = 384, β = –0.17, p = 0.46; for TSH: n = 384, β = –0.05, p = 0.21).

Table 3 shows mean serum T_4 and log TSH levels in women with and without three potential risk factors for reduced uptake of iodine into the thyroid gland and thus reduced production of thyroid hormone. These are: *a*) urinary iodine < 100 µg/L (the median urinary iodine concentration in a population at which no endemic goiter is found) (Vanderpas 2006; WHO 2004)), *b*) current smoking, and *c*) urinary perchlorate (creatinine adjusted) above the median. Mean T_4 levels were lower in women who had all three risk factors than in those with none (7.16 vs. 8.41 µg/dL, p = 0.04). Mean log TSH was higher in the group with these risk factors than in those without [0.24 vs. 0.11 (IU/L), p = 0.001]. These differences were smaller and not statistically significant when the perchlorate risk factor was removed. That is, the mean T_4 level in women smokers with iodine < 100 µg/L (regardless of urinary perchlorate level) was 8.58 µg/dL [95% confidence interval (CI), 8.11 to 9.05, n = 66] whereas the mean T_4 in nonsmokers with iodine ≥ 100 µg/L (regardless of urinary perchlorate level) was 8.39 µg/dL (n = 406, 95% CI, 8.06 to 8.72; p = 0.63). The mean log TSH values in these two groups were 0.12 µg/dL (95% CI, –0.00 to 0.24) and 0.16 µg/dL (95% CI, 0.13 to 0.19; p = 0.36).

Discussion

A previous analysis of NHANES 2001–2002 showed that commonly found urinary perchlorate levels may be associated with decreases in serum T_4 and increases in TSH in some women (Blount et al. 2006a). Our independent analysis of the same raw data confirms these findings and has also found that in women with low urinary iodine, the association between urinary perchlorate and decreased serum T_4 is stronger in smokers than in nonsmokers and stronger in those with high urinary thiocyanate levels than in those with low thiocyanate levels. These findings provide evidence that perchlorate at relatively low levels can interact with tobacco smoke or thiocyanate to diminish iodine uptake and decrease thyroid function. The large magnitude of the differences identified suggest that these findings are not owing to chance, and the finding of similar effects across different measures of exposure (i.e., self-reported smoking, serum cotinine, and urinary thiocyanate) provides further evidence that these results represent true effects.

The findings identified in this study are biologically plausible. That is, they are consistent with the mechanisms by which perchlorate, iodine, and thiocyanate are known to affect thyroid function. Perchlorate competitively inhibits the sodium iodide symporter (NIS), the membrane protein that actively transports iodide into the thyroid follicular cell for thyroid hormone production (Stanbury and Wyngaarden 1952; Wyngaarden et al. 1952). Sufficient suppression of iodide uptake can diminish production of thyroid hormone. Smoking has been linked to increases in various thyroid diseases (Vestergaard 2002), although data on the relationship between smoking and serum levels of thyroid hormones have been mixed (Bertelsen and

Table 2. Association between the logarithm of urinary perchlorate (µg/L) and serum T_4 (µg/dL) and the logarithm of TSH (µg/dL) in women with urinary iodine < 100 µg/L,[a] 2001–2002 NHANES.

	T_4[b]				Log TSH[c]			
	No.	β	SE	p-Value	No.	β	SE	p-Value
All	362	–0.73	0.22	0.004	369	0.13	0.05	0.02
Smoking[d]								
Current	63	–1.66	0.37	0.0005	62	0.13	0.11	0.23
Nonsmoker	245	–0.54	0.23	0.04	45	0.11	0.03	0.009
Cotinine (serum)								
High (> 10 ng/mL)	64	–1.47	0.30	0.0002	68	0.15	0.08	0.09
Medium[e]	185	–0.57	0.25	0.03	192	0.10	0.06	0.09
Low (ND)	101	–0.16	0.29	0.59	106	0.11	0.05	0.04
Thiocyanate (urine)[f]								
High (> 1,800 µg/L)	78	–1.67	0.40	0.0009	82	0.13	0.09	0.19
Medium	107	–0.68	0.37	0.09	108	0.20	0.04	0.0003
Low (< 751 µg/L)	176	–0.49	0.30	0.11	178	0.10	0.05	0.06

Abbreviations: ND, nondetectable; β, regression slope; p, two-sided p-value.
[a]This value was selected because a urinary iodine level > 100 µg/L is the WHO definition of sufficient iodine intake in populations (WHO 1994). [b]T_4 models were adjusted for fasting time, kilocalories, BMI, c-reactive protein, nitrate, race, estrogen use, and pregnancy. T_4 model with cotinine was also adjusted for menopause status. [c]LogTSH models were adjusted for age, fasting time, body mass index, race, premenarche, and lactation. LogTSH model with smoking status was also adjusted for menopause status. [d]Smoking data were not available on all women, and recent former smokers are excluded. [e]Medium category includes all subjects with serum cotinine levels between 10 ng/mL and nondetectable. [f]Based on tertiles in all women ≥ 12 years of age.

Table 3. Comparing mean T_4 (µg/dL) and the logarithm of TSH (IU/L) values in groups of women.

	T_4		Log TSH	
	Mean	95% CI	Mean	95% CI
Group 1 (n = 21)	7.16	6.28–8.05	0.24	0.13–0.36
Group 2 (n = 161)	8.41	7.96–8.86	0.11	0.08–0.14
Difference	1.25		0.13	
p-Value	0.04		0.001	

Group 1: Current smokers, perchlorate residual (µg/L) > median, and urinary iodine < 100 µg/L. Group 2: Nevermokers, perchlorate residual (µg/L) ≤ median, and urinary iodine ≥ 100 µg/L. Urinary perchlorate residuals are adjusted for creatinine using the method described by Willet and Stampfer (1998).

Hegedus 1994). Smoking does increase serum levels of thiocyanate (Foss and Lund-Larsen 1986), which, like perchlorate, also competitively inhibits the NIS (Tonacchera et al. 2004). Thiocyanate has also been shown to increase the risk for development of goiter, both in those with moderate to severe iodine deficiency (< 50 µg/g creatinine) and in those within the lower range of adequate iodine intake (100 µg/g creatinine) (Brauer et al. 2006). Based on their common effects, it is not surprising that thiocyanate from smoking could interact with perchlorate to inhibit the NIS and subsequently decrease thyroid hormone production and that this effect would be greater in those with lower iodine levels.

A remarkable aspect of these findings is that the perchlorate levels in NHANES 2001–2002 are generally much lower than levels shown not to affect thyroid function in previous studies. In the 385 women with low iodine in our study, 50% had urine perchlorate levels < 1.7 µg/L and 90% had levels < 5.7 µg/L. Several experimental and observational studies have reported that perchlorate had no effect on T_4 or TSH levels at exposure levels orders of magnitude higher than the median levels found in our study (Braverman et al. 2005, 2006; Greer et al. 2002; Lamm and Doemland 1999; Lamm et al. 1999a, 1999b, 2002; Tellez et al. 2005). There are several possible explanations for this discrepancy. One is that most previous studies did not evaluate effects in women with low iodine. It is possible that iodine levels must be sufficiently low for environmental levels of perchlorate and thiocyanate to overcome compensatory mechanisms that maintain thyroid hormone. This is consistent with a previous study showing that goiters due to the consumption of thiocyanate in cassava were more likely when iodine levels were low and were reversed with iodine supplementation (Delanghe et al. 1982). It is also possible that the effects on T_4 we identified in women with low urinary iodine also occur in women with higher iodine levels but are less strong and the statistical power to identify them has been too low in most studies. Other possible reasons are that occupational studies have involved primarily men and, as was found in our study, effects may predominate in women; that experimental studies may have missed effects because dosing durations were too short; and that ecologic studies may have missed effects because of the greater misclassification of perchlorate exposure that can occur when exposure is assessed ecologically rather than individually. We do not know why the effects we identified were seen only in women. Women do have greater incidences of some iodine-related and other thyroid conditions (Laurberg et al. 2000), and estradiol has been shown to inhibit TSH-stimulated expression of the sodium–iodide symporter in rats (Furlanetto et al. 1999). It is possible that these effects may be related to our finding effects in women but not in men.

The results of this study are based on a single assessment of urinary perchlorate, urinary iodine, and serum thyroid hormones. Previous studies have shown that after short-term perchlorate administration in humans, most perchlorate is excreted in the urine within 48–72 hr (Greer et al. 2002; Selivanova and Arefaeva 1986). Other studies have shown that thyroid hormone levels, especially TSH, and iodine levels can have marked intraindividual variability over time (Hollowell et al. 1998; Surks et al. 2005). Because of this variability and the relatively short half-life of perchlorate, single measurements of these analytes might not reflect true long-term levels. Another issue that could lead to misclassification is that serum T_4 was measured as total T_4 rather than as free T_4 (the physiologically available form). Importantly, though, biologic samples in NHANES 2001–2002 were collected and analyzed similarly in all subjects, independent of perchlorate, thyroid, iodine, or smoking status. Thus, any misclassification of these exposure or outcome variables is likely to be nondifferential, and therefore likely to bias estimates of association toward the null, not toward the positive effects identified in this study (Rothman and Greenland 1998).

The presence of certain factors such as estrogen use, the presence of thyroid disease, exercise, menstruation disturbances, or antithyroid antibodies could potentially confound the association between perchlorate and thyroid hormone levels. However, confounding variables must be related to both the exposure and the outcome. Because many of the variables linked to serum thyroid hormone levels are not necessarily associated with urinary perchlorate concentrations, they are not likely to be confounding variables in our analyses. Some variables could be associated with both thyroid hormone levels and urinary perchlorate and therefore could have acted as confounders. However, many potential confounders were controlled for either by adjusting for them in the analyses (e.g., estrogen use) or by applying restriction criteria (e.g., excluding subjects with known thyroid disease).

The presence of antithyroid antibodies is a risk factor for hypothyroidism and decreased T_4, but were not measured in NHANES 2001–2002 and therefore not included in our analyses. The actual impact of this is unknown. However, an analysis of a previous NHANES data set (NHANES III) found that antithyroid antibodies were less prevalent in smokers (11%) than in nonsmokers (18%) (Belin et al. 2004). This suggests that, based on antithyroid antibody status alone, smokers would tend to have higher T_4 levels than nonsmokers. In the study reported here, we found somewhat of the opposite effect. That is, we found that perchlorate was associated with decreased T_4, and the strength of this decrease was greater in smokers than in nonsmokers. This suggests that if we were able to account for antithyroid antibodies in our analyses, this could actually strengthen, not weaken, the associations we identified for smoking.

The results of some of our analyses are slightly different than those reported by Blount et al. (2006a), although the results of these two studies are close and the differences have no impact on the conclusions drawn from either study. Our analysis was done independently from Blount et al., so these differences are likely related to differences in the definitions and categorization of some variables (e.g., postmenopause or premenarche status), the use of different statistical programs, and different methods of selecting independent variables to remain in the final regression models. Despite these differences, the results of these two studies are similar. For example, for women with low urinary iodine the adjusted regression coefficient between log perchlorate and serum T_4 was –0.89 (SE = 0.18, $p < 0.0001$, $n = 348$) in Blount et al. (2006a) and –0.73 (SE = 0.22, $p = 0.004$, $n = 362$) in this study. The similarity of these results, despite different statistical methods and independent analyses, supports the validity of the methods used in both studies.

Tobacco smoke, with its > 4,000 chemicals, is associated with many abnormalities of thyroid function likely occurring via multiple mechanisms (Utiger 1995). Although we found evidence of interaction between smoking and perchlorate on reducing serum T_4 levels, no clear interaction was seen on TSH. As seen in Table 2, the magnitudes of the regression coefficients between log perchlorate and log TSH were similar in nonsmokers and smokers, suggesting that the impacts of perchlorate on TSH are similar regardless of smoking status. In many conditions, suppression of T_4 is accompanied by a compensatory rise in serum TSH. However, this is not always the case. For example, iodine deficiency is characterized by decreases in serum T_4 with normal or slightly elevated levels of serum triiodothyronine (T_3) and normal levels of serum TSH (Obregon et al. 2005). It has been shown that with iodine deficiency T_4 is deiodinated to T_3 (LaFranchi 2004). Based on this, it has been suggested that although iodine deficiency may cause a decrease in serum T_4 levels, an associated increase in T_3 exerts a negative feedback limiting any compensatory rise in TSH (Maruta and Greer 1988). This could explain why we found clear differences across smoking, cotinine, and thiocyanate categories for T_4 but not for TSH.

There are other possible reasons why we found less effect on TSH. For example, a previous NHANES survey found that smokers had lower TSH levels than nonsmokers, possibly related to the greater prevalence of serum thyroid autoantibodies among nonsmokers (Belin et al. 2004). Although the data from other studies regarding the impacts of smoking and thyroid function have been mixed (Hegedus et al. 1985; Muller et al. 1995; Petersen et al. 1991; Sepkovic et al. 1984), it is possible that smoking causes an overall suppression of TSH that counterbalances any TSH stimulation caused by reductions in serum T_4. Another reason why effects on TSH may not be found is that intra- and interindividual variability is generally much greater for serum TSH than for serum T_4, and this variability diminished the ability of this study to identify associations with a single assessment of TSH.

The public health significance of this study lies in *a*) the large number of people in the United States who appear to be exposed to perchlorate, *b*) the large number of women with low iodine levels, *c*) the variety of factors that can inhibit the sodium iodide symporter, and, *d*) the potential importance of relatively small changes in thyroid hormone levels. With regard to perchlorate exposure, NHANES was designed to provide information on a nationally representative level. Thus, the perchlorate exposure levels of the subjects in this study are supposed to represent those in the large majority of people in the United States. Although statistically significant findings in this study were seen only in women with urinary iodine levels < 100 µg/L, this group represents a large fraction of the U.S. and world population. In NHANES 2001–2002, 35% of all women ≥ 12 years of age had iodine levels < 100 µg/L.

Importantly, our findings may not be relevant just for smokers. We did find effects on TSH in both smokers and non-smokers. In addition, we found a borderline statistically significant effect on T_4 in nonsmokers and a statistically significant effect in subjects with urinary cotinine levels associated with environmental tobacco smoke exposure (i.e., our medium cotinine category). Also, thiocyanate not only results from smoking but also is present in various foods including cruciferous vegetables and cassava. Elevated levels of thiocyanate have been noted in the milk of cows that were fed rapeseed (a member of the Cruciferae family), with resulting decreases in iodine in milk presumably from inhibition of the sodium–iodide symporter expressed in the lactating breast (Laurberg et al. 2002). Similarly, iodine levels in breast milk are decreased in human mothers who smoke (Laurberg et al. 2004). Other chemicals known to inhibit the thyroid sodium–iodide symporter include nitrates [which are estimated to contaminate 22% of domestic wells throughout the United States above the U.S. EPA maximum concentration limit (Ward et al. 2005)] and iodine in excess (Riesco-Eizaguirre and Santisteban 2006; Wolff and Chaikoff 1948). *In vitro* data have shown that perchlorate, nitrates, and thiocyanate may have additive effects on inhibiting the sodium–iodide symporter (Tonacchera et al. 2004). In preliminary analyses, we did not find evidence of strong associations between urinary nitrate levels and thyroid function or clear interactions with perchlorate. Whether this may be caused by the use of urinary nitrate rather than serum or dietary nitrate, differences between *in vivo* and *in vitro* effects, or some other reason is unknown and requires investigation beyond the scope of this paper. Regardless, the *in vitro* data on the interactions between these agents, combined with our findings regarding thiocyanate, provide some evidence that the effect of perchlorate on thyroid function can be increased in people exposed to similarly acting agents. A previous concern about the interpretation of the report by Blount et al. (2006a) was that they identified associations with perchlorate but not with other goitrogens (American Thyroid Association 2006). The study reported here adds importantly to the evaluation of the NHANES data by showing that other goitrogens, specifically thiocyanate and smoking, can also affect thyroid function.

The effects we identified, although relatively small, could have important implications in people who have borderline low T_4 levels for reasons other than exposure to perchlorate. In these potentially susceptible subgroups, additional reduction in T_4 levels caused by perchlorate could increase their risks of developing signs or symptoms of hypothyroidism. Some research indicates that even small decrements in maternal free T_4 (fT_4) during the first trimester, including those within what is generally considered the "normal" range (lowest 10%), can be associated with impaired neuropsychologic development in the child (Haddow et al. 1999; Kooistra et al. 2006; Pop et al. 2003). This suggests that any exposure that would result in altered production or utilization of fT_4 should be considered a potentially detrimental effect. Sizable subpopulations for which underlying fT_4 levels may be low or borderline include women with iodine deficiency or thyroid peroxidase antibodies. These women constitute a large subpopulation potentially sensitive to the additional burdens of thiocyanate (from smoking or diet) and perchlorate.

Conclusions

The results of this study suggest that thiocyanate and smoking can have marked impacts on the association between perchlorate, iodine uptake in the thyroid, and the production of T_4. The results also provide an example of how an environmental chemical exposure could potentially interact with nutritional and lifestyle factors, including smoking, iodine sufficiency, and thiocyanate intake, to affect an important health outcome. In a time when chemical risk assessments are under mandate to identify and protect susceptible subpopulations, this study illustrates the need to evaluate interactions of not only chemicals but lifestyle choices, nutritional status, medications, and other factors. The results of this and other studies suggest that thyroidal effects of perchlorate are seen at commonly occurring perchlorate levels and fairly common iodine levels, and therefore could be affecting a large segment of the U.S. population. Further research is needed to confirm these findings and to identify other groups who may be particularly susceptible to the health effects of perchlorate, and information on these groups should be incorporated into public health policies aimed at preventing perchlorate toxicity.

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Intake of Iodine and Perchlorate and Excretion in Human Milk

PURNENDU K. DASGUPTA,*,† ANDREA B. KIRK,† JASON V. DYKE,‡ AND SHIN-ICHI OHIRA†

Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, Texas 76019-0065, and Department of Chemistry, Texas Tech University, Lubbock, Texas 79409-1061

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Perchlorate, thiocyanate, and iodine excretion in urine and milk of 13 breastfeeding women was investigated and the results were interpreted by a model of parallel/competitive transport of these species by the sodium iodide symporter. For each species *i*, we assumed physiological homeostasis, where $i_{T,in}$ equals the corresponding total excretion in urine and milk ($i_{e,u} + i_{e,m}$). The fraction of the total excretion that appeared in milk $f_{i,m}$ was measured and ranged from 0.394−0.781, 0.018−0.144, and 0.086−0.464 for perchlorate, thiocyanate, and iodine, respectively. The corresponding median values were 0.541, 0.053, and 0.177, respectively. The selectivity factors of perchlorate over iodide transport, and thiocyanate over iodide transport, defined as $f_{PC,m}/f_{I,m}$, and $f_{SCN,m}/f_{I,m}$, respectively, were 3.14 ± 1.20 and 0.27 ± 0.26 while $PC_{T,in}$, $SCN_{T,in}$, and $I_{T,in}$ among individuals varied 4.9, 5.0, and 8.4×, respectively. These transport selectivities are an order of magnitude lower than those indicated by in vitro studies, suggesting that the impact of both these anions on inhibiting iodide transport in milk may have been overestimated in the extant literature. On the other hand, our results showed that 12 of 13 infants did not have an adequate intake of iodine as defined by the Institute of Medicine and 9 out of 13 infants were likely ingesting perchlorate at a level exceeding the reference dose suggested by the National Academy of Science panel.

Introduction

Iodine is an essential nutrient needed for formation of thyroid hormones (TH). The need for TH is especially strong during infancy, when TH-dependent neurodevelopmental processes are still underway. Iodine is transported as iodide by a membrane protein called the sodium iodide symporter (NIS) to the thyroid gland and to breastmilk in a lactating mother through the mammary NIS. Several similarly charged anions are believed to inhibit iodide transport through the NIS by competition. While the need for iodine is undisputed, considerable debate has focused on risks posed by environmental iodine-uptake inhibitors, particularly perchlorate, exposure to which appears pervasive within the United States (*1*−*4*). The affinity of perchlorate and two other common iodide-transport inhibitors, thiocyanate and nitrate, for Chinese hamster NIS-expressing cells was studied in vitro by Tonacchera et al. (*5*), who concluded that perchlorate is transported by the NIS with a selectivity 30-fold greater than that for iodide. Even more recent in vitro transport experiments with rats or with human NIS expressing cells in vitro have shown that in the presence of perchlorate the transport of iodide can be significantly delayed (*6*).

While thiocyanate and/or nitrate have been discussed as posing greater risk of low iodine uptake (*7, 8*) based on the selectivity factors for the NIS determined in vitro (*5*) and projected dietary intake amounts, the merit of this argument, with specific reference to breastfed infants may be doubtful. Little nitrate is excreted in milk and bears little relationship to dietary nitrate. Having lactating mothers consume 45 and 100 mg of nitrate a day raised breast milk nitrate levels to 5.1 and 5.2 mg/L, respectively, relative to 4.4 mg/L when they were fed no additional nitrate at all (*9*).

For thiocyanate, either urinary excretion or ingested amounts may not provide a reliable index of the circulating levels of thiocyanate seen by the mammary NIS. Urinary excretion may not reflect circulating levels because in part thiocyanate is formed in vivo from cyanide (*10*), present in certain foods (*11*), and formed during protein metabolism (*10*). In smokers, cigarette smoke is an important source of HCN (*12*). The cyanide to thiocyanate conversion primarily takes place in the liver and the kidney (*13*). On the other hand, ingested thiocyanate is known to be oxidized by a variety of mechanisms (*14*) and forms various adducts (*15*). Of interest is that thiocyanate also has benefits: its *lactoperoxidase*-mediated oxidation products are powerful antibacterial agents (*16*−*18*) and in infants may provide protection against the human immunodeficiency virus (*19*).

There is no universal agreement on the extent of threat posed by perchlorate in breast milk (*20*−*23*). There is also no conclusive data as to if and to what extent perchlorate inhibits iodide transport to human milk. Extrapolation from mouse NIS experiments to a human mother−infant pair is tenuous, especially when such in vitro experiments involve concentrations far removed from reality and perchlorate is known to be transported through the NIS in a manner different from that of iodide (*6*).

In the present paper, we try to ask this question with a cohort of breastfeeding mothers: Does perchlorate inhibit iodide transport to milk? If so, with what selectivity factor and how much does it vary among individuals?

Experimental Section

Cohort. Fifteen lactating women participated in the study, having given informed consent under a protocol approved by the University of Texas at Arlington. The prelabeled sampling kit given to subjects contained a waterproof pen for recording sample information directly on the appropriate tube. Thirteen sample sets were returned following instructions but the completeness of the sample sets varied (see Supporting Information (SI) for details). The 14th sample set was labeled by the participant with water-labile ink that became illegible and mostly could not be used. The 15th participant was found to have substituted formula for at least one of the purported breast milk samples; we chose to discard the entire sample set. Donors were 24−34 years old; one was Hispanic, one was Asian, and one described herself as of both Asian and Caucasian origin; the rest were Caucasian. No subjects reported smoking or living with a smoker. The participants were specifically asked and reported not taking any prescription medicine, having no known thyroid disease or taking any form of a thyroid medication. Donors were in varying stages of lactation with infants ranging in age from 55−253 days (on the first sample collection day). These and

* Corresponding author e-mail: Dasgupta@uta.edu.
† The University of Texas at Arlington.
‡ Texas Tech University.

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other details of the cohort, including iodized salt use status, are noted in Table S1 in the SI.

Sample Collection. Each subject was provided with a prelabeled kit with tubes color-coded for different sample types (50 mL capacity capped polypropylene centrifuge tubes, P/N 89004-364, VWR Scientific, all from one manufacturer lot) and 24 h urine collection bottles (high density polyethylene, P/N 82028-222, VWR). Iodide, thiocyanate, and perchlorate were measured in replicate in container extracts; collection tubes were extracted with 10 mL of ultrapure water, and 24 h urine collection bottles were extracted with 500 mL of ultrapure water. Iodine and thiocyanate content in both extracts were below the respective limits of detection (LOD) of 0.1 and 0.01 μg/L. Perchlorate concentration in the urine collector extract was also below the LOD of 0.005 μg/L. Perchlorate concentration in the 10 mL collection tube extracts averaged 0.17 ± 0.035 μg/L ($n = 5$), the highest measuring 0.216 ± 0.073 μg/L. Because sample volumes were usually larger than 10 mL and the determined perchlorate concentrations much higher, no efforts were made to subtract blank values.

Ideally, the subjects collected 9 sets of milk and urine samples on consecutive days or without major gaps; with a single set comprising a 24 h urine sample along with four breast milk samples collected at different times on that same day; specific time requirements for milk sampling were not imposed. All subjects collected milk samples with breast pumps. They were asked to alternate between fore and hind milk collections, if practical. While most complied with instructions and we received sample sets worth 9 days, the range of usable samples from individual subjects varied from 3 to 10 days. Details are presented in the SI.

Urine samples were collected by urinating directly into a urine collection bottle from the second morning micturition to the following day's first micturition. Total urine volume was recorded on a sample record sheet. After shaking to mix, a ~40 mL subsample was transferred to a collection tube on which the total volume was recorded. This was frozen without addition of preservatives; the rest was discarded.

All samples were frozen in the donors' home freezers as soon as possible after collection. Subjects contacted us to request that samples be picked up either at the completion of sample collection or earlier if desired. Samples were transported on dry ice to our facility, and stored at −20 °C until processed and analyzed.

Analytical Methods. *Milk.* Samples were spiked with quadruply ^{18}O labeled perchlorate ($^{35}Cl^{18}O_4$) and ^{129}I-labeled iodide, amounting to 5 and 10 μg/L in concentration, respectively, to act as internal standards for isotope dilution mass spectrometry (IDMS). Milk was processed according to Dyke et al. (*24*). The samples were analyzed for perchlorate, iodide, and thiocyanate using a TSQ Quantum Discovery Max MS/MS using a heated electrospray ionization probe (Thermo). Chromatography was performed using 25-μL filled loop injections on a Dionex DX-600 ion chromatograph on 2 mm AG-16/AS-16 column sets with a 60 mM KOH eluent at 0.25 mL/min before analysis by MS/MS. Iodide eluted at 6.6 min, SCN^- eluted at 8.9 min, and perchlorate eluted at 10.9 min. The column effluent was diverted to the MS from 4.7 to 14 min. Analyte perchlorate was monitored by the mass transition of m/z 99 → m/z 83 ($^{35}Cl^{16}O_4 \rightarrow {}^{35}Cl^{16}O_3$). The internal standard was quantitated by the mass transition of m/z 107→ m/z 89 ($^{35}Cl^{18}O_4 \rightarrow {}^{35}Cl^{18}O_3$). Thiocyanate was monitored without fragmentation: m/z 58 → 58 using $^{35}Cl^{18}O_4$ as the internal standard. We experimented with ^{13}C-labeled thiocyanate but given 1.1% natural abundance of ^{13}C, a significant response was already present at this m/z, to compensate for which a relatively large concentration of the expensive isotopically labeled internal standard had to be added. Compared to the use of labeled thiocyanate, the use of $^{35}Cl^{18}O_4$ as internal standard for thiocyanate determination produced results within ±15% and was henceforth used. Samples were analyzed for total iodine using an X Series II ICP-MS equipped with a Peltier-cooled nebulizer (Thermo). ^{127}I and ^{129}I were monitored in the "peakjump" mode using vendor-supplied software; each isotope was monitored for 50 ms and 200 sweeps were performed.

Urine. Perchlorate internal standards for IDMS (5 μg/L) were first added. The spiked samples were passed through a cation exchange resin column in H^+-form (Dowex 50Wx8, ~5 g), then pH adjusted to ~10 with ammonium hydroxide and passed though a basic alumina column (~0.5 g) and filtered with a 0.45 μm membrane filter. Samples were analyzed for perchlorate and thiocyanate by MS/MS in much the same manner as for milk. For urinary iodine analysis, samples were first filtered through a 0.45 μm pore size membrane filter (the material retained by the filter was checked to have contained no iodine within our limits of detection). The filtrate was diluted 20-fold and ^{129}I-iodide was added to attain a concentration of 10 μg/L as an internal standard for IDMS and analyzed for total iodine using ICP-MS (X Series II, Thermo).

Urinary creatinine was measured by a kinetic adaptation of the spectrophotometric Jaffe method (*25*).

Model: Methods of Estimation of Excretion Amounts and Calculation of Selectivity. The data we have available are not by themselves sufficient for a physiologically based pharmacokinetic model. As a first approximation, we invoke a standard parallel/competitive reaction model widely used in chemical kinetics (*26*) where A reacts independently with B, C, D, etc. individually to produce E, F, G, respectively. Here we assume that the role of the common reagent A is catalytically played by the NIS (it is not itself consumed). We assume that homeostasis prevails: total input and output of any of the analytes of interest are equal. We assume NIS transport processes to take place in a steady state, a constant steady state input concentration, B_{ss}, C_{ss}, D_{ss}, etc., of B, C, D (e.g., iodide, perchlorate, thiocyanate, etc., respectively) are maintained in circulation. We further assume that these steady state concentrations are linearly proportional to the total 24 h excretion (in milk and urine combined) of each respective analyte. The rate at which E is formed from B is thus proportional to $[A]B_{ss}$. If B represents iodide and E is the iodide that has been transported into milk, the amount of iodine in excreted in milk over 24 h, $I_{e,m}$, can be written as

$$I_{e,m} = k_I[A](I_{e,m} + I_{e,u}) \quad (1)$$

where $I_{e,u}$ is the amount of iodine excreted in urine during the same period and B_{ss} is proportional to $I_{e,m} + I_{e,u}$, k_I is a transport constant that includes this foregoing proportionality and $[A]$ is a measure of the extent of NIS expression. Eq 1 is readily transposed to eq 2, where $f_{i,m}$ denotes the fraction of the total excretion of species i that is excreted in milk.

$$I_{e,m}/(I_{e,m} + I_{e,u}) = f_{I,m} = k_I[A] \quad (2)$$

One similarly writes

$$PC_{e,m}/(PC_{e,m} + PC_{e,u}) = f_{PC,m} = k_{PC}[A] \quad (3)$$

We define the selectivity with which perchlorate is transported over iodide as

$$S_{PC/I} = f_{PC,m}/f_{I,m} = k_I/k_{PC} \quad (4)$$

Effectively, the selectivity is thus a ratio of these transport constants. $S_{SCN/I}$ is similarly defined.

The total daily urinary excretion for species i ($i_{e,u}$), is readily computed from the volume of the composite 24 h urine sample ($V_{u,24}$), and the measured analyte urine concentrations, $[i_u]$:

$$i_{e,u,}\ \mu g = V_{u,24},\ L\ *[i_u],\ \mu g/L \quad (5)$$

where i is I, PC, or SCN.

It is less straightforward to measure the corresponding milk excretion values; this must remain an estimate. Within a single day, the concentrations of these analytes in milk can vary significantly with respect to trace analyte content (*27*). Thus, a single sample is inadequate. We estimated milk excretion by taking the respective average analyte concentrations ($[i_{m,av}]$) of the milk samples collected on that day. These average analyte concentration data were multiplied by the volume of milk ($V_{m,24}$) that an average infant of that particular age consumes per day, as interpolated from the detailed age-dependent average milk consumption data listed by Neville et al. (*28*); this varies between 0.600 and 0.813 L for the age of the infants in our study. The daily excretion of each analyte in milk ($i_{e,m}$) was thus calculated:

$$i_{e,m},\ \mu g = V_{m,24},\ L\ *[i_{m,av}],\ \mu g/L \quad (6)$$

Homeostasis was assumed: the sum of the urinary and milk outputs equals total intake ($i_{T,in}$):

$$i_{T,in},\ \mu g = i_{e,u},\ \mu g + i_{e,m},\ \mu g \quad (7)$$

For each day, for each participating subject, we calculated $f_{i,m}$ values for i = I, PC, and SCN. The averages and standard deviations for all three $f_{i,m}$ values for each subject are listed in Table 1.

Results and Discussion

The objective of the present study was to study the excretion of perchlorate, thiocyanate, and iodine in milk and urine and relate the observed pattern within the broad framework of parallel/competitive transport by the NIS. The basic assumption is that the mammary NIS represents a controlled selective gate through which all three ions are expressed and the remainder of the intake is excreted in urine. We have admittedly neglected some other routes of excretion. The fecal excretion of iodide has been reported to be 1.2% of total excretion of iodide (*29*). Iodide is also lost in sweat but data on this are scarce. It is not clear that this route of loss is significant except in a situation where profuse sweating is induced, e.g., when major physical exertion is carried out in a hot environment (*30*).

Sample Numbers and Analysis. To resolve any ambiguities as to whether noniodide forms of iodine are excreted in either urine or milk, we used ICP-MS rather than IC-MS/MS data for iodine. Within experimental error, the two methods produced essentially the same values, suggesting that iodide is essentially the only form of iodine in both urine and milk; this aspect is not discussed here. While a cohort of thirteen may seem small, note that our analysis and discussion are based on 402 separate milk samples and 103 24-h urine samples (each analyzed by IC-MS/MS for three analytes and by ICP-MS for iodine). Each sample was analyzed in duplicate and if the results were more than 5% different from each other, the sample was analyzed a third time; averages are reported in all cases. All analytes in all samples were far above the LOD (0.1, 0.005, and 0.01 μg/L for I^-, ClO_4^-, and SCN^- by IC-MS/MS and 0.1 μg/L I by ICP-MS); typical analytical precision ranged between 2 and 2.5%. A large number of samples were needed for any given individual because previous studies suggested considerable within-day and between-day variations (*27*). We conducted pilot studies to see how well creatinine (CR) adjustment of spot urine samples can predict 24-h excretion. Such studies, to be discussed elsewhere, showed that CR adjustment could not properly predict 24-h iodine excretion and 24-h samples had to be collected.

TABLE 1. Perchlorate, Iodide, Thocyanate Fractional Expression in Milk

donor	milk samples	urine samples	total[a] iodine excreted μg (SD)	estimated infant I intake μg (SD)[b]	percent of iodine in milk (SD)[c]	total PC excreted μg (SD)	estimated infant PC intake μg/kg/d (SD)[d]	percent of perchlorate in milk (SD)	total SCN excreted μg (SD)	estimated infant SCN intake μg (SD)	percent of SCN in milk (SD)
1	37	8	109 (40.4)	13.8 (6.7)	11.6 (3.2)	22.2 (4.5)	1.2 (0.2)	41.1 (8.8)	1610 (294)	28.6 (14.6)	1.8 (0.8)
2	36	9	233 (46.6)	31.8 (8.0)	13.9 (3.1)	15.0 (1.4)	1.4 (0.2)	54.1 (5.5)	1980 (350)	143 (65.6)	7.7 (3.0)
4[e]	*35*	*9*	*110 (56.1)*	*20.8 (10.7)*	*17.7 (7.7)*	*5.9 (1.5)*	*0.7 (0.2)*	*62.2 (9.7)*	*737 (241)*	*23.1 (24.5)*	*14.4 (1.4)*
5	36	9	158 (48.6)	21.2 (10)	13.5 (5.3)	5.3 (1.5)	0.3 (0.1)	52.1 (5.4)	1560 (453)	41.2 (18.5)	2.7 (1.1)
7[e]	*30*	*8*	*223 (91.8)*	*42.6 (26.6)*	*18.3 (7.2)*	*6.8 (1.3)*	*0.4 (0.1)*	*53.7 (7.4)*	*1400 (347)*	*143 (109)*	*10.7 (8.9)*
8	27	8	286 (105)	24.8 (21.7)	8.6 (6.1)	14.2 (3.8)	1.3 (0.5)	47.5 (14.4)	3050 (921)	15.2 (17.6)	4.9 (4.7)
11	37	10	237 (137)	55.0 (32.3)	23.4 (8.2)	12.1 (6.4)	1.2 (0.9)	63.8 (16.4)	684 (187)	17.7 (7.8)	2.8 (1.5)
12[e]	*35*	*9*	*139 (31.8)*	*47.4 (21.5)*	*35.8 (16.9)*	*10.7 (9.9)*	*0.7 (0.8)*	*68.9 (19.4)*	*608 (201)*	*41.1 (26.6)*	*6.4 (4.3)*
13	9	3	913 (906)	320 (191)	45.1 (19.8)	16.9 (10.4)	2.1 (1.0)	78.1 (2.0)	1170 (216)	114 (81.0)	5.7 (1.6)
15	36	9	286 (252)	45.1 (47.3)	14.4 (4.6)	15.8 (3.8)	1.8 (0.6)	68.6 (9.1)	1415 (492)	21.1 (18.4)	1.4 (0.8)
16	28	7	607 (215)	77.4 (21.8)	15.0 (5.3)	26.0 (16.1)	1.6 (0.6)	39.4 (10.8)	1820 (1460)	189 (236)	13.9 (1.8)
18	36	9	107 (24.6)	24.2 (7.6)	22.4 (7.2)	12.5 (14.1)	0.6 (0.2)	45.5 (20.7)	819 (378)	40.8 (27.2)	5.3 (3.5)
20	20	5	138 (93.6)	61.7 (17.8)	33.5 (18.4)	8.3 (5.2)	0.9 (0.4)	55.0 (12.7)	1061 (529)	61.1 (64.1)	5.2 (4.7)

[a] This is total iodine excreted in both milk and urine; the milk volume was estimated from infant intake. [b] Computed by averaging the products of daily average milk iodine concentration and the volume of milk consumed by an average infant of that specific age in days, as interpolated from ref *28*. [c] The data in this column are not always equal to (col. 5/col. 4) × 100 because if $z = x/y$, the average of individual z-values may not equal $x_{average}/y_{average}$. [d] Based on age and gender specific infant weights interpolated from 50th percentile values in Table 11−1 in ref *41*, the reference dose is 0.7 μg/kg/d according to ref *40*. [e] Donors 4, 7, and 12 had average urinary creatinine excretions of 0.58, 0.60, and 0.54 g creatinine a day. Bingham et al. (*36*) suggests <0.6 g creatinine/d is indicative of incomplete collection. However, no specific range of creatinine excretion has been established for lactating women.

Creatinine. Mean urinary CR excretion in our cohort was 0.894 ± 0.486 g/day and fell at the low end of the reference range of 1.26 ± 0.21 g/day (*31*) for adult women. However, no reference values exist specifically for lactating women. Creatinine has been reported in milk although most of these data are quite dated (*32*−*34*). The most recent analysis of breast milk for CR was reported to be 52 μM or 7.8 mg/L (*35*). Assuming on the average <1 L milk production, milk is unlikely to be a significant excretory pathway for CR. Arguably, some subjects may not have followed instructions and the 24-h urine collections were not complete. Bingham et al. (*36*) suggested <0.6 g of CR in a 24-h urine collection to be indicative of an incomplete collection. We had three subjects, one averaged exactly at the borderline and the two others averaged 0.58 and 0.54 g/d, respectively. Since these are borderline and there are no real guidelines specifically for lactating women, we have marked these subjects as such in the data presented in Table 1, rather than omitting them altogether. Six of the individual 24-h urine collections also exceeded the high limit of the reference range. Animal protein intake can increase urinary CR. For children, animal protein intake must be taken into account when urinary CR is used for adjustment of excretion data (*37*). In cattle, it is long known that urinary CR does increase with protein intake (*38*). Further research would be necessary to characterize a reference range specifically for lactating women.

Perchlorate and Iodide Doses and Relationships. Table 1 presents data on the average $i_{T,in}$ for each of the three species for each subject during the study period and $f_{i,m}$, along with the standard deviations. According to the Institute of Medicine (IOM (*39*),), for 0−6 month and 6−12 month olds, adequate intake (AI) of iodine is 110 and 130 μg/d, respectively. Four infants at the time of the study were aged between 6 and 12 month category; all others were younger (Table S1, SI). The iodine intake data make it obvious that only one out of thirteen infants in this study receives iodine that would be judged adequate. The results for the bottom half of the pool gives cause for concern: the infants are getting 12, 16, 19, 19, 22, and 29% of the IOM suggested AI values. We would also point out that relative to virtually all other previous studies carried out with spot samples, this is the first study involving multiple samples on sequential days and should thus provide a better measure of iodine nutrition, albeit for a very limited cohort. Coupled to the iodine nutrition situation is the perchlorate intake. The National Academy of Science (NAS) panel has opined that the reference safe dose for perchlorate is 0.7 μg/kg/d (*40*). The weight of each infant was estimated by the tabulated gender specific age-dependent fiftieth percentile infant weight data (*41*) and thence the dose for each infant was calculated. In 9 out of 13 cases, the reference dose was exceeded, in the worst case, by 3×.

When we examine the fraction of $f_{PC,m}$ (range 0.394−0.781; mean(±SD) 0.562 ± 0.116) relative to $f_{I,m}$ (range 0.086−0.451; mean(±SD) 0.210 ± 0.108), it becomes obvious that perchlorate is excreted to a much greater degree in milk than is iodine. No relationships between infant age and $f_{i,m}$ were found for any of the species.

Thiocyanate: How Potent an Iodide Transport Inhibitor? On a molar basis, average $SCN_{T,in}$ was 11× and 180× higher than average $I_{T,in}$ and $PC_{T,in}$, respectively. Based on the selectivity data given for thiocyanate over iodide in ref *5* (ca. 2×) one would expect a far greater $f_{SCN,m}$ than the observed value of 0.060 ± 0.045. Possibly much of the thiocyanate is formed in the liver and the kidney (*13*) and is not reabsorbed to be seen by the mammary NIS and/or the human NIS has a different selectivity behavior compared to other mammalian NIS systems examined in vitro. In any case, the very low $f_{SCN,m}$ despite high $SCN_{T,in}$ suggests that the effective selectivity factor for thiocyanate over iodide transport must be considerably less than that suggested in ref *5*. A high selectivity of the NIS for thiocyanate over iodide and its high intake have previously been used to argue its relative importance over perchlorate as an iodide transport inhibitor (*8*).

Funderburk and Van Middlesworth (*15*) has long reported that unlike iodide, thiocyanate is *not* concentrated in human milk relative to plasma. They found that with the exception of one mother whose milk to plasma thiocyanate ratio (MPTR) value was 2.1, other subjects ($n = 7$) exhibited an MPTR of 0.40 ± 0.08. For cows, the MPTR value was higher at 1.10 ± 0.58 ($n = 6$) and for rats it was much higher at 5.26 ± 1.9 ($n = 13$). These data also serve to point out differences among different mammalian NIS systems. Free iodide in maternal plasma was recently measured to be 16 ± 4 μg/L ($n = 121$) (*42*). The median and the geometric mean values of human milk iodine concentrations for all the samples in the present study were 43 μg/L (Table 2). Taking this milk iodide concentration and a plasma concentration of 16 μg/L leads to a milk to plasma iodide ratio (MPIR) of 2.7. If we take the MPTR to be 0.40 (*15*), the thiocyanate to iodide transport selectivity will be the ratio of MPTR to MPIR, or 0.15. The data in Table 1 allow the calculation of $S_{SCN/I}$ (column 12/column 6). It may be fortuitous but the calculated median value $S_{SCN/I}$ from the data in Table 1 is also 0.15; the average (SD) value $S_{SCN/I}$ from the results in Table 1 will be 0.27 (0.26). If we take the milk iodide values from Pearce et al. (*43*), selectivity calculated from the MPTR to MPIR ratio will be <0.05. We suggest therefore that until proven otherwise in vivo, the role of thiocyanate as a iodide transport inhibitor in milk, especially vis-à-vis perchlorate, should not be overemphasized, especially when such analysis is based on urinary thiocyanate content and selectivity factors determined in vitro on nonhuman NIS systems.

Comparison of Fractions Transported. Figure 1 shows $f_{PC,m}$ and $f_{SCN,m}$ plotted against $f_{I,m}$. Within the limits of our experiments (few subjects), $f_{PC,m}$ is rather well correlated with $f_{I,m}$, consistent with the NIS being responsible for transporting both. In contrast, there is no correlation between $f_{SCN,m}$ and $f_{I,m}$. This is again consistent with the argument that thiocyanate in urine may have independent and variable sources.

Figure S1 (SI) shows plots of $f_{,m}$ vs $i_{T,in}$ for all three species. The correlations are weak and possible implications are discussed therein.

Transport Selectivity of Perchlorate over Iodide. The effective selectivity of perchlorate over iodide transport $S_{PC/I}$, (Table 1, column 9/column 6) is shown in Figure 2 for each individual along with one standard deviation error bars. While there is some variation in the $S_{PC/I}$ values determined in each day for each individual (the relative standard deviation (RSD) is lowest for donor 2 and highest for donor 8; and no significant correlation of the RSD with the absolute magnitude of $S_{PC/I}$ was found), it is to be noted that in terms of daily total excretions across individuals, the iodine excretion varied by >150× and the perchlorate excretion varied by >30×. Even after the data are averaged for each individual, these total excretions vary by ∼9× and ∼5×, respectively. Under these circumstances, the average computed $S_{PC/I}$ value of 3.14 ± 1.20 across all individuals is remarkably constant. This value is ∼10× lower than the selectivity factor of 30 reported by Tonacchera et al. (*5*). Both the Tonacchera et al. and Dohan et al. (*6*) experiments were generally conducted with high levels of transported ion concentrations where NIS availability may become a limiting factor. Such a situation may not prevail in vivo, either due to changing NIS expression as hormone levels and ratios change, or because of variations in the structure and properties of different mammalian NIS systems (*44*).

Perchlorate and Iodide in U.S. Mothers. The levels of iodine and perchlorate in milk found in this study is compared to those reported in previous studies on U.S. mothers by us

TABLE 2. Milk and Urine Perchlorate and Iodine Content of Breastfeeding Mothers[a]

source	perchlorate					iodide				
	N^b	range μg/L	average (SD) μg/L	geometric mean[c] (SEM[d]range) μg/L	median μg/L	N	range μg/L	average (SD) μg/L	geometric mean[c] (SEM[d]range) μg/L	median μg/L
					breast milk					
Kirk et al., 2005 (*3*)	36	1.4−92	15 (21)	7.3 (6.1−8.8)	3.2	24	4.5−180	63 (63)	37 (29−46)	35
Kirk et al., 2007 (*27*)	110	0.5−40	5.8 (6.3)	3.9 (3.6−4.3)	3.8	108	3.1−330	88 (81)	54 (48−59)	56
Pearce et al. 2007 (*43*)	49	1.3−410	33 (77)	11 (9.0−13)	9.1	49	27−11000	420 (1600)	140 (120−160)	140
This work	457	0.01−48	9.3 (7.5)	6.9 (6.7−7.2)	7.3	447	1−1200	120 (75)	43 (40−45)	43
Laurberg et al., 2004 (*45*)[e]						90[f]	na[h]	na	54 (49−58)	na
Laurberg et al., 2004 (*45*)[e]						50[g]	na	na	26 (23−29)	na
					urinary					
Pearce et al. 2007 (*43*)	49	0.37−130	7.7 (19)	3.6 (3.1−4.2)	3.3	49	25−920	150 (150)	110 (100−120)	110
This work	110	0.6−80	4.0 (3.4)	3.2 (3.0−3.4)	3.2	117	26−630	140 (110)	110 (100−120)	110
Laurberg et al., 2004 (*45*)[e]						90[f]	8−670	na	41	na
Laurberg et al., 2004 (*45*)[e]						50[g]	9−140	na	40	na
NHANES 2001−2002 (*46*)	26	0.19−19	3.0 (4.6)	1.5 (1.2−1.9)	1.4	27	10−800	160 (160)	99 (80−120)	110

[a] All results rounded to two significant figures. [b] Total number of samples. In ref *27* and this work, multiple samples have come from each individual. [c] Generally closer to the median than arithmetic mean; given for comparison as only parameter given in ref *45*. [d] Standard error of the mean, range is ± 1 SEM. [e] All other data from U.S.; this study was in Denmark, no perchlorate was measured. [f] Nonsmokers, all subjects in refs *3* and *27* and the present study were also nonsmokers. [g] Smokers; a minority of subjects in ref *43* were smokers but the data are pooled together here. [h] Data not available.

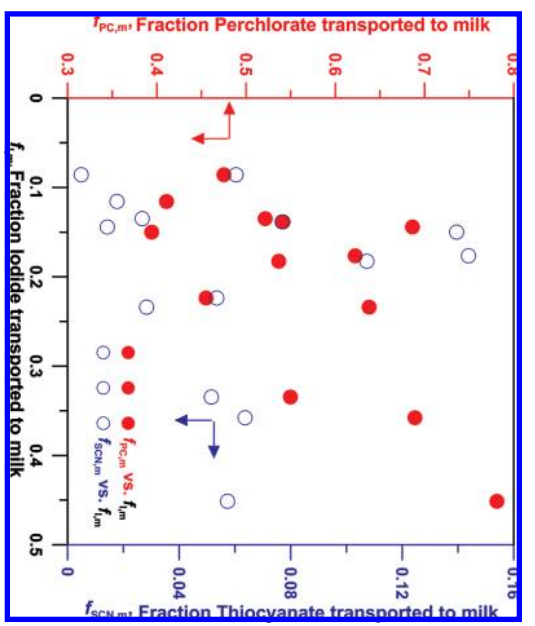

FIGURE 1. Fraction of perchlorate and thiocyanate expressed in milk. The Pearson correlation coefficient (r) for the $f_{PC,m}$ vs f_{m} data (filled circles) is 0.67; the corresponding correlation for the $f_{SCN,m}$ vs f_{m} data (open circles) is essentially nonexistent (r < 0.06).

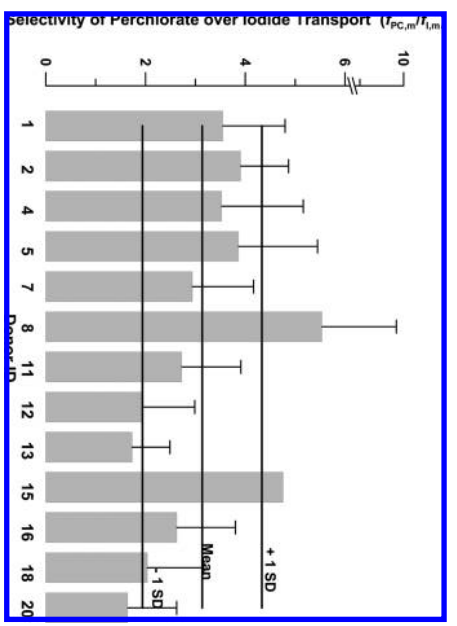

FIGURE 2. Selectivity factor of perchlorate over iodide transport as observed for various donors. Individual standard deviations are indicated as the vertical error bars. The composite means ± SD (3.14 ± 1.20) are shown as the heavy horizontal lines.

and by Pearce et al. (*43*) in Figure 3 and Table 2. The plots have only those samples for which both iodide and perchlorate data were available. Both the plots and table include some milk samples where corresponding urine samples were not available. In Table 2, we also include the data of Laurberg et al. (*45*) from Denmark and the NHANES urinary data for lactating mothers (*46*) in Table 1.

Any comparison among studies is limited by the different study populations. In addition, this is the first time milk iodine data are being reported by us as total iodine by ID-ICP-MS (our previous studies relied on iodide measurement by IC-MS with isotopically labeled perchlorate as internal standard). For studies that relied on one-time spot samples (all but this study and ref *27*), there is also the problem of large temporal variability for the same individual (*27*). Recently Andersen et al. (*47*) concluded that estimating population iodine excretion requires 100−500 urine samples and for an individual, ≥12 urine samples are needed to obtain ± 20% accuracy. If this applied to milk, only the present data and the data set in ref *28* will qualify.

Nevertheless, with the exception of some samples containing high milk iodine concentrations in the present study (all from the same donor) and some samples containing high

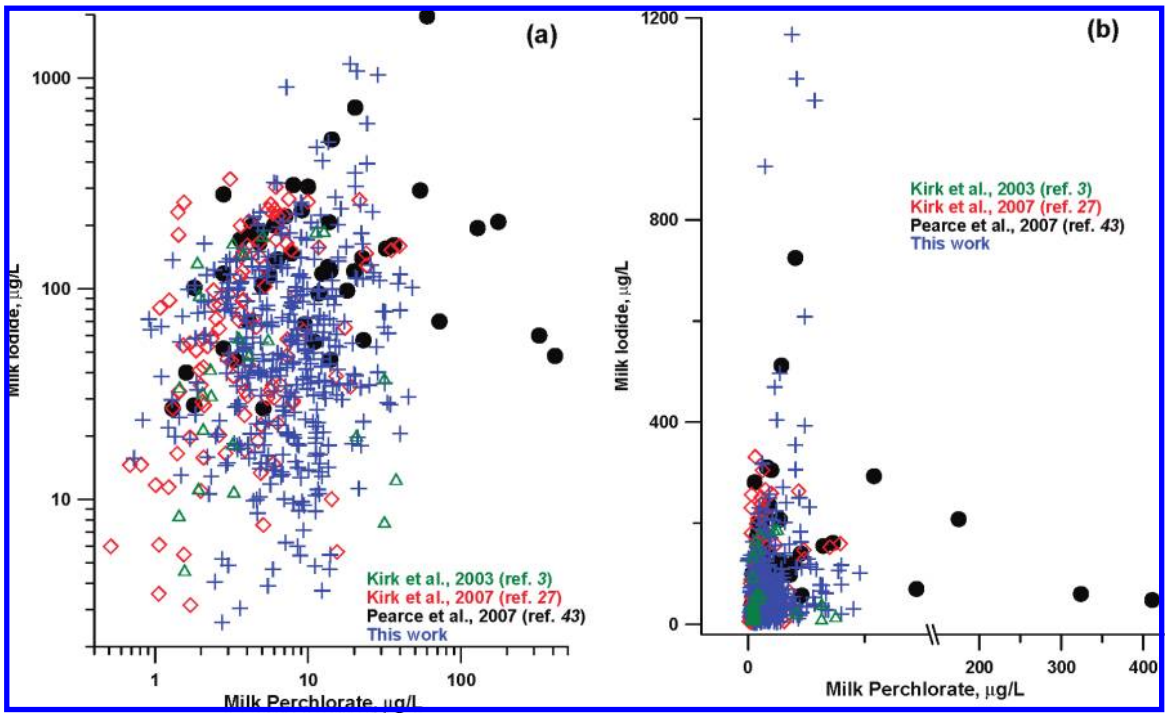

FIGURE 3. Breast milk iodide and perchlorate levels from four studies conducted in the U.S. thus far: (a) logarithmic and (b) linear axes. Note that the axes intersection point does not correspond to 0,0 in either plot. To provide greater visibility, four points (two too low perchlorate, one too low I, and one too high I in (a), and two points in (b) (both too high I) were not plotted.

concentrations of perchlorate and one containing very high iodine concentration (not in the plot) in the Pearce et al. (*43*) study, the spread of the data from the different studies do substantially overlap. The median urinary iodine values agree closely between this study (*43*) and the study reported in ref *47*. The median urinary perchlorate values also agree closely between this study and ref *43* but *46* has a lower value. Median breastmilk perchlorate value is only marginally higher in *43* compared to this study but median breastmilk iodine is much higher in *43*. While the median or average values of both perchlorate and iodide concentrations in ref *43* are significantly higher, both the present study and that in *43* were largely regional, underscoring the need for a large, nationwide study. In the U.S. Food and Drug Administration's Total Diet Study (*48*), 25−30 and 40−45 year old women were estimated to have a daily intake of 5.4−6.8 and 5.9−7.3 μg of perchlorate and 148−196 and 145−197 μg of iodine, respectively. This substantially underestimates the median daily perchlorate intake (excretion) of our cohort. At 223 μg/d, the iodine intake (excretion) of our cohort is also slightly higher than that predicted above, but both are substantially lower than the desired value of 290 μg/d.

When we first pointed out the widespread occurrence of perchlorate in U.S. mother's milk (*3*), we were criticized (*22*) for the statement regarding a breast milk iodide vs perchlorate plot that *it is remarkable that not a single datum fell within the high perchlorate high iodide quadrant*. After several hundred milk analyses later, albeit without the benefit of any lines drawn to define "high" and "low", not a single datum still falls in the high perchlorate—high iodide sector, most obvious from Figure 3b. This continues to suggest that in real mothers perchlorate *does* inhibit the transport of iodine into milk and because of competitive inhibition both analytes cannot be high at the same time.

Even though the number of subjects was not large, in terms of the number of total samples analyzed, this is the most extensive study on the topic. The majority of the infants in our study ingested perchlorate at a level that exceeds the NAS reference dose. It is not clear how and if the NAS reference dose takes into account iodine intake, or for that matter the perchlorate/iodide selectivity of the NIS. While the reference dose thus remains a gray area, we were intrigued, and dismayed, to note that while little of the maternal iodine (21.0 ± 10.8%) finds its way to milk, the bulk of the perchlorate intake (56.2 ± 11.6%) ends up in milk. The low iodine intake in this small cohort of breastfed U.S. infants is disconcerting. It is doubtful that these infants would have received adequate levels of iodine even without the influence of iodide transport inhibitors. Most of the donors in this study came from the local metropolitan area. We will report on this elsewhere in more detail but our analysis of their drinking water generally did not indicate drinking water to be a major contributor to their perchlorate intake.

Acknowledgments

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Supporting Information Available

Table of cohort description, sample details and irregularities, figure showing fraction of each species transported in milk as a function of the total intake and accompanying description. This material is available free of charge via the Internet at http://pubs.acs.org.

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Assessing the outlook for perchlorate remediation

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BRUCE E. LOGAN

Promising technologies for treating this widespread water contaminant are emerging.

Perchlorate (ClO_4^-) may appear to be just another addition to a growing list of halogenated chemicals that persist in the environment, but the chemical characteristics of this inorganic anion make it quite unusual. Typical chlorinated aliphatic compounds, such as trichloroethylene (TCE), are relatively insoluble carbonaceous compounds, strictly used for industrial purposes. They are volatile, adsorb, and are reduced by metals such as zerovalent iron. In contrast, perchlorate is a highly soluble inorganic anion (2.09 kg/L for $NaClO_4^-$) (*1*) that adsorbs poorly to mineral surfaces and activated carbon and is not retarded during groundwater transport.

The resulting perchlorate contamination is difficult to treat. Compared with an average useful lifetime of 18 months for TCE removal, granular activated carbon (GAC) columns used at the Texas Street Well Facility in Redlands, CA, have an operational lifetime of about one month for perchlorate removal, making remediation of the anion uneconomical. This well facility and 29 others in California have been shut down until cost-effective methods are found for treating perchlorate-contaminated water (*2*).

The U.S. EPA has identified perchlorate users and manufacturers in 44 states and releases in 18 states (Figure 1), estimating that perchlorate affects the drinking water of 15 million people in the United States (www.epa.gov/safewater/ccl/perchlor/r9699fac.pdf). Widespread perchlorate contamination of groundwaters only became known when a new ion chromatography (IC) method lowered the anion's detection limit in water from 400 parts per billion (ppb) to 4 ppb. The first survey of perchlorate in groundwaters in California in 1997 using the new IC method found perchlorate in 109 of 428 wells—27% of those surveyed—and concentrations at 33 sites above the state's action level of 18 ppb. A more recent survey of 367 groundwater wells in 17 states found perchlorate in only 9 wells at <4–7 ppb (*3*).

Perchlorate is manufactured in large quantities as ammonium perchlorate, primarily for use as an oxidizer in solid rocket propellants. It is also used in fireworks, batteries, and automobile air bags. It occurs naturally in small concentrations in nitrate deposits in Chile and has been found in fertilizers derived from these deposits but not in other fertilizers (*4–6*). Major sites of perchlorate groundwater contamination are associated with nonregulated past releases of perchlorate salts by manufacturers located in arid regions in the western and southwestern United States. For example, a perchlorate concentration of 1680 ppb has been found in the Nevada wash, a storm drainage canal feeding Lake Mead, part of the Colorado River serving major cities in Utah, Arizona, and California. Perchlorate concentrations in Lake Mead as high as 165 ppb have been reported, and monitoring well data from manufacturing sites where perchlorate was produced show concentrations as high as 0.37% w/w (*3*).

The health effects debate

Perchlorate is unique because it has been used as a medical treatment for Graves' disease (hyperthyroidism). At high oral doses, perchlorate competes with iodide in the thyroid and reduces hormone production. The health impact of perchlorate at low doses is unresolved. On the basis of health effects of perchlorate that is administered therapeutically, EPA determined that the oral reference dose

(RfD) for perchlorate is 0.5 mg/kg/d. This is the level used by the California Department of Health Services to set a drinking water action level of 18 ppb.

EPA's National Center for Environmental Assessment prepared a draft toxicological review document for perchlorate in 1999. The final report was scheduled for release in June 2000 but has been delayed. The draft considers carcinogenic, neurodevelopmental, developmental, reproductive, and immunotoxic effects of perchlorate exposure. The anion is not genotoxic (*2*). The draft contains a tentative revised RfD of 0.9 mg/kg/d, but an EPA-funded review performed by a team of scientists concluded that further work is needed before a final RfD can be definitively established.

The drinking water standard could therefore be as high as 32 ppb based on the revised RfD (*2*), but at least one environmental group has advocated regulation down to a 4.3-ppb contamination level (*7*). It may be another 12 years before perchlorate can be federally regulated in a uniform manner (*2*). Meanwhile, states have been left to set their own limits, such as 14 ppb in Arizona and 22 ppb in Texas. Site-specific limits are being set near the undetectable limit by IC. A recent agreement between EPA (Region 9) and Aerojet at a Superfund site in Rancho Cordova, CA, calls for treating water to less than 5 ppb. EPA is regulating perchlorate levels in water down to a 1.5-ppb contamination level in Region 1.

Physical treatment options

Although there are many treatment options, there is no obvious treatment technology for removing perchlorate from water. Perchlorate can be removed using ion exchange (IX), but some resins remove all other anions before binding perchlorate, making the final product water too corrosive for use in water distribution systems without restoring water hardness. Perchlorate binds tightly to strong base anion resins so that very high salt concentrations (7–12%) are needed for resin regeneration (*2*). Disposing of these IX brines can be problematic because the perchlorate is concentrated but not destroyed. One commercially available IX treatment process includes a module that uses a high-temperature, rare-earth metal for perchlorate reduction to chloride (*2*). An improved method for resin regeneration using material that selectively binds perchlorate over other anions has been developed, but this technology has only been demonstrated in the laboratory (*8*). Additional IX resins for removing perchlorate are being developed, along with techniques that extend GAC bed life, through in situ resin regeneration.

Ambient temperature treatment methods using metals, such as zerovalent iron, which successfully remediate chlorinated aliphatic compounds, such as TCE, do not work for perchlorate. That perchlorate does not react with zerovalent iron is not surprising to most inorganic chemists. The anion is extraordinarily inert in aqueous solutions and is used by chemists to provide a constant ionic environment in otherwise reactive solutions. Perchlorate has long half-lives with transition metal complexes such as $[Ti(H_2O)_6]^{3+}$ (0.17 yr) and $[V(H_2O)_6]^{2+}$ (53 yr). The organometallic compound, methylrhenium trioxide, has produced a reasonably short half-life of 2.3 min, but this requires solution conditions quite different from typical groundwaters (*2*). Recent studies with rhenium catalysts and sulfides show greater promise for perchlorate reduction, although water treatment technologies based on these new catalysts are not available (*9*).

Microbiological degradation

Bioremediation of perchlorate-contaminated waters is promising (*10, 11*). Although perchlorate only occurs naturally in Chile, bacteria capable of perchlorate degradation appear to be widely distributed in nature at concentrations ranging from one to thousands of bacteria per gram of water, wastewater, sediment, and soil (*12, 13*). Perchlorate is used as an electron acceptor by some bacteria for cellular respiration and is degraded completely to chloride ion (Figure 2). The bacteria that degrade perchlorate are diverse. Almost all of them fall within new species' classifications based on a 16s rDNA classification scheme—a recombinant DNA methodology based on the 16s gene, which can be used to assess the

phylogeny of bacteria. Most perchlorate-respiring microorganisms (PRMs) are capable of functioning under varying environmental conditions and use oxygen, nitrate, and chlorate (ClO_3^-)—but not sulfate—as a terminal electron acceptor. Perchlorate can be successively degraded to chlorate and then chlorite (ClO_2^-) by a novel chlorate reductase respiratory enzyme. A chlorate-respiring bacterium was the first isolate shown to be capable of benzene degradation, although only under denitrifying, and not chlorate-reducing, conditions (*14*).

Because chlorite is toxic to bacteria, the key to bacterial growth using chlorate and perchlorate is the presence of chlorite dismutase, a nonrespiratory enzyme that catalyzes the disproportionation of chlorite to O_2 and Cl^-. Rates of chlorite disproportionation by chlorite dismutase are greater than chlorate reduction by chlorate reductase and oxygen utilization by cytochromes; the slowest step is perchlorate reduction. As a result, no intermediates ordinarily accumulate in solution during perchlorate biodegradation. The heme-based chlorite dismutase is produced in such large quantities by PRMs that the addition of chlorite to a concentrated cell suspension grown anaerobically on chlorate or perchlorate will produce visible frothing due to O_2 release. The release of small amounts of dissolved oxygen by the perchlorate degrader *Dechlorimonas agitatus* CKB using chlorite, but not chlorate, has been shown to support naphthalene degradation by *Pseudomonas sp*. JS150 (*15*).

Microbial reduction of perchlorate supports very high growth rates of some PRMs. Although kinetic data are scarce, the maximum observed growth rates of two isolates (*Dechlorosomas sp.* KJ and PDX) using perchlorate (0.14 h^{-1} and 0.21 h^{-1}, respectively) were found to be only slightly less than or equal to growth rates using oxygen (0.27 and 0.28 h^{-1}, respectively) or chlorate (0.26 and 0.21 h^{-1}, respectively) (*16*).

The reason why these bacteria are so widely distributed in the environment and can grow so quickly using perchlorate is unknown. It may be due to the relatively greater abundance of chlorate in the environment than perchlorate. Chlorate has been produced for many years by the pulp and paper industry from bleaching operations and was used as an algicide. Some bacteria can respire using chlorate but not perchlorate. Chlorate reducers are up to 50 times more abundant than perchlorate reducers in water and soil samples (*12, 13*). The maximum chlorate reductase enzyme reduction rate is 3 times faster with chlorate than with perchlorate (*17*). Thus, it appears that perchlorate degradation may be linked to the ability of some respiratory enzymes to substitute perchlorate for chlorate.

Engineering green degradation

Biodegradation of perchlorate in engineered systems offers the greatest potential for inexpensive and complete perchlorate degradation. Several reactor technologies have been shown to treat perchlorate, for which four patents have been obtained (*18-21*). Table 1 lists treatment methods and bioreactor systems for degrading perchlorate (*2, 22–29*).

Suspended growth systems were first used to treat the high concentrations of perchlorate produced from washing rocket casings during replacement of solid rocket propellant. Since then, research has concentrated on reducing perchlorate from the low-parts-per-million (ppm) and parts-per-billion levels to nondetectable concentrations. Two bioreactor types—fluidized- and fixed-bed reactors—have been used.

In a fluidized-bed reactor, the support medium (usually GAC or sand) is kept suspended and mixed in the reactor by using a high recycle flow rate. The biomass on the packing is kept uniform in the reactor by mixing, and biomass thickness is controlled by shear and particle collisions. The main system disadvantage is the pumping cost for maintaining high recycle rates. Fluidized beds have completely removed perchlorate under laboratory and field conditions at influent perchlorate concentrations of 6–13 ppm using an ethanol feed (*2*). In a fixed-bed bioreactor, the biofilm support medium (sand or plastic media) does not move during water treatment. Biomass buildup on the packing requires that the system be

periodically backwashed to prevent clogging.

Using biological treatment for processing drinking water is not new. Biological denitrification for drinking water pretreatment has been practiced in Europe for some time now and is used at one location in the United States. All recent studies reducing perchlorate concentrations in contaminated water to acceptable drinking water levels have used acetic acid/acetate or hydrogen gas as substrates. Acetic acid is relatively inexpensive but, unlike alcohols and sugars, it is not lost to fermentation. It remains to be seen if the public would accept this for addition to drinking water supplies. Packed-bed reactors using acetic acid have been extensively tested in the laboratory and are currently being evaluated in the field at the pilot scale.

The disadvantage of using an organic feed is that the unoxidized substrate could remain in the drinking water. Residual substrate can stimulate bacterial growth in water distribution systems and contribute to the formation of disinfection byproducts in water disinfected with chlorine.

Although residual organic matter can be biologically removed in aerobic filters, several investigators are looking at using hydrogen gas as an electron donor for perchlorate biodegradation. Like oxygen, hydrogen is only sparingly soluble in water. Little biomass is expected from unused dissolved hydrogen because of the gas's low solubility and experiments showing that biomass yields using hydrogen gas are low. To overcome low solubility, different methods have been used to supply hydrogen to perchlorate-degrading biofilms, including unsaturated water flow over biofilm particles in a partial (5%) hydrogen atmosphere, pressurized hydrogen gas injection into the feed, and membranes for gas sparging (*22, 23*). Hydrogen reactors for perchlorate degradation have only received laboratory-scale testing.

Perchlorate is completely removed in both acetate- and hydrogen-fed packed-bed reactors, but at rates dependent on the perchlorate concentration in feed water (*30*). There are now enough perchlorate bioreactor studies that engineers can scale the size of systems needed for perchlorate removal. Overall perchlorate removal rates are a first-order function of perchlorate concentration in the fixed-bed reactors. Thus, the most highly contaminated streams have the most rapid reaction rates in fixed-bed bioreactors.

In situ degradation

In situ bioremediation of perchlorate-contaminated waters eliminates the need for aboveground treatment. Anoxic conditions necessary for in situ perchlorate treatment can be established either by creating permeable reactive biobarriers containing high concentrations of organic matter, or by injecting substrates into the ground.

In one example, groundwater leaving a MacGregor, TX, site, at which soils contained 23–1,800,000 mg/kg perchlorate concentrations, was contaminating nearby surface waters. By digging trenches and directing the water flow through biobarriers containing gravel and organic amendments (compost, vegetable oil, or cottonseed), perchlorate was removed from a 27,000-ppb level down to nondetectable levels (4 ppb) (*31*). Adding lactate to perchlorate-contaminated soils achieves perchlorate removal in a few days under optimal laboratory conditions (*13*). Lactate can be dissolved in water or supplied as a polylactate compound that slowly dissolves (*32*). In Sacramento, CA, pulsed injection of acetate into a deep aquifer (100 ft) removed perchlorate from contaminated water from 12,000 ppb to below the detection limit. The hydrogen evolved from anaerobic fermentation of lactate and other substrates can also drive the reductive dehalogenation of chlorinated aliphatic compounds, such as TCE, which are common copollutants at perchlorate-contaminated sites (*32*).

Outlook and challenges

A pilot-scale study at the Naval Weapons Industrial Reserve Plant in McGregor, TX, evaluated ex situ treatment of perchlorate-contaminated soil and groundwater in a fixed-bed anaerobic bioreactor. ENSAFE, INC.

Despite the unique nature of the perchlorate anion, the outlook for remediating perchlorate-contaminated water looks promising. For small volumes of water, new IX technologies that selectively remove perchlorate from water show the greatest promise. Chemical methods can degrade perchlorate in regenerated systems that use NaCl brines, and it has recently been shown that perchlorate can be biologically degraded even in high salt solutions (11%), which are typical for these brines (*33*). For treating widespread contamination of drinking water, in situ and ex situ (see photo on preceding page) biological systems appear to be the most cost-effective solutions. These systems are in the developmental stage for drinking water applications, but successful laboratory and field tests demonstrate the potential that this technology has for treating perchlorate-contaminated water and reducing contaminant concentrations to potable water levels. Although the full costs of these systems remain unknown, they are certain to increase current drinking water treatment costs.

Many sites contaminated with perchlorate also contain high nitrate levels and low concentrations of chlorinated aliphatics, such as TCE. Nitrate is removed along with perchlorate in bioreactors because most perchlorate reducers are denitrifiers. The effect of a perchlorate-reducing environment on TCE degradation and on downstream processes, such as those using GAC columns, also need to be investigated, although there appear to be no technical roadblocks for process trains using both bioreactor and GAC systems. Biological drinking water treatment systems, however, have not yet been approved for use for public water systems, and it remains to be seen if the public will accept the use of these treatment systems for degrading perchlorate. What does seem certain is that perchlorate will remain in groundwater sources used for drinking water supplies for a long time unless steps are taken to treat the aquifers or the water removed from these sources.

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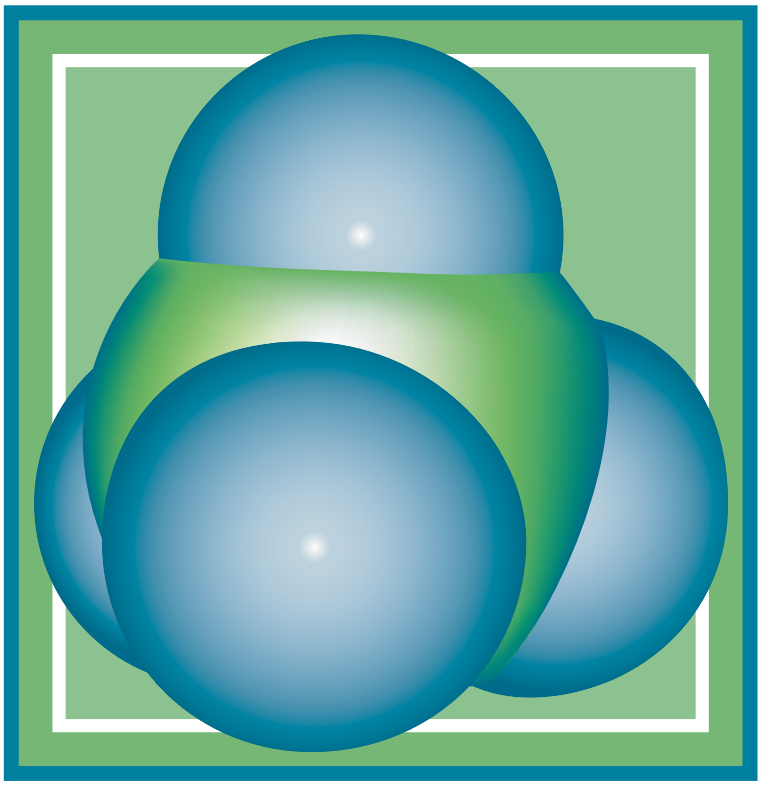
Bruce E. Logan *is the Kappe Professor of Environmental Engineering in the Department of Civil and Environmental Engineering at the Pennsylvania State University, University Park, PA; e-mail: blogan@psu.edu.*

Technology Overview

Perchlorate: Overview of Issues, Status, and Remedial Options



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Prepared by
The Interstate Technology & Regulatory Council
Perchlorate Team

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Established in 1995, the Interstate Technology & Regulatory Council (ITRC) is a state-led, national coalition of personnel from the environmental regulatory agencies of some 40 states and the District of Columbia, three federal agencies, tribes, and public and industry stakeholders. The organization is devoted to reducing barriers to, and speeding interstate deployment of, better, more cost-effective, innovative environmental techniques. ITRC operates as a committee of the Environmental Research Institute of the States (ERIS), a Section 501(c)(3) public charity that supports the Environmental Council of the States (ECOS) through its educational and research activities aimed at improving the environment in the United States and providing a forum for state environmental policy makers. More information about ITRC and its available products and services can be found on the Internet at **www.itrcweb.org.**

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Perchlorate: Overview of Issues, Status, and Remedial Options

September 2005

Prepared by
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Perchlorate Team

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EXECUTIVE SUMMARY

Perchlorate is both a naturally occurring and manmade anion consisting of chlorine bonded to four oxygen atoms (ClO_4^-). It is typically found in the form of perchloric acid and salts such as ammonium perchlorate, potassium perchlorate, and sodium perchlorate. This introduction provides basic information regarding perchlorate and perchlorate contamination. It is important to understand that information on perchlorate is continually being updated and that this document provides a snapshot in time of the current perchlorate situation.

While perchlorate was once thought to occur naturally only in one location in Chile, ongoing study has found naturally occurring perchlorate in other locations as well. As a manmade compound, it has been manufactured since before the turn of the last century, primarily for use in defense activities and the aerospace industry.

Highly soluble and mobile in water, perchlorate is also very stable. Most of the attention focused on perchlorate contamination concerns groundwater and surface water contamination. However, perchlorate can also contaminate soil and vegetation. The potential for perchlorate contamination in drinking water and food supplies is a human health concern because it can interfere with iodide uptake by the thyroid gland and, through this mode of action, result in decreased thyroid hormone production.

In general, past management practices did not prevent the release of perchlorate to the environment because it was not recognized or regarded as a contaminant of concern. Widespread perchlorate contamination in the United States was observed after the spring of 1997, when an analytical method with a reporting limit of 4 ppb was developed. Additional sampling and analysis techniques have since been developed that can detect perchlorate at concentrations of 1 ppb and lower.

A variety of remediation technologies are currently commercially available and being used for perchlorate remediation. These remediation technologies fall into two broad categories—ion exchange and biological processes. The majority of these treatment technologies have been applied to remediation of groundwater; however, biological processes are also being applied to the remediation of soils. This document provides an overview of the commercially available technologies (and summaries of emerging technologies) still at the bench or pilot-scale stage.

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PERCHLORATE: OVERVIEW OF ISSUES, STATUS, AND REMEDIAL OPTIONS

1. INTRODUCTION

This overview document is designed primarily for state[1] regulators and stakeholders who may not be familiar with issues related to perchlorate. This introduction provides basic information regarding perchlorate and perchlorate contamination. Subsequent chapters of this document provide more detailed information regarding sources of perchlorate (Section 2), sampling and analysis techniques (Section 3), a discussion of the risk-related issues concerning perchlorate contamination (Section 4), risk management strategies and regulatory status (Section 5), and a summary of current remediation technologies (Section 6). It is important to understand that information on perchlorate is continually being updated and that this document provides a snapshot in time of the current perchlorate situation.

1.1 What Is Perchlorate?

Perchlorate is an anion consisting of a chlorine atom bonded to four oxygen atoms (ClO_4^-) (Figure 1-1). It is typically found in the form of perchloric acid and salts such as ammonium perchlorate, potassium perchlorate, and sodium perchlorate. Perchlorate is usually found as the anion component of a salt most often associated with one of the following common cations: ammonium (NH_4^+), sodium (Na^+), or potassium (K^+). The resulting salts are ammonium perchlorate (NH_4ClO_4), potassium perchlorate ($KClO_4$), and sodium perchlorate ($NaClO_4$).

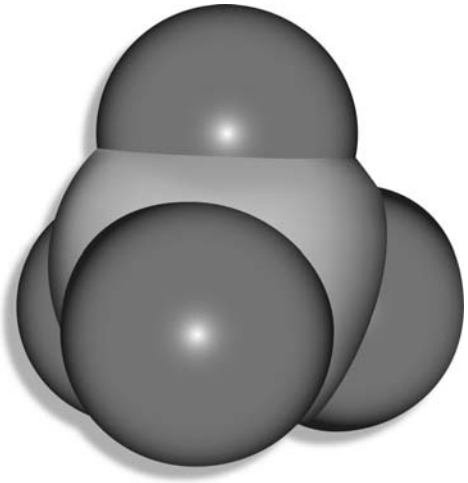

Figure 1-1. Perchlorate anion.

Table 1-1 lists the physical properties of the common perchlorate compounds. Perchlorate exhibits the characteristics of high solubility and mobility in water, as well as being very stable. These characteristics lead to the formation of long and persistent contaminant plumes when it is released into either groundwater or surface water. Like the water contaminant nitrate, perchlorate is not attenuated to any great degree by soil surface chemistry. However, it can be broken down by naturally occurring bacteria in the environment.

1.2 Sources of Perchlorate

Perchlorate occurs both naturally and as a manmade compound. While it was once thought to occur naturally only in one location in Chile, ongoing study has found naturally occurring perchlorate in other locations as well. The United States Geological Survey (USGS) is currently conducting studies on natural occurring sources of perchlorate (Section 2.1).

[1] Throughout this document, the term "state" is used to refer to all regulatory entities having the general regulatory responsibilities of the states, including U.S. territories and commonwealths.

Table 1-1. Properties of perchlorate compounds

Properties*	Ammonium perchlorate (NH_4ClO_4)	Potassium perchlorate ($KClO_4$)	Sodium perchlorate ($NaClO_4$)	Perchloric acid ($HClO_4$)
CAS#	7790-98-9	7778-74-7	7601-89-0	7601-90-3
Molecular weight	117.49	138.55	122.44	100.47
Color/form	White orthorhombic crystal	Colorless orthorhombic crystal or white crystalline powder	White orthorhombic deliquescent crystal	Colorless oily liquid
Taste/odor	Odorless	Slightly salty	Odorless	Strong odor
Density/specific gravity	1.95 g/cm^3	2.53 g/cm^3	2.52 g/cm^3	1.77 g/cm^3
Solubility	200 g/L water at 25ºC	15 g/L water at 25ºC	2096 g/L water at 25ºC	Miscible in cold water
Sorption capacity	Very low	Very low	Very low	Very low
Volatility	Nonvolatile	Nonvolatile	Nonvolatile	Volatile
Octanol/H_2O partition coefficient (log K_{ow})	–5.84	–7.18	–7.18	–4.63
Vapor density (air = 1)	No information	4.8	No information	3.5
pH	5.5–6.5	6.0–8.5	7.0	Highly acidic

**Vapor pressure and evaporation rate are insignificant and therefore not included in this table.*

Although perchlorate was first manufactured commercially around the turn of the last century, its widespread manufacture in the United States began only in the mid-1940s. Since then, it has found widespread use in industry. Approximately 90% of perchlorate compounds, primarily ammonium perchlorate, are manufactured for use in defense activities and the aerospace industry. For example, ammonium perchlorate is used in a variety of commercially available products and industrial processes (Section 2.2). Besides salts of perchlorate, other forms of perchlorate exist, such as perchloric acid ($HClO_4$), reagents for experimental use, and some fertilizers. Perchlorate has been used medically to control hyperthyroid conditions and Graves disease in the human thyroid (Wolf 1998).

1.3 Perchlorate Occurrences

Advances in analytical chemistry have allowed for the detection of perchlorate at gradually lower levels since 1997. More sensitive analytical detections have increasingly proven perchlorate to be more widespread in the environment than previously thought. In addition, recent investigations indicate that natural sources of perchlorate exist in the environment. As a result, contamination of soil, vegetation, groundwater, and surface water has been detected in a number of states.

In general, past management practices did not prevent the release of perchlorate to the environment because it was not recognized or regarded as a contaminant of concern. Widespread perchlorate contamination in the United States was observed after the spring of 1997 when an analytical method with a reporting limit of 4 ppb was developed. Additional sampling and analysis techniques have since been developed that can detect perchlorate at concentrations of 1 ppb and lower (Section 3.2).

USEPA has monitored for perchlorate in public drinking water systems through the Unregulated Contaminant Monitoring Rule (UCMR) program. Under UCMR 1, detections of perchlorate were analyzed using USEPA Method 314.0 at approximately 2,800 large public water systems and a representative sample of 800 (out of 66,000) small public water systems. As of January 2005, perchlorate had been detected in 153 public water systems and 25 states across the United States (USEPA, n.d.). Geographically, the highest density of perchlorate detection is in southern California, west central Texas, along the east coast between New Jersey and Long Island, and in Massachusetts. The apparent absence of perchlorate occurrence in some regions may merely be because relatively few sources have been sampled. More intensive sampling, particularly of small systems, may detect perchlorate-contaminated drinking water sources in these regions (Brandhuber and Clark 2005). Monitoring under UCMR 1 has been completed. The proposed rule for monitoring of perchlorate and other contaminants under UCMR 2 was published in August 2005. The proposed rule includes the list of proposed contaminants and methods for monitoring (Federal Register 2005). Monitoring for perchlorate and other contaminants under UCMR 2 is proposed for 2007–2011.

Additional sampling efforts have been undertaken by the Department of Defense, other federal agencies, site owners, and universities. The majority of detections in drinking water have not been associated with USEPA-identified perchlorate releases, and most detections have been below 12 ppb (Figure 1-2).

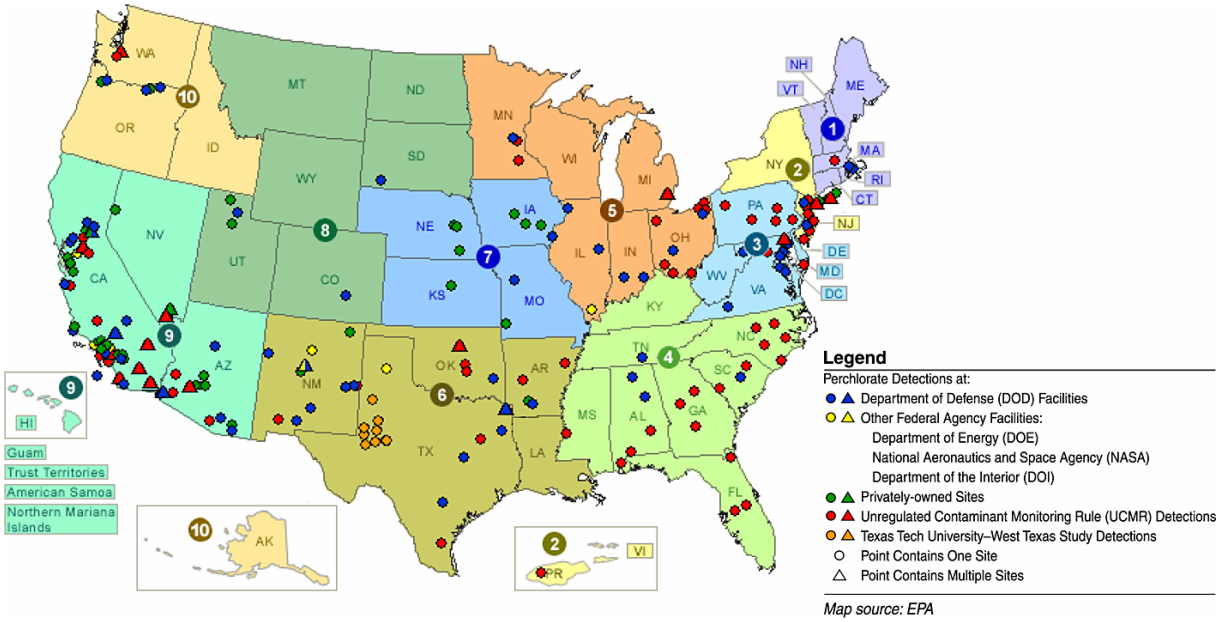

Figure 1-2. National perchlorate detections as of September 2004 (USEPA 2004a).

The greatest amount of attention to perchlorate contamination concerns drinking water; however, recent studies have also found perchlorate in the food supply. In December 2004, the U.S. Food and Drug Administration (FDA) released an initial set of exploratory data on perchlorate levels in individual samples of lettuce, milk, spring water, and bottled water (USFDA 2004a). Information on the full extent of perchlorate occurrences in the United States has yet to be determined.

1.4 Perchlorate Risk

Perchlorate is of concern because it can interfere with iodide uptake by the thyroid gland. Because iodide is an essential component of thyroid hormones, perchlorate exposure may result in decreased thyroid hormone production. Section 4 of this document discusses toxicity, exposure, and risk in detail.

1.5 Perchlorate Regulation

The U.S. Environmental Protection Agency (USEPA) established a human reference dose (RfD) for perchlorate at 0.0007 milligrams/kilogram/day (mg/kg/D) in February 2005. A reference dose is a scientific estimate of a daily exposure level that is not expected to cause adverse health effects in humans. The 0.0007 mg/kg/D RfD equates to a drinking water equivalent level (DWEL) of 24.5 parts per billion (ppb) (Section 4.4.2). A DWEL, which assumes that all of a contaminant comes from drinking water, is the concentration of a contaminant in drinking water that will have no adverse effect with a margin of safety. Because margins of safety are built into the RfD and the DWEL, exposures above the DWEL are not necessarily considered unsafe. However, DWELs are not an enforceable standard. In most cases, the standard is a maximum contaminant level (MCL), the maximum permissible level of a contaminant in water delivered to any user of a public water system.

USEPA is in the process of establishing an MCL for perchlorate. Some states have adopted advisory levels for perchlorate in drinking water, and a few are considering or are in the process of promulgating state levels. Section 5 of this document discusses the regulatory status of perchlorate in greater detail.

1.6 Perchlorate Remediation

The majority of remediation technologies associated with perchlorate contamination address perchlorate in groundwater and drinking water. This document provides an overview of proven and commercially available technologies, specifically ion exchange and bioremediation. Emerging technologies with tested bench-scale and/or pilot-scale studies, as well as those in the development stage, are also briefly discussed (Section 6). A more detailed review and discussion of perchlorate treatment technologies, including a number of case studies and associated costs, will be provided in a subsequent technical and regulatory guidance document planned by the ITRC Perchlorate Team for publication in 2006.

2. SOURCES, USES, AND OCCURRENCES

Perchlorate occurs both naturally and as a manufactured compound. Knowing the sources of perchlorate and the variety of uses it has served will help to guide perchlorate investigations. While a variety of sites where perchlorate contamination is known to occur have already been identified, it can be assumed that additional sites will be discovered as more geographical areas are tested and additional information becomes available.

2.1 Sources of Perchlorate

At this time, most naturally occurring sources of perchlorate appear to be geographically limited to arid environments. These deposits tend to be low in concentration, except for the relatively high natural perchlorate concentrations found in Chilean caliche[2] and some potash ores. In contrast, manmade perchlorate sources can be many times more concentrated than most natural sources. In environments where both types exist, research to discriminate between the two types is ongoing.

Sites that been identified with high concentrations of perchlorate contamination (in the thousands of part per billion or more) have involved manufacturing, testing or disposal of solid rocket propellant; manufacturing of perchlorate compounds; and industrial manufacturing operations where perchlorate compounds were used as reagents. In addition to covering these kinds of sources of contamination, this section will also address potential sources of manmade perchlorate that are likely to have created lower concentration perchlorate contamination. In these cases, it is assumed that the quantities of perchlorate causing the contamination are smaller or that the sources are disseminated. It should be noted that in some cases the source of perchlorate contamination has not been determined.

2.1.1 Natural Sources of Perchlorate

2.1.1.1 Theory of the Origin of Natural Sources of Perchlorate

A current theory regarding the origin of naturally occurring perchlorate in the environment centers on natural atmospheric processes. While the exact mechanism for the creation of perchlorate is unknown, the theory suggests that chloride, possibly in the form of sodium chloride from the sea or land-based chloride compounds blown in from the atmosphere, reacts with atmospheric ozone to create perchlorate. This process probably occurs over much of the earth and is analogous to nitrate formation in the atmosphere (Walvoord et al. 2003). In addition, there is the possibility that lightening may play a role in the creation of some atmospherically produced perchlorate (Dasgupta et al. 2005 and Jackson et al. 2003a), but this theory has not been confirmed. The rate of perchlorate creation in the atmosphere has not been determined, although it is thought to be a relatively slow process.

[2]"Caliche" is generally defined as a desert soil formed by the near-surface crystallization of calcite and/or other soluble minerals by upward-moving solutions. Commonly referred to as "hardpan" in the United States, caliche also results when precipitation dissolves salts in the soil, percolates downward, and then precipitates these cementing salts at some generally shallow depth, where the evaporation rate exceeds the rate of precipitation.

Following atmospheric creation, perchlorate returns to the earth's surface dissolved in precipitation. In arid environments, where the rate of deposition exceeds the rate of dissolution by ongoing precipitation, perchlorate can be incorporated into certain geologic formations (Orris 2004). Sampling and analysis of geologic materials from both existing collections and new field additions is ongoing by USGS. Initially, samples were taken in the southwestern United States, but now this sampling effort includes other geographical areas, more diverse terrains, and areas outside the United States. Samples terrains include playas, caliche-containing soils, dry lakebeds, and evaporite deposits (see Appendix B). USGS is also studying perchlorate in groundwater around the United States to help determine the geographical extent and concentration of perchlorate in the environment; determine which geologic materials contain perchlorate; and confirm the rate, concentration, and pervasiveness of perchlorate in precipitation and groundwater. Although USGS studies are ongoing, preliminary analytical results show that perchlorate appears to be naturally present in arid environments and appears to concentrate in a manner similar to that of nitrate (Walvoord et al. 2003).

In addition to these USGS studies, analysis of precipitation samples collected from weather station evaporation pans is being conducted by the National Weather Service in cooperation with USGS. Sampling of the atmosphere at altitude for perchlorate and precursor chemicals may be an additional area for investigation (Orris 2004).

2.1.1.2 Chilean Nitrate

Until recently, naturally occurring perchlorate was known to exist in the environment at only one location—the Atacama Desert in Chile. Similar but less extensive deposits have also recently been found in Peru and Bolivia. The perchlorate in Chile exists in mineralogical association with nitrate of soda caliche deposits that may have been derived in part from past local volcanic activity (Ericksen 1983 and Schumacher 1960). Chilean nitrate deposits have been mined to produce fertilizer and saltpeter for gunpowder for export since the 1830s. Chilean nitrate ore has been imported into the United States since at least the late 1800s for use as fertilizer, for saltpeter used in gunpowder, and as a feedstock to making nitric acid, explosives, fireworks, and additional end products.

2.1.1.3 Evaporite Deposits

Evaporite deposits are those formed by evaporation concentration in arid environments. These marine and nonmarine deposits include salts of bromine, boron and borates, gypsum and anhydrite, nitrogen compounds, potash, iodine, sodium sulfate, and sedimentary phosphate (Lefond 1975). Evaporites tend to be deposited in a specific chemical sequence as the concentration increases, such that potassium or other salts that precipitate after halite (rock salt or sodium chloride) are those most likely to contain perchlorate, based on current sample analysis.

In an initial round of USGS testing, more than 90% of the natural materials samples had detectable perchlorate, some at low concentrations and others involving potash (sylvite) deposits with perchlorate values up to 489 parts per million (ppm) (Orris et al. 2003, Orris 2004; see Appendix B). Potash is mined and milled in the United States, Canada, and elsewhere. Potash ore has also been recovered via solution mining and exists in solution in the Great Salt Lake in

Utah. Economic ore minerals of potash include sylvite, sylvinite, langebinite, kiainite, and carnallite. Most potash production is dedicated to feedstock for making fertilizers. The remaining commercial and industrial uses include potassium-bearing chemicals and reagents, flux in the aluminum industry, as an alternative to deicing salt, water conditioning, detergents, ceramics, and pharmaceuticals (Downey 2002). Samples of processed potash products have not tested positive for perchlorate to date.

Other evaporite deposits besides potash may also have the potential of associated perchlorate. Some examples include trona, borax, gypsum, Epsom salts, and others. Borates have been used for boric acid production, as a pesticide/lumber preservative, and as an ointment. Borax is also used as part of an abrasive hand cleaner. Colemanite is used as a component for some fertilizers for alfalfa and clover (Lefond 1975).

2.1.1.4 Other Potentially Naturally Occurring Perchlorate Sources

Perchlorate has been detected in seaweed at a concentration of 885 ppm in a sample of kelp collected and analyzed by the USGS (Orris et al. 2003). Whether other types of seaweed or marine algae contain perchlorate has not yet been determined.

2.1.2 Manmade Perchlorate

Perchlorate was first manufactured in commercial quantities in Masebo, Sweden in the 1890s by Stockholms Superfostfat Fabrisk AB. Commercial production elsewhere in Europe and the United States followed shortly thereafter. The earliest production in the United States appears to have been by Oldbury Electro-Chemical in Niagara Falls, New York, in 1910. Several perchlorate production plants are known to have operated in the United States since that time (Table 2.1). In 1960, Schumacher documented over 40 different perchlorate compounds that had been produced in laboratory and industrial settings (Schumacher 1960). One chemical manufacturer lists 80 perchlorate chemicals in its product line. However, the vast majority (>99%) of manufactured perchlorate compounds consist of the following four: ammonium perchlorate, sodium perchlorate, potassium perchlorate, and perchloric acid. See Appendix C for a compilation of other, less-common manufactured specialty perchlorate compounds.

A number of processes have been patented for the production of perchlorates. In general, sodium perchlorate is manufactured electrolytically using sodium chlorate as the feedstock. Potassium perchlorate and ammonium perchlorate are produced in a second step by reacting sodium chlorate as a water solution with other chemicals to create concentrated solutions of either potassium perchlorate or ammonium perchlorate, depending on the added chemical(s). Perchlorate crystals are precipitated from the solution and are then dried to produce a homogeneous, dry, granular product that is shipped in sacks and drums for sale to manufacturers of various perchlorate-containing end products.

Table 2-1. U.S. perchlorate manufacturers[3]

Company	Location	Years of operation or production	Comments
Oldbury Electro-Chemical (later became Hooker Electrochemical)	Niagara Falls, New York	1910–1940	Hooker Electrochemical was acquired by Occidental Chemical Company in 1968
Western Electrochemical Company	Los Angeles, California	1943–1945	Manufactured potassium perchlorate
Western Electrochemical Company	Henderson, Nevada	1945–2002	Merged with American Potash and Chemical Company in 1955; acquired by Kerr-McGee in 1967; manufactured ammonium perchlorate, sodium perchlorate, and potassium perchlorate
Hooker Chemical and Foote Mineral (joint venture H.E.F., Inc.)	Columbus, Mississippi	1958–1965	Currently Eka Nobel
Pennsalt Chemicals Corp.	Portland, Oregon	1958–1965	Currently Arkema, Inc.
Pacific Engineering and Production Company of Nevada	Henderson, Nevada	1958–1988	Ammonium perchlorate plant destroyed by explosion in 1988; never reopened
American Pacific Corporation	Cedar City, Utah	1989–present	Sole remaining North American producer of ammonium perchlorate for solid propellant

USEPA has compiled information on known or suspected users or manufacturers who have shipped more than 500 pounds of perchlorate in any one year (USEPA 2003a). American Pacific Corporation manufactures ammonium perchlorate in Cedar City, Utah, and is currently the sole domestic manufacturer of commercial quantities of propellant-grade ammonium perchlorate.

2.1.3 Differentiating Between Natural and Manmade Perchlorate

Some locations may have a mixture of manmade and naturally occurring perchlorate (Duncan, Morrison, and Varicka 2005). The western half of the United States appears to represent the most likely area for mixed plumes to occur due to favorable geological and precipitation conditions. The continued evolution of analytical forensic techniques may permit the fingerprinting of detected perchlorate plumes to ascertain whether the source is natural or manmade and to what extent each source type is represented (see Section 3.4).

[3] The information in this table is derived from many sources and is not comprehensive. Western Electrochemical Company, Pacific Engineering and Production Company of Nevada, and American Pacific Corporation are linked through successive corporate acquisitions. Other plants are believed to have operated and continue to operate, especially for the production of perchloric acid and specialty reagent compounds.

2.2 Uses for Perchlorate and Associated Releases

Indications are that perchlorate use was limited prior to World War II, with the most prevalent applications being fireworks and railroad signal flares. In 1939, *Uses and Applications of Chemicals and Related Materials* lists uses only for perchloric acid (Gregory 1939). Volume II of the same document, published in 1944, added uses of potassium perchlorate (Gregory 1944). Potassium perchlorate was placed on the list of strategic chemicals in 1940. See Appendixes C–E for more information.

Because it is an exceptional oxidizer with additional useful properties, perchlorate is widely used today by industry, the U.S. Department of Defense (DoD), and National Aeronautics and Space Administration (NASA) and in a few specific medicinal applications. Perchlorate usage appears to be ubiquitous across the United States, with new information on applications and locations of usage increasing as time passes (see Appendixes D and E). In the United States, approximately 90% by weight of industrial perchlorate production is dedicated to making ammonium perchlorate for use as an oxidizing agent for solid propellant rockets and missiles. The majority of the remaining U.S. production capacity consists of perchloric acid, sodium and potassium perchlorate, and a variety of other perchlorate salts.

2.2.1 Solid Propellants

Of the four main manufactured perchlorate compounds, ammonium perchlorate as used for solid propellant rockets and missiles makes up the largest proportion by volume of U.S. production. However, the earliest use of perchlorate as a solid propellant was in the form of potassium perchlorate. The Guggenheim Aeronautical Laboratory at the California Institute of Technology developed a formulation that combined asphalt as a binder and fuel with the oxidizer potassium perchlorate for use in jet-assisted take-off units (Hunley 1999). In the middle to late 1940s and early 1950s, perchlorate-based rocket motors that used potassium perchlorate were developed for smaller tactical missiles.

In the early to middle 1950s, ammonium perchlorate began replacing potassium perchlorate as the preferred oxidizer for solid propellants in large rocket motors. By 1958, the NIKE Hercules missile, which replaced the NIKE Ajax missile, used a solid propellant motor of polysulfide–ammonium perchlorate. In the 1960s, solid propellant mixtures of ammonium perchlorate and powdered aluminum replaced liquid propellant systems in intercontinental ballistic missile systems. Other examples of solid rocket motors that use ammonium perchlorate include the space shuttle and commercial satellite vehicles. Each of NASA's space shuttle booster rockets contains solid propellant made up of fine aluminum powder fuel and ammonium perchlorate oxidizer. Many commercial satellite launch vehicles also use solid rocket motors with ammonium perchlorate propellant as strap-on boosters to increase payload capacity.

Small rockets attached to ejector seats for pilots, explosive bolts for separating missile stages or other components, and oxygen generators for both civilian and defense aircraft also use perchlorate. Due to degradation issues, many of these devices are replaced as the shelf life expires.

2.2.1.1 Disposal of Solid Propellants

Perchlorate-containing debris, scraps of solid propellant and explosives, and rejected rocket motors have been disposed of by burning in open burn/open detonation (OB/OD) areas. However, in the past, solid propellant or explosives not burned to completion could permit perchlorate to be dissolved and cause contamination in soils and waters. Current practice is to use burn pas for the destruction of propellants. After the initial burn, a clean up is performed and any unconsumed material is treate again. At many DoD sites, even the ash is reburned, collected in drums and tested to ensure complete combustion of all energetic material.

Other processes have been used to dispose of solid propellants. For example, hydro-mining or a hog-out process is used to wash out solid propellant with high-pressure water jets to enable reuse of rocket motor hardware. Unfortunately, in the original system configuration, the liquid waste from the hog-out process was discharged untreated to the ground surface or into leaky lagoons and contaminated surface and groundwaters. This practice of untreated discharge is no longer employed due to the discovery of associated groundwater plumes. Current practice is to capture and treat the waste stream prior to discharge.

2.2.1.2 Replacement of Ammonium Perchlorate in Solid Rocket Propellants

DoD has development programs under way to replace ammonium perchlorate in solid rocket propellants. While alternative energetic oxidizers exist, significant cost, availability, environmental, and performance issues remain that have so far prevented their use in fielded weapon systems and launch vehicles. Each rocket or missile systems has unique performance demands that require consideration when attempting to replace ammonium perchlorate. The Green Missile Program is a development program to demonstrate the viability of replacing ammonium perchlorate in large rocket or missile systems with an environmentally friendly alternative oxidizer.

NASA recently announced a new paraffin-based solid propellant being developed and tested to replace perchlorate-based fuels for spacecraft use (NASA 2003). In testing since 2001, the fuel's advertised advantages include nontoxicity, carbon dioxide and water combustion products, increased safety due to high stability, and the ability to be shut down and restarted quickly. However, the applicability of this paraffin-based fuel to meet DoD requirements for solid propellants is unknown.

2.2.1.3 Missile Recycling

Within DoD, a backlog of perchlorate-based solid propellant rockets and missiles that have exceeded their perchlorate shelf life are currently in storage. These will eventually require treatment or perhaps recycling of the perchlorate. If not treated or recycled, corrosion of these weapon systems will eventually become a concern.

The Army Aviation and Missile Command's Research Development and Engineering Center has developed and demonstrated a missile-recycling capability. In this process, the energetic materials processing module uses supercritical anyhydrous ammonia in a closed-loop system to recover HMX (high-melting-point explosive), RDX (royal demolition explosive), and

ammonium perchlorate for recycling. In 2003 and 2004, 14,600 tactical optical wire-guided missiles were processed in this way. Up to 15,000 missiles are projected for recycling in 2005.

2.2.1.4 Perchlorate Contamination Associated with Solid Fuel Launch Vehicles

Perchlorate releases to groundwater associated with the space shuttle and other solid-fuel launch vehicles at various locations within the NASA sphere of operations have been documented at Jet Propulsion Laboratory, Cape Canaveral, and elsewhere. At least one study assessing the potential for perchlorate release from launching operations has been published (Lang et al. 2002).

2.2.2 Munitions

All of the services within DoD have current and/or past weapon systems that contain perchlorate in varying amounts. A 2001 DoD survey of weapons systems containing perchlorate listed 259 different munitions and related items such as fuzes, flares, illumination rounds, simulators, grenades, etc., as well as 41 missile systems in the DoD Munitions Items Disposition Action System (MIDAS) database. For example, current families of munitions containing perchlorate in use by the Army include training simulators, insensitive munitions, smokes or obscurants, pyrotechnics, grenades, signals and flares, and fuzes. Some types of simulators contain relatively high perchlorate concentrations, as do most of those with solid rocket motors.

The Army, Navy, and Air Force are all looking more thoroughly at historical records related to research and development, manufacture, use, storage and disposal to develop a timeline for perchlorate-containing munitions to better understand the residues that may be on various training and testing ranges.

2.2.2.1 Munitions Manufacturing

In the past, munitions manufacturing facilities and operators conducted hydraulic wash out (often referred to as hog-out) of equipment used in solid propellant and munitions production. These operations present another opportunity for potential releases of perchlorate into the environment.

2.2.2.2 Munitions Disposal

Prior to 1970, unused munitions were buried on ranges. Over long periods of time, corrosion degrades the munitions casing, resulting in the potential release of incorporated perchlorate into the environment. However, the potential for perchlorate release to the environment can vary greatly, depending on the length of use and the types and amounts of munitions disposed. For example, not all of the munitions contained any appreciable amount of perchlorate. In addition, the larger munitions that contained ammonium perchlorate would have been subject to OB/OD (See Section 2.2.1.1). These factors would reduce the probability of the burial sites contributing perchlorate.

2.2.2.3 Perchlorate Replacement Programs

Efforts are under way to replace perchlorate in at least some munitions. For example, the Army has a preliminary perchlorate replacement program focused on two specific munitions that constitute a large percentage of perchlorate usage. Edgewood Chemical Biological Center (ECBC) has proposed replacing the photoflash power (the explosive charge inside the pyrotechnic device that contains perchlorates and provide the "bang") with an organic compound to eliminate the use of perchlorate in the two simulators—the M115A2 Artillery Simulator and the M116A1 Hand Grenade Simulator. Alternatively, Picatinny Arsenal has proposed replacing the photoflash powder with a metallic base material. One compound from ECBC and one compound from Picatinny Arsenal will be selected and compared to determine the better one for replacement of these two simulators; however, these two compounds have yet to be chosen. These alternatives will undergo selective testing and comparison to determine better replacement. Other services are also exploring perchlorate replacement.

In addition to service specific programs, DoD's Strategic Environmental Research and Development Program (SERDP) has a new project investigating perchlorate alternatives. This project is designed to develop propellants that have a modifiable burn rate, meet or exceed current performance specifications, and are environmentally benign (SERDP 2005).

2.2.2.4 Perchlorate Contamination at Current and Former Military Facilities

A number of military facilities have documented perchlorate groundwater and surface water contamination (selected examples, Table 2.2 and GAO 2005). Some defense-related facilities, such as some ammunition and missile/rocket manufacturing facilities, also have known releases (Table 2.2). However, it is generally difficult to ascertain which military bases, depots, formerly used defense sites, weapons manufacturing installations, and other defense-related facilities might have perchlorate releases associated with them because site specific documentation may not be available. It is also important to note that the storage, processing and/or use of perchlorate-containing weapons systems does not necessarily correlate to a probable release of perchlorate release to the environment.

Expended munitions and simulators found in the impact areas can contribute to perchlorate contamination in two ways: (a) munitions containing perchlorate or rocket motors do not function as intended through low-order detonation or (b) function as intended by completely detonating but do not completely consume the propellant or main change and subsequent precipitation leaches perchlorate into the environment. These release mechanisms may contribute a relatively low but long-term mass loading of perchlorate to the environment. The current perchlorate groundwater contamination at the impact areas of the Massachusetts Military Reservation in Cape Cod, Massachusetts, reflects this condition. As more ranges are tested for perchlorate contamination, it seems likely that more contamination will be discovered over time. In addition to impact areas, burial areas, OB/OD areas, launching points for rockets and missiles, and missile test stands could also be areas of contamination potential (see Section 2.2.2.2 for discussion of burial areas and OB/OD areas).

Table 2-2. Example DoD facilities with known perchlorate contamination*

Installation	Military service	State	Perchlorate concentration initially detected or reported (ppb)	Perchlorate cleanup demonstration projects under way?
Edwards Air Force Base	Air Force	California	160,000 groundwater (detected 1997)	Yes
Holloman Air Force Base	Air Force	New Mexico	16,000 surface water (detected 1999)	
Aberdeen Proving Ground	Army	Maryland	5 drinking water, 24 groundwater (reported 1998)	
Redstone Arsenal	Army	Alabama	160,000 groundwater (as of 2003)	Yes
White Sands Missile Range	Army	New Mexico	21,000 groundwater (reported in 1998)	
Naval Air Weapons Station, China Lake	Navy	California	560 groundwater (detected in 2001)	
Naval Surface Warfare Center, Indian Head	Navy	Maryland	1,000 surface water (reported in 1998)	Yes

** Not a comprehensive list of DoD facilities with perchlorate contamination.*

2.2.3 Commercial Explosives

2.2.3.1 Black Powder

Black powder is made of a blended mix of saltpeter (potassium or sodium nitrate), charcoal, and sulfur in a 75:15:10 ratio by weight. Nitrate from Chile was used as a source of sodium nitrate in black powder. Chilean nitrate ore, containing naturally occurring perchlorate, was first imported in the United States in 1857. The sodium nitrate content of the ore made it particularly suitable for use in manufacturing explosives, specifically black powder, and replaced the more expensive potassium nitrate. Black powder consumption for commercial blasting peaked in 1917 at nearly 300 million pounds, but by 1970 had decreased to 83,000 pounds, used primarily for safety fuses and fireworks (*Blaster's Handbook* 1980).

2.2.3.2 Black Powder Substitutes

There are several black powder substitutes on the market that contain perchlorate. The addition of perchlorate is intended to increase velocity and range. These substitutes are mainly ascorbic acid (vitamin C). The use of substitute black powders is becoming increasingly popular, especially with hunters. It is believed that the substitute black powder operations in general are small in terms of overall production, but past practices may have resulted in perchlorate releases and contamination.

2.2.3.3 Nitric Acid

An explosives manufacturing site in Arizona uses Chilean nitrate to manufacture nitric acid as an intermediate for explosives manufacture, including the production of dynamite and other explosive compounds. This process resulted in an otherwise unexpected perchlorate groundwater plume (Arizona Department of Environmental Quality n.d.). Although most nitric acid today is made using other chemical processes, Chilean nitrate has been used in the past for its production. Consequently, historical locations of nitric acid manufacturing using Chilean nitrate are potential areas of perchlorate contamination.

2.2.3.4 Modern Commercial Explosives

A number of modern commercial explosives products may contain sodium perchlorate, ammonium perchlorate, or potassium perchlorate as a chemical sensitizing agent. These products may include emulsions,[4] water gels,[5] delay elements in detonators, and some seismic explosives.

Under some circumstances, an explosives manufacturer may use a chemical sensitizer such as perchlorate to increase the shock initiation sensitivity of an emulsion or water gel product. This type of product sensitized using perchlorates is generally designed for specialized applications such as wet/hard/dense rock blasting, in applications to expand drilling patterns or to address excessive rock burdens, in tight underground cuts and tight trenching situations, high-precompression conditions, and deep wet trenches and boreholes. In these applications, including certain trenching and utility work, some mining blasting, and specific construction-related blasting activities, perchlorates may be used to preserve product sensitivity where normal sensitizing agents may be conditionally compromised. In these applications, perchlorates have been found particularly effective in maintaining the sensitivity of the explosive.

The amount of perchlorate present in typical perchlorate-containing explosives is quite variable. Some illustrating examples of perchlorate-containing explosives by weight as derived from material safety data sheets (MSDSs) include some seismic products: 66%–72% sodium perchlorate; bulk and packaged water gel products: 0%–4% sodium perchlorate; packaged continuous water gel explosives: 0%–7% sodium perchlorate; emulsion explosives: 0%–30% perchlorate; electric detonators: 0%–0.5% potassium perchlorate; and nonelectric detonators: 0%–0.89% potassium perchlorate. Some emulsion and water gel explosives may exceed even these concentration ranges.

2.2.3.5 Perchlorate Contamination Associated with Explosives Manufacture, Storage, and Use

Manufacture. At some explosives manufacturing locations, the past practice of using unlined ponds to collect production-derived wastewater may have resulted in releases of perchlorate to groundwater. Explosive solids containing perchlorate also may have accumulated in ponds as sludge. In other instances, wastewaters may have been discharged to surface waters.

[4] The Institute of Makers of Explosives (IME) defines an "emulsion" as an explosive material containing substantial amounts of oxidizer dissolved in water droplets, surrounded by an immiscible fuel, or droplets of an immiscible fuel surrounded by water containing substantial amount of oxidizer (IME 2002).

[5] IME defines a "water gel" as an explosive material containing substantial portions of water, oxidizers and fuel, plus a cross-linking agent (IME 2002).

Explosives manufacturing has resulted in significant groundwater perchlorate contamination at some locations. In Kansas, for example, a former manufacturer of slurry explosives has contaminated the groundwater as well as surface water ponds. Plants surrounding the ponds have tested positive for perchlorate, as have largemouth bass and channel catfish from the ponds, and local cattle have significant perchlorate plasma as a result of drinking from the ponds (Kansas Department of Health and Environment n.d.). Plumes associated with these situations may contain perchlorate as well as explosives and nitrates, the presence of which make it more difficult to bioremediate the perchlorate due to selective chemical uptake preferences, depending upon the bioremediation technology (see Section 6.1). Therefore, these situations may pose remediation challenges.

At other explosives manufacturing facilities, wastes containing perchlorates may have been disposed of at OB/OD units with the potential for perchlorate residue generation and subsequent groundwater contamination. Past practices at manufacturing facilities may represent the largest environmental release potential in the commercial explosives industry. Certainly, older explosives manufacturing facilities that utilized Chilean nitrate as feedstock should be carefully examined due to the presence of perchlorate in historically higher concentrations as well as past management practices.

Soil, surface water, and an associated groundwater plume have also been found at the site of a black powder substitute manufacturer in Kansas. At an adjacent property, sampling conducted by the Kansas Department of Health and Environment has detected perchlorate in agricultural products associated with use of this contaminated water in chicken meat, eggs, milk, beets, and cucumber pickles.

Storage. Historical releases of perchlorate from storage areas used for perchlorate-containing raw materials may be a concern at some locations. Potential historical releases could be due to leakage of perchlorate from bags and containers, such as dust from sacks of perchlorate salts. Other concerns related to the storage of perchlorate include the disposal of bags and containers of perchlorate in landfills. However, contemporary raw material storage areas are designed and constructed to prevent or minimize any releases of product. Therefore, there is little contemporary risk of release from complete and packaged explosives unless carelessness results in packaging puncture with subsequent leakage.

Explosives Use. Contamination at blasting sites may occur if detonation is incomplete; for example, some rock formations may contain cracks and fissures angling off the main borehole into which explosives may migrate during the loading process (not all explosives are packaged). The explosives contained in such fissures may then fail to detonate in the blast. In addition, the potential for residual contamination is increased in the event of a misfire, in which a loaded hole or group of holes in a blasting pattern fails to detonate. Undetonated explosive products remaining after a misfire or incomplete detonation will have more residence time to contact and contaminate groundwater. This scenario is of particular concern where the explosives contain highly soluble perchlorates. Blasting misfires do occur with some variable frequency. Significant effort is made to avoid misfires, primarily because they represent a serious safety hazard. Blast efficiency and cost considerations are secondary concerns. If possible, attempts are usually made

to detonate the misfired hole or holes. In some cases, perchlorate contamination associated with blasting may be attributable to preblast loss of explosives due to poor housekeeping practices and/or improper spill cleanup.

Groundwater contamination associated with explosives use is suspected at a construction site in Westford, Massachusetts. In a water sample from a pond near the site, Massachusetts Department of Environmental Protection (MADEP) officials detected a perchlorate concentration of 819 ppb and detected a perchlorate concentration of 12 ppb in an on-site retention pond. One town water supply well with a detection of 3.3 ppb has been shut down, while a privately owned water well several hundred feet from the site also has a perchlorate concentration of 425 ppb. MADEP officials believe the perchlorate contamination is related to explosives used in rock blasting. An examination of the MSDSs by MADEP officials for the emulsion and water gel type explosives used by the sole contractor at these sites showed the explosives contained 20%–30% by weight of perchlorate. According to MADEP, the cause (blasting explosives) and effect (water contamination) relationship at this time appears clear (MADEP 2005a). Mandated testing of the public water supplies by MADEP led to this discovery and others related to perchlorate impacts.

2.2.4 Fireworks

In general, fireworks manufacturers encase their chemical compounds in cardboard cylinders or spheres called “shells.” The lofting charge or propellant usually consists of black powder, which may also be a component of the explosive charge. When fireworks have a loud, concussive bang and a flash of white light, they are termed a “photoflash” or a “flash and sound” effect. This effect is produced using a mixture of potassium perchlorate and fine aluminum or magnesium powder. Common applications include special effects for rock concerts, firecrackers, illumination for night photography, and of course fireworks.

Perchlorate or chlorate oxidizers are also typically used because they decompose at high temperatures and release free chlorine. The chlorine is then available to combine with barium, strontium, or copper incorporated as compounds that produce the characteristic green, red, and blue hues respectively (Conkling 1990). In some fireworks shells, an oversupply of potassium perchlorate beyond the stoichiometric need is used to suppress the effects of certain chemical elements during reactions.

2.2.4.1 Perchlorate Contamination Associated with Fireworks Manufacture and Use

Manufacture. Whether fireworks-making facilities have had perchlorate releases during manufacture or storage of perchlorate in the United States is unknown and deserves some scrutiny due to the stability of perchlorate in water. It is likely that some of the older sites probably used perchlorate containing Chilean nitrate. Currently, according to the American Pyrotechnics Association, close to 100% of fireworks are imported, and in 2003 approximately 221 million pounds of fireworks were sold in the United States. However, some current domestic fireworks production still exists, with several facilities having accidentally exploded over the past 30 years.

Fireworks display designers have been building custom made shells in the United States for their shows since before the turn of the last century. Some of these may constitute potential sources, at least for those that were using perchlorate in their formulations and some older production that was based on Chilean nitrate.

Fireworks Use. In Massachusetts MADEP is investigating perchlorate contamination that appears to be from the residue of fireworks displays conducted over time. Fireworks-based perchlorate residue is suspected to have contributed to perchlorate groundwater contamination located in the Northwest Corner at Massachusetts Military Reservation (MMR). This area has perchlorate groundwater plumes that emanate from both off and on base with perchlorate concentrations as high as 19 ppb along with associated explosives such as RDX at up to 7 ppb. The groundwater contamination appears to be the result of annual fireworks displays that occurred 1996–2003, as well as military pyrotechnics such as smoke pots, smoke grenades, and various perchlorate-containing simulators. Further, perchlorate contamination potentially related to the use of fireworks has been found following water supply well sampling and testing in several other locations around the state (MADEP 2005a).

MADEP is conducting a fireworks residue field test at the University of Massachusetts Dartmouth Campus. Predisplay analytical results show perchlorate concentrations in various types of fireworks from nondetect to 36 ppb. The site has hosted displays for about 10 years. The amount of perchlorate available for groundwater contamination from fireworks depends upon how many displays, the types of fireworks involved, amount of misfiring, and the length of time over which displays were conducted in a specified area. Misfires may contribute significant perchlorate to the environmental loading as well, and their frequency, although relatively low, does vary. Disposal of these misfires may also be of concern (MADEP 2005a).

2.2.5 Safety or Hazard Flares

Perchlorate is one of the primary components found in emergency and signal flares. Flare use is believed to be widespread across the United States. In Santa Clara County, California, more than 40 metric tons of flares was used/burned in 2002 alone (Silva 2003). Flares containing perchlorate have also been used in aircraft seeding operations in some locations.

In safety or hazard flares, strontium nitrate is combined in a mixture with an oxidizer and a chlorine source (potassium perchlorate), along with various fuels. The available chlorine from the perchlorate and the strontium combine to color the emitted light bright red (Conkling 1990). Tests indicate that the residue from fully burned flares may still contain a significant leachable amount of perchlorate, up to almost 2000 µg of perchlorate per flare, and that partially burned flares leach even greater concentrations of perchlorate when placed in contact with water (Silva 2003).

The manufacturing sites of flares are known to have precipitated perchlorate releases into groundwater in California, and releases are also possible in other locations where similar facilities are or were situated.

2.2.6 Matches

Potassium perchlorate is used in the production of common stick matches, which use a blend of potassium chlorate and sulfur to act as a fuel and binder (Conkling 1990). If an environmental concern exists associated with matches, it is likely to be at the production facilities. As of 1997, only four American companies produced matches: Lion Corp., Superior Match Co., Atlantis Match Co., and D. D. Bean & Sons Co. (Retskin 1997).

2.2.7 Industrial Uses

Industrial uses of perchlorate vary widely in scope, as perchlorate is incorporated into or used to make many common products (Appendix E). Laboratories also make use of the strong oxidizing and other properties particular to perchlorate. Perchloric acid, for example, is used in some industrial processes, such as in processing rare-earth element ores. In Tewksbury, Massachusetts, discharges of perchlorate to a river were found to be associated with a medical device manufacturer's use of perchloric acid). It is expected that the number of industrial uses will continue to expand as our understanding and awareness of its usage matures. Also, some previous list of perchlorate uses contained erroneous information. Efforts were made in this document to correct these errors, but work to verify all of the reported uses through reliable documentation is still under way.

The applications of the various perchlorate compounds are so varied that it is difficult to characterize the practices or mechanisms that may lead to releases to the environment. This problem is further complicated by the fact that perchlorate compounds may be used in solid or liquid form. The practices at each facility producing, handling, or using perchlorate will have to be examined individually to determine what possibilities exist for releases to the environment to occur.

2.2.8 Laboratories

Some laboratories in industry, academia, DoD, Department of Energy (DOE), or other settings are using or may have used perchlorate compounds or perchloric acid in research or analytical work. Several examples follow where perchlorate compounds or perchloric acid have been released, or are suspected to have been released, from a laboratory setting. At Los Alamos National Laboratory (LANL), perchlorate found in groundwater has been associated with past actinide research and high-explosives synthesis and testing (Hjeresen et al. 2003). There has also been at least one case of a university chemistry building being temporarily closed due to an accumulation of perchlorate in the ventilation system. As a result, special fume hoods specific to perchloric acid use are now available.

Some detergents may contain perchlorate. For example, detergent-based laboratory glassware cleaning agents such as Alconox, Alcotabs, Liquinox, and NeuTrad have been tested and shown to contain up to 2.5 mg/kg perchlorate. (Some types of laundry detergent could also potentially contain perchlorate.)

2.2.9 Agricultural Uses

Some naturally occurring perchlorate is present in products used to enhance agricultural output, e.g., fertilizers. Commonly, nitrates are added to phosphates and potash to produce fertilizers, the ratios of which can be varied to provide for specific plant needs. Potash, a source of soluble potassium essential for plant growth, is mined to produce a fertilizer for agricultural use. USEPA tested various fertilizers used in the United States and determined that these fertilizers do not generally contain perchlorate. This conclusion appears to contradict the USGS findings of perchlorate in some potash samples. Domestic production of potash occurs in Michigan, Utah, and New Mexico. Canada also produces potash, as do some foreign sources. Potash is also used as feedstock in the production of other chemicals (Milford 1999, USEPA 1999a). Other evaporate-derived minerals such as borate are components of certain fertilizers used for plants that need them as trace elements, e.g., alfalfa and clover (Lefond 1975).

Bulldog Soda, marketed by Sociedad Quimica Y Minera De Chile S.A. (SQM) and derived from Chilean nitrate deposits (containing 0.03% perchlorate on average, as mined), is used as approximately 0.14% of the total fertilizer currently applied in the United States. On a historical basis prior to the 1960s, Chilean nitrate–derived fertilizer was the principal fertilizer used in the United States. The USEPA fertilizer study completed in 2001 found that fertilizer derived from Chilean nitrate contained accessory perchlorate in significant concentrations. Subsequently, SQM, the sole mining and processing company of caliche-type deposits, has changed the process for refining the ore, going from 0.5–2 mg/g to 0.1 mg/g, or 0.01% perchlorate. This fertilizer is still applied to a small percentage of cropland in the United States. SQM promotes the use of its products in agriculture for the cotton, tobacco, and citrus sectors. The historical application of higher concentration perchlorate-containing fertilizer may present a legacy of unknown contamination potential to groundwater, as may the lower concentration product applied currently (Urbansky et al. 2001, UC SAREP 2002).

2.2.10 Medical/Pharmaceutical

Historically, potassium perchlorate has been used in medical practice for the treatment of thyroid disorders to suppress the overproduction of hormones due to an overactive thyroid gland (see Section 4.1 for more on the effect of perchlorate on thyroid hormones). Potassium perchlorate is employed in current medical procedures in three different ways. First, it is used in the treatment of induced hypothyroidism or thyrotoxicosis resulting from the primary treatment of tachyarrhythmia or ischemic heart disease by the iodine-containing drug amiodarone. Potassium perchlorate is also used to limit the uptake of sodium pertechnetate in the thyroid when pertechnetate is administered in the course of brain and blood-pool imaging and placenta localization. Third, potassium perchlorate has been used as a diagnostic agent in the treatment of certain thyroid disorders. The potassium form of perchlorate appears to be used exclusively for medicinal purposes over other salts of perchlorate probably due to lessened physiological impacts of the potassium over other possible cations (California Department of Toxic Substances Control n.d.).

The likelihood of medical perchlorate source release to the environment appears to be slight given that amounts stored for medical purposes are small, storage occurs in containers and structures, and hospitals have waste disposal programs.

2.2.11 Water and Wastewater Treatment

Sodium hypochlorite (NaOCl) is one commonly used method to disinfect water supplies. It is also used to treat pool water, to disinfect groundwater production wells, to treat wastewater in publicly owned treatment works, and other instances where an effective disinfectant is required. Sodium hypochlorite in solution normally produces some perchlorate ions during the dissociation reactions. This effect is evidenced by the formation of highly unstable and shock-sensitive perchlorate crystals that can form around the rim and cap of long-stored sodium chlorite solutions in laboratories. Thus, the use of sodium hypochlorite has the potential in these applications to introduce detectable perchlorate into the environment. MADEP has measured perchlorate levels of 0.20–0.28 µg/L in samples of finished drinking water from three drinking water plants where perchlorate levels in raw water coming into the plants were below the 0.20 µg/L detection limit. MADEP has attributed the perchlorate detections at all three plants to the sodium hypochlorite used for water disinfection (MADEP 2005b).

Household bleach may also contain perchlorate. According to MADEP, some preliminary testing of household bleach from store shelves shows the presence of perchlorate up to 390 µg/L (equivalent to ppb). Chemical age appears to be a factor for perchlorate concentration strength in bleach, as another sampled bottle of bleach on the shelf for two years tested for perchlorate at 8000 ppb. Other applications for sodium hypochlorite include its use as a bleaching agent in laundry cleaning; for brightening, oxidizing, deodorizing, and sterilizing in general industry; for decolorizing in textile manufacturing; and for bleaching in the paper and pulp industry. It is also used for skinning of vegetables in the food processing industry.

MADEP has also sampled and tested for perchlorate in the effluent from two separate septic tanks where the influent source water contained approximately 1000 and 500 µg/L perchlorate. Both effluents were nondetect for perchlorate using liquid chromatography/mass spectrometry/ mass spectrometry (LC/MS/MS) analytical technology (see also Section 3.2.2 for more information on analytical methods). It is possible that perchlorate degraded in the anaerobic environment of the septic effluent, although this proposed relationship remains to be proven.

2.2.12 Landfills

Historically, landfills have received waste perchlorate and perchlorate-contaminated wastes and debris as a matter of course. Some of these landfills were or are located on site near a facility using perchlorate, while other landfills were or are located some distance off site from the facility. It is believed these perchlorate wastes were primarily in the solid form, although whether any perchlorate-containing liquids were also disposed is unknown. Users of perchlorate products who discarded the packaging are also a potential source of perchlorate to landfills due to the perchlorate residue adhering to that packaging. How many landfills may be impacted by perchlorate is unknown.

2.2.13 Sodium Chlorate Manufacture

In the electrolytic cell process for manufacturing sodium chlorate, the perchlorate ion is produced as an unintended by-product. In 1999, total U.S. sodium chlorate production capacity was 946,000 short tons per year, produced at 10 manufacturing sites (Tables 2-3 and 2-4).

Table 2-3. Sodium chlorate production capacity and locations in 1999 in the United States

Facility	Location	Capacity (short tons/year)
CXY Chemicals, USA	Hahnville, La.	134,000
Eka Chemicals (Eka-Columbus)	Columbus, Miss.	219,000
Eka Chemicals (Eka-Washington)	Moses Lake, Wash.	63,000
Elf Atochem North America, Inc.	Portland, Oreg.	58,000
Georgia Gulf Corp.	Plaquemine, La.	27,000
Huron Tech-442 Corp. (Huron Tech 442)	Perdue Hill, Ala.	40,000
Huron Tech (Huron Tech-Augusta)	Augusta, Ga.	145,000
Kerr-McGee Chemical LLC	Hamilton, Miss.	143,000
Sterling Pulp Chemicals	Valdosta, Ga.	110,000
Western Electrochemical	Cedar City, Utah	7,000
Total		946,000

Source: USEPA 2000b.

Table 2-4. Former sodium chlorate production facilities in the United States and changes as of 1999

Facility	Location	Capacity (short tons/year)	Comments
Elf Atochem	Tacoma, Wash.	25,000	Closed 9/97
Georgia-Pacific	Brunswick, Ga.	27,000	Closed 4/97
Huron Tech Corp.	Eastover, S.C.	90,000	Came on line 3/99
Huron Tech 442 Corp.	Perdue Hill, Ala.	40,000	Scheduled closure mid-2000

Source: USEPA 2000b.

Sodium chlorate is used in agriculture as a nonselective herbicide, mainly on noncropland for spot treatment of weeds and as a defoliant and for desiccant purposes for crops (PMEP 1995, Pesticide Action Network North America n.d.). Nonagricultural uses of sodium chlorate include household and industrial bleaching, pulp and paper bleaching, and food processing. Sodium chlorate is also used in numerous applications as well as a feedstock to make other chemical products (PMEP 1995).

It is possible that some current and former sodium chlorate production facilities could also be potential perchlorate sources, as could locations where sodium chlorate is being used for intended purposes.

2.2.14 Uncertain Sources

The problem when investigating an emerging environmental contaminant is that new information continues to come to light regarding past management practices, current uses, locations of use, or newly suspected but uncertain sources. In the case of the latter, there is a small but apparently growing list of suspected perchlorate sources. Confirmation and verification testing has not necessarily been done in all cases, and research in these areas is ongoing. A short list of these sources would include cloud-seeding operations, clandestine methamphetamine laboratory wastes, and certain anticorrosion cathodic protections systems.

Cloud-seeding operations have used potassium perchlorate as a component of some flare designs to produce nuclei for water-drop formation leading to precipitation. Whether this formulation is still in use is unknown.

There is also the possibility that in some clandestine methamphetamine laboratories the process of obtaining red phosphorus from matches and also road flares containing perchlorate may produce a waste stream containing concentrated perchlorates as a by-product.

A Texas Tech University study showed perchlorate being produced at measured rates of 71–77 µg/L by a cathodic protection system in a steel chlorinated water supply storage tank in Levelland, Texas (Jackson et al. 2003, 2004). The Texas Tech University Water Resources Center is also investigating the potential for the generation of perchlorate by pipelines, buried tanks, and water and oil wells protected by anticorrosion cathodic protection systems in the presence of natural chlorides in soil and groundwater (Jackson et al. 2003, 2004).

2.3 Environmental Fate and Transport

As previously discussed, perchlorate may be released into the environment in the form of a number of different salts, including ammonium perchlorate, potassium perchlorate, sodium perchlorate, and others. All are highly soluble in water, though the solubility of the various salts varies (Table 1-1). Perchlorate may also be released into the environment in the form of a liquid, such as in solution with water as a concentrated brine or as perchloric acid. This liquid form of perchlorate increases the potential as well as the speed of a spill reaching groundwater or surface water.

Very little is known about the distribution of perchlorate in soil. What is known is that the perchlorate does not bind to soil particles appreciably and that the movement of perchlorate in soil is largely a function of the amount of water present. Perchlorate salts that are released to the soil in solid form will readily dissolve in whatever moisture is available. If sufficient infiltration occurs, the perchlorate will be completely leached from the soil. Soil moisture containing perchlorate in solution can be taken up by plants through the roots, and several ecological studies have demonstrated the tendency of some plants to concentrate the perchlorate in plant tissues (Urbansky et al. 2000; Ellington et al. 2001). Some perchlorate may be held in solution in the vadose zone by capillary forces. In arid regions, crystallized perchlorate salts may accumulate at various horizons in the soil due to evaporation of infiltrating rainfall that leached perchlorate from shallower depths.

In dilute concentrations typically found in groundwater, perchlorate behaves conservatively, with the center of mass of the plume moving at the same average velocity as the water. Dispersion will cause the contaminant front actually to move faster than the average groundwater velocity. Perchlorate is kinetically very stable under environmental conditions and will not react or degrade in solution under ambient conditions. Biodegradation of perchlorate in groundwater will not occur unless significant levels of organic carbon are present, oxygen and nitrate are depleted, and perchlorate-degrading anaerobic bacteria are present. The combination of high solubility, low sorption, and lack of degradation tends to create plumes that are large and persistent.

If perchlorate is released as a high-concentration brine solution, the movement of the brine in a groundwater system may be controlled by density effects (Flowers and Hunt 2000). The density contrast between the brine and groundwater may cause the brine to move vertically with minimal influence by groundwater movement and little or no dilution. Brine pools may form on top of confining layers, and significant perchlorate mass may move into low-permeability confining layers by diffusion. The brine pools and perchlorate mass absorbed by the confining layers may serve as a long-term source of dissolved contaminant as perchlorate is released to the groundwater by diffusion. This type of release may occur where perchlorates have been manufactured, at rocket motor washout facilities, or other locations where perchlorate has been slurried or handled in concentrated brines.

2.4 Environmental Management

2.4.1 Past Practices

In general, some past management practices were inadequate to contain or prevent the release of perchlorate to soils and surface/groundwater because perchlorate was not recognized or regarded as a contaminant of concern. Efforts to contain perchlorate releases were primarily directed at product retention or recovery to maximize production output. Even though the historical practices should no longer occur or are being corrected when recognized, they have left a legacy of known and unknown sites.

2.4.2 Current Practices

Due to the properties of perchlorate, namely high solubility, little attenuation, stability, persistence, and the fact that a relatively small amount of perchlorate can contaminate a large amount of water, the management of perchlorate requires that users exercise the utmost in prevention techniques to prevent release to the environment. Also, since perchlorate compounds and the perchlorate ions in water are not volatile, there is no risk of perchlorate air emissions.

It is apparent that for some applications, there may be no adequate or cost-effective substitute for perchlorate, at least for some time. Banning the use of perchlorate is not necessarily a solution, but effective management practices certainly can be. Therefore, best management practices (BMPs) should be developed and rigorously followed where perchlorate is used. Some of these BMPs are general and apply to the use of any chemical, and others are industry and use specific.

Examples of these would include spill contingency plans, secondary containment, waterproof storage, and treatment of waste streams, where necessary. Some facilities also practice zero discharge. These efforts are doubly important when liquid forms of perchlorate such as concentrated solutions and perchloric acid are stored, used, and transported. Generally, these general techniques are familiar to practitioners in industry and DoD and have been known to environmental professionals for a considerable time, especially those with experience with the requirements of the Resource Conservation and Recovery Act (RCRA) and other environmental laws. It should be kept in mind that even though perchlorate is not currently regulated, it is likely to be in the future.

2.5 Site Characterization Approaches

Sampling for possible perchlorate contamination on a site requires some knowledge of the perchlorate usage at the site. This knowledge can be acquired through a historical review and interviews with on-site or former personnel. Knowing the quantity of perchlorate released at any one time, the number of occurrences, and the time period over which the releases occurred can provide some guidance for testing. In addition, knowledge of the environment and geology can help guide sampling approaches. For example, in dry or desert environments with a deep groundwater table, there can be a precipitation front of perchlorate below the surface but above the groundwater as a caliche layer. If the area has significant precipitation, diffuse source(s), or dispersed source(s), then groundwater and/or adjacent surface water should be tested, as the soil is likely flushed.

Perched aquifers, windows in confining layers, seasonal water-level changes, and potential density currents point to the importance of understanding the groundwater flow regime. Existing groundwater monitoring wells can be taken advantage of, and temporary push-point wells permit investigators to scope the nature and extent of a source rapidly. Since perchlorate acts like nitrate when dissolved in water, perchlorate contamination tends to move with groundwater flow unless stagnant conditions exist. Depending on specific uses, perchlorate may be associated with other contaminants, such as nitrates, explosives, solvents, or metals, and more associations may become apparent over time. The association is site specific but may provide important clues.

Releases of perchlorate, either continuous or intermittent, should lead to soil testing as well as testing of groundwater/surface water at any point sources, especially in dry or desert environments. Because deeper soil samples may indicate the presence of perchlorate even if surface soil samples do not, both surface and at depth samples should be taken if soil testing is indicated.

3. SAMPLING AND ANALYSIS

In the spring of 1997, an analytical method for perchlorate detection with a reporting limit of 4 ppb was developed. Since then, additional sampling and analysis techniques have been developed that can detect perchlorate at concentrations of 1 ppb and lower. It is important to note that perchlorate sampling and analytical techniques require special considerations due to

potential interferences, laboratory contamination, and potential false positives. This section will address sampling protocols, analytical methodologies, and forensics techniques for perchlorate.

3.1 Sampling Protocols

A brief discussion of sampling requirements specific to perchlorate for water and for soil is provided below. General information regarding surface water, sediment, soil, and groundwater sampling can be found in many documents including, but not limited to, the following:

- *Contract Laboratory Program Guidance for Field Samplers***,** EPA/540/R-00-003 (USEPA 2004b)
- *Requirements for the Preparation of Sampling and Analysis Plans*, EM 200-1-3 (USACE 2001b)
- *Model Field Sampling Plan*, Vers. 1.1 (AFCEE 1997)
- *Interim Guidance on Sampling and Testing of Perchlorate at DOD Installations (*U.S. Navy 2004)
- *U.S. Geological Survey Techniques of Water-Resources Investigations* (USGS variously dated)

The primary concern regarding perchlorate detection is the potential for false positives and false negatives. The secondary concern regarding perchlorate detections is the potential for bias in the analytical results due to field or laboratory activities. To address these concerns in the field, one or more equipment rinseate blanks should be collected during each sampling event when sampling equipment is reused, because analysis of solutions containing some of the commercial detergents commonly used during field decontamination (such as Alconox, Alcotabs, Liqui-Nox and Neutrad) have been shown to have detectable levels of perchlorate. To address these concerns in the laboratory, method blanks should be routinely analyzed and evaluated by the laboratory. Also, if reusable equipment is used for sampling, decontamination must be documented as effective through the use of quality control (QC) samples to ensure contributions from laboratory and field equipment are not causing high bias in analytical results.

3.1.1 Water

For groundwater and surface water, sampling for perchlorate can be performed with typical techniques discussed in the referenced sources. The holding time for perchlorate in water is currently established at 28 days, when the sample is held at 4º ± 2ºC. Although Method 314.0 (USEPA 1999b) does not require chemical preservation, there is anecdotal evidence of microbial degradation (see Section 3.2.1 for more information on Method 314.0). According to USEPA, two new sampling requirements will be added to updated or new perchlorate methods (USEPA 2005a, b, c). The first requirement is preservation in the form of field ultrafiltration through a sterile 0.2-micron filter into a presterilized nalgene bottle. The second requirement is that the sample be collected with significant headspace.

3.2.1 Soil

For soil and sediment, sampling for perchlorate can be performed with typical techniques discussed in the referenced sources. One anticipated issue specific to perchlorate is sample

representativeness due to anticipated heterogeneity (Gerlach and Nocerino 2003). Very little is known about distribution of perchlorate in soil.

Perchlorate salts are solids at ambient temperature. The distribution almost certainly depends on the form of the source (i.e., contaminated groundwater or other dissolved source vs. distribution in solid phase). If the perchlorate is distributed in a dissolved source, it should be expected to be very mobile in the soil. If the perchlorate is distributed in the solid phase (such as via a detonation), it could be expected to be distributed due to the physical transport of the detonation and it should be expected to initially be distributed similarly to secondary explosives.

Cold Regions Research Engineering Laboratory (CRREL) has conducted numerous studies led by Dr. Thomas Jenkins regarding the distribution of secondary explosives on active ranges. Secondary explosives are often dispersed as variously sized and shaped particles that slowly dissolve in precipitation because they are sparingly soluble and are wetted on only a periodic basis. They also possess low vapor pressures and hence do not volatilize to any extent. Their distribution is typically very heterogeneous, and they are transported through soil only after they are dissolved in water. The primary difference between secondary explosives and perchlorate is the solubility. Given perchlorate's greater solubility, it should be expected to migrate through the soil more readily even if it is initially distributed in particles. Until more data have been gathered, it would be prudent to conduct perchlorate sampling in soil based on the type of anticipated source. If the anticipated source is a detonation, composite sampling is recommended (Walsh et al. 1993; Crockett et al. 1996; Jenkins et al. 1996, 1997a, 1997b, 1997c, 2004; Thiboutot et al. 1997; Thiboutot, Ampleman, and Hewitt 2002.)

Concerns regarding sample heterogeneity do not end when the samples are collected. It is critical that laboratory subsampling also be conducted appropriately, regardless of what analytical methodology is used, particularly if a particulate source is anticipated. For additional information on laboratory subsampling, see *Guidance for Obtaining Representative Laboratory Analytical Subsamples from Particulate Laboratory Samples* (Gerlach and Nocerino 2003). The holding time for perchlorate in soil has not been established. In lieu of an established holding time for soil, the water holding time (28 days) has been used on an advisory basis when the sample is held at 4º ± 2ºC.

3.2 Analytical Methodologies

Analytical methodologies for perchlorate are discussed briefly below. Tables 3-1 and 3-2 (in Section 3.2.2) provide a comparison of the primary analytical methodologies in use. Key factors for choice of analytical methodology include the following:

- regulatory acceptance of method,
- state/USEPA certification of laboratory (if required by the state or the program),
- sensitivity, and
- selectivity.

Table 3-1. Perchlorate analytical laboratory methods comparison

Method (technique)	Applicability	Analytical limitations	Aqueous reporting limits (µg/L)
EPA 314.0 (ion chromatography [IC])	• Mandatory for drinking water samples reported under UCMR 1 • Aqueous samples with low dissolved solids (conductivity <1 mS/cm total dissolved solids [TDS]) and chloride, sulfate, and carbonate concentrations <100 mg/L each • Conductivity of samples must be below the laboratory's established matrix conductivity threshold	• Analysis is subject to false positives due the unspecific nature of the conductivity detector • Method has been validated in drinking water only; no guidance provided for use with soils, biota, etc. • The lower reporting limit of 0.5 ppb is achievable only in samples with very low TDS • Inappropriate for use in samples with high TDS	4
EPA 314.1 (IC)	• Method has been used on aqueous samples, including those with high TDS • Published EPA method (EPA 2005a) • Planned option for UCMR 2	• Analysis may be subject to occasional false positives due to the unspecific nature of the conductivity detector • Uses second dissimilar chromatographic column to aid in qualitative identification • Requires the use of anion reduction cartridges if used to analyze samples with high TDS	0.5–1
EPA 9058 (IC)	• Aqueous samples w/ <1 mS/cm TDS • Soil samples • EPA method published (EPA 2000a)	• Analysis may be subject to false positives due to lack of confirmation requirements or conformational chromatographic column • EPA method currently under revision	0.5–1
EPA 6850 (LC/MS)	• Aqueous samples to include those with high TDS • Soil samples • Biota samples • Determinative method for perchlorate • Published EPA method undergoing validation studies	• None reported	0.2 for water and soil; 0.6 for biota
EPA 331.0 (LC/MS or LC/MS/MS)	• Method limited to aqueous samples to include those with high TDS • Planned option for UCMR II • Determinative method for perchlorate • Published EPA method available (EPA 2005b) • Planned option for UCMR 2	• Pretreatment recommended in Winkler, Minteer, and Willey (2004) method • May be subject to false positives unless ion ratio monitored • Under MS/MS, method is highly selective, but may be subject to false negatives unless adequate separation from common anions is achieved	0.02
EPA 332.0 (IC/MS or IC/MS/MS)	• Method has been used on aqueous samples, including those with high TDS, and on milk and biota samples • Determinative method for perchlorate • Published EPA method (EPA 2005c) • Planned option for UCMR 2	• May be subject to false positives unless ion ratio monitored • Under MS/MS, method is highly selective but may be subject to false negatives unless adequate separation from common anions is achieved	0.1
FDA Method (IC/MS/MS)	• Fruits and vegetables, bottled water, and milk	• None noted in literature	0.5 (limit of quantitation)

To detect perchlorate in the environment, analytical chemists use several techniques. As of the writing of this document, the only method that has been approved for compliance monitoring (UCMR 1) is USEPA Method 314.0. Method 314.0 is a presumptive method, and when perchlorate is detected for the first time in an environmental medium and this method is used, the presence of perchlorate should be confirmed using a determinative method. To confirm the presence of perchlorate in an environmental sample, it is preferable to use the analytical technique MS, which confirms the chemical composition of unknown ions by their molecular weight (mass-to-charge ratio).

As noted previously, some supplies of the laboratory detergents contain detectable levels of perchlorate. Considering the potential bias from these detergents, laboratories using these products either directly or indirectly during perchlorate analysis should consider analyzing a diluted sample of the detergent to eliminate the potential for this bias. Use of disposable equipment for any sample manipulation is recommended to limit the potential for cross-contamination.

3.2.1 Laboratory Methods

Published USEPA methods include Method 314.0 (promulgated) and Method 9058 (draft, Method 846, Revision IVB), Method 331.0, and Method 332.0. Methods 331.0 (LC/MS and LC/MS/MS) and 332.0 (IC/MS and IC/MS/MS) have extensive discussion of interferents. USEPA's Office of Solid Waste is currently performing method validation studies on a determinative method—Method 6850.

QC requirements are similar for most of the determinative laboratory methods. Some of the QC evaluations that are unique to emerging laboratory methods include the analysis of a suppression standard (500 mg/L bicarbonate, carbonate, chloride, and sulfate) spiked at the reporting limit, comparison of the isotopic ratio for chlorine in the perchlorate to natural isotopic abundance ratio, and the use of an $18O_4$-labeled perchlorate internal standard. Analysis using the determinative methods is more sophisticated than for the ion chromatography (IC) methods, requiring more education/training for both the analysts and the data reviewer. However, IC/MS/MS, LC/MS, and LC/MS/MS are more expensive than IC methods alone.

A description of the published and emerging methods, and their limitations, are discussed in the following subsections.

3.2.1.1 Method 314.0—Ion Chromatography

Method 314.0, the only method for perchlorate promulgated by the USEPA to date, was developed for drinking water. Aqueous samples are introduced into an ion chromatograph. The perchlorate ion is separated from other ions in the sample based on its affinity for the material in the chromatographic column and is detected using a conductivity detector. The conductivity detector cannot specify the ion producing the analytical response; ions are differentiated based solely on retention times.

Sample matrices with high TDS and high concentrations of common anions such as chloride, sulfate, and carbonate can destabilize the baseline in the retention time window for perchlorate and also add or suppress the response of the detector to perchlorate. These can be indirectly assessed by monitoring the conductivity of the matrix. Therefore, the laboratory must determine its instrument-specific matrix conductivity threshold (MCT), and all sample matrices must be monitored for conductivity prior to analysis. When the MCT is exceeded, sample dilution and/or pretreatment must be performed. However, sample dilution leads to elevated reporting limits and pretreatment to remove potential interfering ions has the potential to reduce the actual perchlorate content of the sample at low concentrations.

There is evidence of cases where Method 314.0 has resulted in the reporting of false positives, falsely elevated results, and false negatives. Additionally, the method has been used as the basis for laboratories reporting to sub-ppb levels despite the method's documented capability of 4.0 µg/L. MADEP set a "demonstration of capability" involving very rigid QC requirements and proficiency evaluation samples rounds to allow laboratories to report sub-ppb levels (see www.mass.gov/dep/brp/dws/files/perchlor.doc).

3.2.1.2 Method 314.1—Inline Column Concentration/Matrix Elimination Ion Chromatography with Suppressed Conductivity Detection

Several options have been explored to improve Method 314.0, including sample enrichment/ isolation techniques intended to improve sensitivity, such as increased sample size and preconcentration/preelution, and resolution and analysis improvement strategies, such as heart cutting/column switching, noise suppression, and the use of dual channels. Samples are collected using a sterile filtration technique and stored with headspace to reduce the potential for degradation by any remaining anaerobic organisms. Laboratories employing these improvements/ alterations report their results as Method 314.0 analyses as the changes are not considered to be outside the method.

This method is intended to add increased sensitivity, better tolerance of TDS, and better selectivity through use of a confirmation column and in-line concentration. Method 314.1 was published in 2005 (USEPA 2005a).

3.2.1.3 Method 9058—Ion Chromatography with Chemical Suppression Conductivity Detection

Method 9058 is the USEPA's Office of Solid Waste (OSW) method for IC. The method is substantially the same as Method 314.0, although the MCT requirement is not included. The method is stated to perform adequately on water samples with conductivities up to 1000 µS/cm and is potentially applicable to surface water, mixed domestic water, and industrial wastewaters. The limitations described above for Method 314.0 apply similarly to Method 9058.

OSW is in the process of revising the November 2000 version of Method 9058 given the known interferences and the high probability of false positive and false negative results. The areas being considered for the optimization of the method are to include an extraction procedure for solids, to broaden the scope so that the method is applicable for aqueous samples having high TDS, to lower the level of detection for perchlorate at sub-ppb level, to have better separation, and to

minimize false positive and negative results. After the revised method is drafted, an inter-laboratory validation study will be conducted.

3.2.1.4 Method 6850—Liquid Chromatography/Mass Spectrometry

The LC/MS method uses a liquid chromatograph with a peptide-impregnated reverse-phase column to perform the separation followed by an MS for detection. Minimal sample pretreatment is required. Perchlorate parent ions (mass-to-charge [m/z] 99 and 101) are used for peak identification. This method has been evaluated with drinking water, soil, biota, synthetic groundwater (7700 $\mu S/cm^2$), and Great Salt Lake water (10× dilution, 21,000 µS) (Di Rienzo et al. 2004). The advantages of LC/MS are the increased sensitivity, increased specificity, the lack of sample pretreatment, and the lack of additional instrumentation. An interlaboratory validation study of Method 6850 is taking place in 2005. The reporting limit in water is reported to be 0.1 µg/L. This method will address environmental matrices other than drinking water.

3.2.1.5 Method 331.0— Liquid Chromatography Electospray Ionization Mass Spectrometry

This method, published in 2005 (USEPA 2005b) is a liquid chromatography/electrospray ionization/mass spectrometry (LC/ESI/MS) method for the determination of perchlorate in raw and finished drinking waters. This method can be used to acquire data using either selected ion monitoring or multiple reaction monitoring detection.

In this method, water samples are collected in the field using a sterile filtration technique. Prior to analysis, isotopically enriched perchlorate is added to the sample as an internal standard. The sample is injected without cleanup or concentration onto a chromatographic column, which separates perchlorate from other anions and background interferences. Perchlorate is subsequently detected by negative electrospray ionization mass spectrometry. A remote-controlled valve is used to divert early-eluting cations and anions to waste. Prior to the elution of perchlorate, the valve is switched sending the chromatographic eluent to the mass spectrometer. This diversion helps prevent unnecessary fouling of the electrospray source. Perchlorate is quantified using the internal standard technique. The reporting limit in water is reported to be 0.02 µg/L.

3.2.1.6 Method 332.0—Ion Chromatography with Suppressed Conductivity and Electrospray Ionization Mass Spectrometry

This IC/MS method, also published in 2005 (USEPA 2005c), is essentially the same as the IC method; however, an MS with an electrospray interface is added. This method requires the use of a suppressor to avoid inorganic salt buildup and uses a conductivity meter to check its efficiency. It uses m/z 99 and 101 ions for peak identification of perchlorate, and monitors the ion ratio of the naturally occurring abundance of Cl-35 and Cl-37, which should be 3.08.

The advantages of IC/MS are the increased sensitivity and increased specificity; however, high hydrogen sulfate (HSO_4^-) content will elevate the baseline at m/z 99 because it elutes prior to perchlorate. High concentrations (~1000 ppm) will tail into the perchlorate peak retention time. However, even with a sulfate concentration of 1000 ppm, 0.1 ppb perchlorate can still be

detected. If the baseline is elevated, there is a mandatory cleanup step to remove the sulfate prior to sample injection. Quantitation is done on the m/z 101, which is not affected by sulfate. The quantitation limit in water is reported to be 0.1 µg/L.

3.2.1.7 FDA Method—IC/MS/MS

IC/MS methodology can be enhanced by coupling the IC with a conductivity detector and a tandem MS, thereby increasing the sensitivity and specificity over that of IC/MS. The second MS allows further fragmentation of the perchlorate ions into the daughter ions (m/z) 83 and 85, eliminating false positives or negatives that can be caused by interferences. The quantitation limit in water is reported to be 0.01 µg/L (Penfold 2004 and personal communication).

The method has been used on water, soil, milk, lettuce, and other biota samples.

3.2.1.8 Availability of Emerging Methods

At this time, more and more commercial laboratories are adding these methods to their capabilities. With the publication of new methods in 2005, availability is expected to increase dramatically as regulatory agencies approve and require their use.

3.2.1.9 Other Laboratory Methods

Capillary electrophoresis (CE) has been used to analyze perchlorate for certain applications (primarily forensics). CE is not currently viable for analysis of perchlorate in environmental media at low concentrations. The best limit of detection available with most widely available equipment and reagents for CE is 100 µg/L (Urbansky 2000).

3.2.2 Field Methods

Two field methods have been employed to varying degrees of success for perchlorate (see Table 3-2 for comparison). The use of ion-selective electrodes and colorimetry is described below.

Table 3-2. Perchlorate field methods comparison

Method (technique)	Applicability	Analytical limitations	Reporting limits
Ion-selective electrode	• Can potentially detect perchlorate in the low-ppb range • Potential for in situ sampling for groundwater monitoring wells • Commercially available models suitable for both field and laboratory applications	• Commercial availability of low-ppb electrodes unknown • Presence of ions can interfere with the perchlorate electrode	• Low ppb (as tested); 200 µg/L (commercially available) • Detection limit may be too high to be useful
Colorimetry	• Used for surface water, well water, bioreactor effluent, and soil extracts. • Method published: USACE ERDC/CRREL TR-04-8 (Thorne 2004)	• Humic and fulvic acids from soil surface or root zone may cause false positives, requiring cleanup • Presence of chlorophyll or machine oils causes false positives	• 1.0 µg/L

3.2.2.1 Ion-selective electrode

A project sponsored by the USEPA and the U.S. Army Corps of Engineers (USACE) in 2001 created an ion-specific electrode to sample for perchlorate in groundwater monitoring wells. The electrode can detect perchlorate in the low-ppb range, but it is not evident whether this particular electrode is commercially available.

However, there are commercially available electrodes, such as the Perchlorate Ion-Selective Electrode by NICO2000 Ltd, which has a solid-state polyvinyl chloride polymer matrix membrane. The electrode is designed for the detection of perchlorate ions in aqueous solutions and is suitable for use in both field and laboratory applications. The detection limit for this electrode is 200 µg/L for perchlorate. The time for a stable reading after immersion is 2–3 minutes. The following ions can interfere with the perchlorate electrode: thiocyanate, iodide, nitrate, chloride, phosphate, and acetate. Nitrate can be tolerated up to the same concentration as perchlorate, and chloride can be tolerated up to 100 times the concentration of perchlorate without significant interference.

3.2.3.2 Colorimetry

A reliable and inexpensive colorimetric method for perchlorate in water and soil extracts has been developed and tested with surface water, well water, bioreactor effluent, and soil extracts. The detection limit for water is 1 µg/L and 0.3 µg/g for spiked soils. This method uses a solid-phase extraction cartridge conditioned with a perchlorate-specific ion pair reagent. The perchlorate that has been isolated from water or a soil extract by the resin cartridge is eluted into a dye, forming an ion pair that is extracted with xylene and measured with a field-portable spectrophotometer. Certain humic materials, colored biological materials (like chlorophyll), and machine oils cause false positives. Cleanup procedures can solve most of these problems but not that caused by chlorophyll. In such a case filtering may solve the problem (Thorne 2004).

3.3 Analytical Strategies

The strategy employed to choose analytical methodologies depends upon data quality objectives (DQOs), site information, and the agency conducting the investigation or oversight.

3.3.1 Data Quality Objectives

The uncertainty of results obtained using the IC method increases as the reporting level necessary to achieve project objectives approaches the lower performance limitations of the instrumentation. Therefore, depending upon the required reporting level, use of determinative methods exclusively could be appropriate. Until USEPA determinative methods are promulgated for perchlorate, some use of Method 314.0 will almost certainly be required by regulatory agencies, particularly for compliance monitoring.

3.3.2 Site Information

Site history and background information (e.g., production or use of explosives, possible releases of perchlorate) provides good information about the possible presence of perchlorate in

groundwater or soil. However, the analytical strategy selected for the analysis of perchlorate depends upon the decision to be made and the DQOs needed to make that decision.

If the site has documented perchlorate releases, minimal use of determinative methods would probably be appropriate. However, if only the use of perchlorate on the site is documented or a known release was very small, the use of determinative methods would be advisable. Additionally, if the site has known interferences with Method 314.0, use of determinative methods would be appropriate. If determinative analyses have already been conducted at a site and have confirmed the quantitative value of Method 314.0 analysis, additional use of determinative analytical techniques may be unnecessary.

Figure 3-1 illustrates one example of a drinking water sampling strategy implemented in California for low TDS. Please note that this is only one example strategy; strategies should be determined based on different needs.

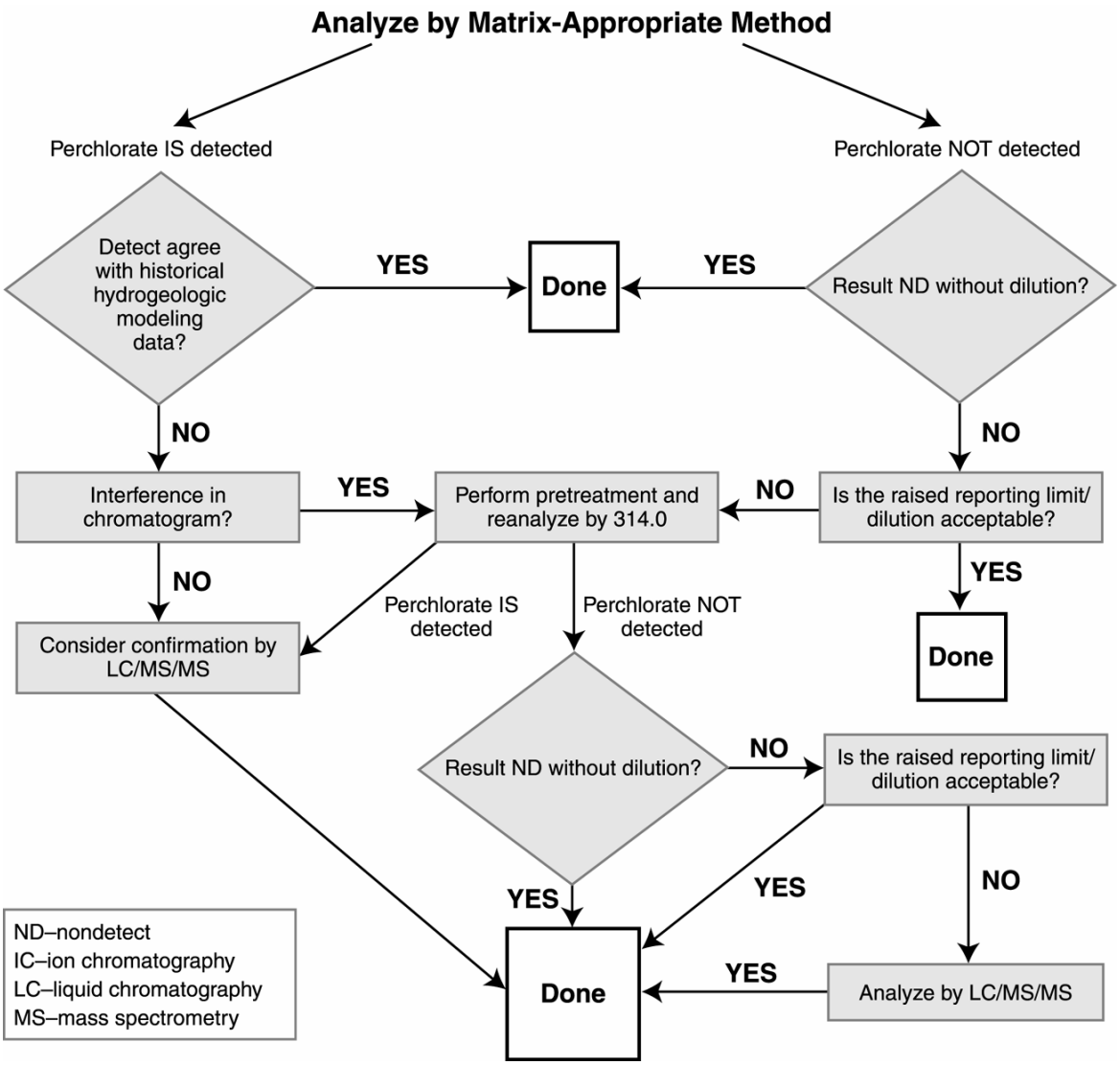

Figure 3-1. Perchlorate decision tree.

3.3.3 Agency Conducting the Investigation

FDA laboratories are anticipating use of the FDA method (USFDA 2004b). DoD agencies are required to follow the "Interim Guidance on Sampling and Testing for Perchlorate" (DoD EDQW 2004), which requires the confirmation of any detections above action levels with determinative methods. State agencies differ in their approaches.

3.4 Forensics Techniques/Chemometrics

Environmental forensics is the systematic investigation of a contaminated site or event focused on defensibly allocating liability for the contamination. Forensic investigative approaches available to identify the source(s) of perchlorate contamination in soil or groundwater include traditional source identification and concentration profiling, association with affiliated chemicals, and isotopic analysis.

Most perchlorate salts have high water solubilities; concentrated solutions have densities greater than water. Once dissolved, perchlorate is extremely mobile and persistent, requiring decades to degrade. Perchlorate is not significantly retarded by organic materials in groundwater; advection is the primary mechanism of dispersal. Therefore, it may be used as a tracer for hydrocarbon and metal contaminants that are significantly more retarded. Possible forensic techniques include chlorine isotopes for defining multiple or commingled perchlorate plumes (Motzer 2001).

As with other forensic investigations, the detection and use of associated chemicals is often of more forensic value in identifying and allocating sources than for the contaminant of concern. For identifying perchlorate associated with highway road flares, for example, identifying the distribution of strontium nitrate, which often composes up to 70% of a road flare, may provide insight as to the source of the perchlorate (see Section 6.1 for more information on cocontaminants.).

Research is being conducted to develop methods for differentiating between naturally occurring and manmade perchlorate in the environment. One approach is to use stable isotope ratio analysis of the perchlorate molecule. Stable isotope ratio analysis relies on the fact that the major elements composing the inorganic molecules occur as isotopes that can be quantified using isotope ratio mass-spectrometry. The ratio of the specific isotopes in the perchlorate molecule, chlorine and oxygen, can be used to track the source of the perchlorate in the environment (Bao and Gu 2004). Limited data collected to date reveal that the chlorine isotope ratio in a naturally occurring perchlorate source is considerably lower than that in manmade perchlorate. Conversely, the oxygen isotope ratio for the natural perchlorate is appreciably higher than in manmade sources. Researchers at Louisiana State University and Oak Ridge National Laboratory (ORNL) have been on the developmental forefront in this technique (Erickson 2004). Some locations may have a mixture of manmade and naturally occurring perchlorate. The western half of the United States would appear to represent the most likely area for mixed plumes to occur due to favorable geological and precipitation conditions.

The ability to use stable isotope ratio analysis depends highly upon the matrix and concentration of perchlorate present. Solid samples typically require multistep cleanup procedures to eliminate the presence of other nonperchlorate oxygen sources and the concentration of perchlorate in trace-level aqueous samples may be too low initially for isotopic analysis and require concentration on an ion exchange resin. The distinction that can be identified through stable isotope ratio analysis is between perchlorate that forms by natural environmental processes and perchlorate that is manufactured through an industrial electrolytic process. Anthropogenic perchlorate that was released to the environment through the use of products manufactured from material containing naturally occurring perchlorate (such as Chilean nitrate) will likely have the same stable isotope ratio as other natural environmental occurrences of perchlorate. The continued evolution of analytical forensic techniques may permit the fingerprinting of detected perchlorate plumes to ascertain whether the source is natural or manmade and to what extent each source type is represented.

4. TOXICITY, EXPOSURE, AND RISK

Perchlorate has been detected in surface and groundwater, drinking water, food, and soil. Therefore, it is important to evaluate the effects of perchlorate exposure in humans and in wildlife and to communicate that information to a broad audience. The types of information presented in this overview are used by federal and state regulatory agencies as the basis for the promulgated standards, guidelines, policies, and procedures that direct the assessment and remediation of perchlorate-contaminated sites. Because of the uncertainty involved in evaluating toxicological data, the states and the federal government evaluating this information may use and evaluate this information somewhat differently to promulgate different standards and advisory levels (see Section 5.3.2). It is also important to note that the status of our knowledge of perchlorate exposure and risks is evolving; it will be important to periodically reevaluate what is known about this chemical.

Perchlorate is one of several compounds that can interfere with the thyroid's uptake of iodide, an essential component of thyroid hormones. Consequently, perchlorate exposure may result in a dose-dependent decrease in thyroid hormone production. Therefore, this chapter begins with an overview of thyroid hormone physiology; continues with a discussion of the potential effects (toxicity) of perchlorate, including a review of studies that examine the potential effects of decreases in thyroid hormone production; examines perchlorate exposure pathways; reviews the current status of perchlorate risk assessment; and explores the remaining data gaps and uncertainties of these topics.

4.1 Importance of Thyroid Hormone

The thyroid is a small gland located at the base of the throat. It synthesizes hormones that play a crucial role in the body's metabolism, reproduction, growth, and function of the cardiovascular and central nervous systems. The thyroid uses iodide (I^-), converted from ingested iodine (I_2), to synthesize the two key thyroid hormones, tetraiodothyronine (also known as thyroxine, T_4) and triiodothyronine (T_3).

Because of the importance of thyroid hormones in human physiological function, thyroid hormone synthesis is tightly regulated by a feedback control loop involving the anterior pituitary gland and the hypothalamus, two regions of the brain. Thyroid hormones are synthesized in response to the secretion of thyroid-stimulating hormone (TSH) from the anterior pituitary. TSH production in the anterior pituitary is regulated by levels of TSH-releasing hormone (TRH) secreted by the hypothalamus. For instance, the anterior pituitary increases the production of TSH in response to decreased circulating thyroid hormone levels. In addition, there are compensatory responses that can include increased thyroidal blood flow, volume, iodide clearance, and preferential synthesis of the more biologically active T_3, which helps regulate the availability of appropriate thyroid hormone levels (Morreale de Escobar, Obregon, and Escobar del Ray 2000). The human thyroid maintains a reserve of thyroid hormones to compensate for fluctuations in iodide content in the diet. Additionally, humans have circulating levels of inactive T_4 attached to thyroid-binding globulin, which also provides reserve thyroid hormones.

Hypothyroidism is the most common type of thyroid disorder and occurs when the thyroid makes too little of the thyroid hormone that the body needs to function properly. Significant and/or sustained decreases in thyroid hormone levels in the bloodstream have been found to result in effects ranging from a decrease in metabolism, dry skin, cold intolerance, and tiredness to impairment in behavior, movement, speech, hearing, vision and intelligence (Felz and Forren 2004). Hypothyroidism is a common disorder that is more likely to affect women than men (Surks et al. 2004). According to Hollowell et al. (2002), 4.6% of Americans have elevated TSH levels, 0.3% of whom could be classified as having overt hypothyroidism and 4.3% of whom could be classified as having mild or subclinical hypothyroidism. For individuals 65 years and older, 1.7% have overt hypothyroidism, and 13.7% have mild hypothyroidism. Surks et al. (2004) estimate the number of individuals with subclinical hypothyroidism to be between 4% and 8.5%, with women over age 60, approaching 20% incidence.

During pregnancy, extra stress is placed on many maternal biological functions, including thyroid activity (Glinoer et al. 1992). Significant and/or sustained decreases in thyroid hormone levels could affect development of the fetus. If the maternal thyroid is not able to maintain adequate levels of thyroid hormones, especially during the first trimester, irreversible alterations in fetal neurological development could occur. Sufficient thyroid hormone (especially T_4) is required during fetal development of the central nervous system. T_4 is solely supplied by the mother before the fetal thyroid gland becomes functional at the end of the first trimester (approximately 12 weeks) (Tillotson et al. 1994). After the first trimester, the fetal thyroid is functional and can maintain its own hormone levels. However, some studies suggest that T_4 supplied by the mother throughout pregnancy has an overall protective effect from fetal neurological impairment (Morreale de Escobar, Obregon, and Escobar del Ray 2000). Unfortunately, the impact of maternal versus fetal hormone production during brain development is not well understood. The American Thyroid Association (2003) recommends that women of childbearing age consult their physician for guidance concerning their proper thyroid hormone levels.

4.2 Perchlorate Toxicity

Perchlorate is one of several compounds that competitively interfere with iodide uptake in the thyroid. Other compounds such as nitrates, thiocyonate in cigarette smoke, and others are more prevalent in the environment than perchlorate. Iodide uptake inhibition is considered the mode of action (MOA) for perchlorate (Figure 4-1). The MOA also identifies that perchlorate has a threshold for effects and that the degree of effects are dependent on the dosage.

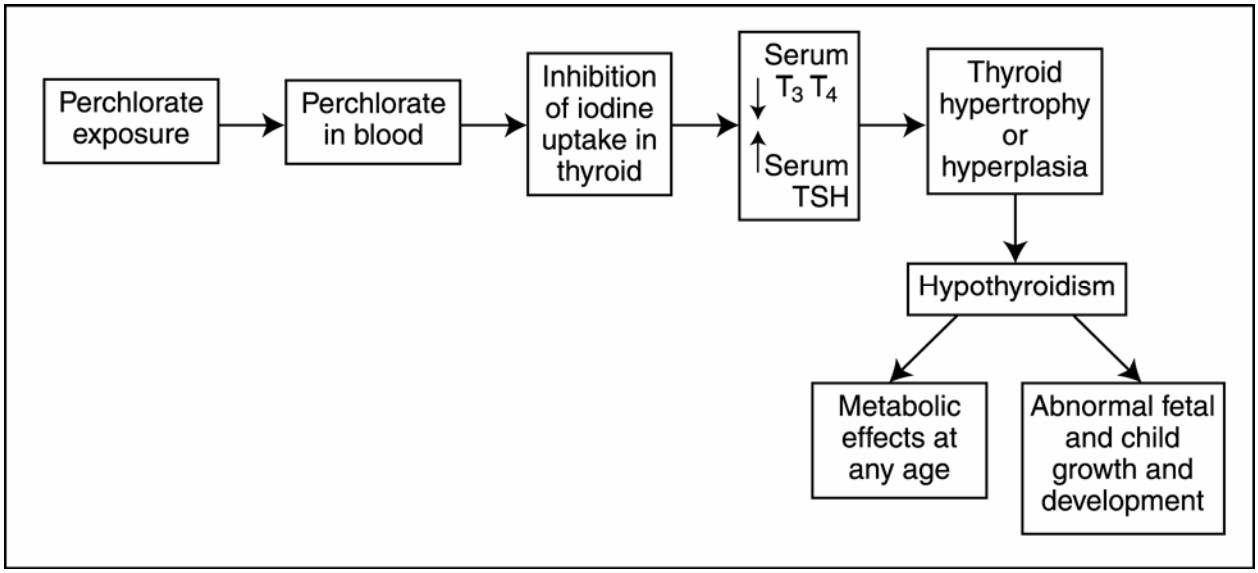

Figure 4-1. Mode of action model for perchlorate toxicity (Adapted from NRC 2005a)**.**

Animal and clinical studies conducted since 1997 were all designed based on this MOA for perchlorate. This MOA has been a point of agreement between toxicologists and risk assessors throughout the process to develop the perchlorate risk assessment; however, there is still some disagreement on defining the adverse or critical effect following perchlorate exposure and iodide inhibition.

4.2.1 Animal Toxicity Studies

To determine the health effects of perchlorate in humans, a fairly extensive database of animal toxicity studies was built in keeping with risk assessment guidelines and the MOA of perchlorate. This database includes a 90-day MOA study in rats (Siglin et al. 2000), immunological effects in mice (Keil et al. 1999), developmental effects in rats and rabbits (York et al. 2001a, 2003), two-generation reproductive studies in rats (York et al. 2001b), and developmental neurobehavioral studies in rats (Bekkedal et al. 2000; Bekkedal et al. 2004; York et al. 2004). It is not in the scope of this chapter to review these studies individually; the reader is referred to the studies listed in the references. The animal study database collectively supports the accepted MOA for perchlorate, competitive iodide uptake inhibition, and does not produce evidence of effects outside of that MOA.

Because rat and human thyroids work similarly, rat toxicity studies are valuable tools for qualitative information regarding the human thyroid; however, there are physiological differences between the human and rat pituitary-thyroid axis, which make rats inappropriate for quantifying predicted changes in humans for risk assessment purposes (NRC 2005a).

4.2.2 Epidemiological Studies

Perchlorate exposure of individuals is difficult to measure and has not been assessed directly in any of the studies conducted outside the occupational setting. Nearly all the studies were ecologic, including those in newborns and children, the groups potentially most vulnerable to the effects of perchlorate exposure. Ecologic studies, epidemiological studies without individual exposure characterization, can provide supporting evidence of a possible association but cannot themselves provide definitive evidence regarding cause. Epidemiologic studies have examined the associations of environmental exposure to perchlorate in drinking water at about 4–120 ppb (4–120 µg/L) and abnormalities of thyroid hormone and TSH production in newborns and thyroid diseases in infants and adults (Lamm and Doemland 1999, Brechner et al. 2000, Crump et al. 2000, F. X. Li et al. 2000, Z. Li et al. 2000, Schwartz 2001, Morgan and Cassady 2002, Kelsh et al. 2003, Lamm 2003, Buffler et al. 2004). Occupational studies of respiratory exposures up to 0.5 mg/kg perchlorate per day and abnormalities of thyroid hormone and TSH production in adult workers have been conducted (Gibbs et al. 1998, Lamm et al. 1999, Braverman et al. 2004). Only one study (Chang et al. 2003) has examined a possible relation between perchlorate exposure and adverse neurodevelopmental outcomes in children (attention-deficit/hyperactivity disorder and autism). A number of the studies have samples that are too small to detect differences in frequency of outcomes between exposure groups, and adjustment for potentially confounding factors was limited. The only study with measures of perchlorate made directly from drinking-water samples taken from faucets potentially used by people was a study in Chile (Crump et al. 2000).

4.2.3 Pharmacological Use and Clinical Studies

In the 1950s and 1960s, potassium perchlorate was given in doses of 400–2000 mg daily to more than 1000 patients for the treatment of hyperthyroid disease for many weeks or months with beneficial results. In general, treatment resulted in few side effects; however, the development of aplastic anemia in six patients raised concerns that resulted in decreased use of potassium perchlorate as a pharmacological agent, despite the fact that a direct cause-effect relationship between perchlorate and aplastic anemia was never established (Wolff 1998).

A number of studies collected clinical data from adult human volunteers in a controlled setting after exposure to known amounts of perchlorate in drinking water ranging from 0.007 to 12 mg/kg per day (Brabant et al. 1992; Lawrence et al. 2000; Lawrence, Lamm, and Braverman 2001; Greer et al. 2002; Braverman et al. 2004). Except for the Brabant study, the clinical studies measured inhibition of iodide uptake into the thyroid glands as well as TSH and thyroid hormones. The Brabant study was conducted for four weeks, the Lawrence and Greer studies for two weeks, and the Braverman study for six months. Serum TSH levels did not increase, and thyroid hormones did not decrease in any group.

4.2.4 Perchlorate Ecological Toxicity

While most of the available research on perchlorate has focused on determining effects of human exposure, perchlorate may have deleterious effects on other species throughout the environment. Field and laboratory studies assist in our understanding of the fate of perchlorate contamination in the environment.

Current field studies have demonstrated an overall lack of bioconcentration. Detectable concentrations of perchlorate were found only in a limited number of terrestrial mammals, birds, fish, amphibians, and insects exposed to elevated levels perchlorate in the environment (Parsons 2001). Similarly, rodent tissue sampled along the Las Vegas Wash had surprisingly low concentrations of perchlorate compared to and correlating with high concentrations in soil and surface water (Smith et al. 2004). Field studies of biota potentially impacted by releases of perchlorate associated with the former Naval Weapons Industrial Reserve Plant in McGregor, Texas, indicated detectable concentrations of perchlorate in periphyton (below detection to 0.376 mg/kg), tree leaves (below detection to 48 mg/kg), aquatic plants (below detection to 61.6 mg/kg) and small bird and mammals (kidney and liver tissue, below detection to 64 mg/kg in mammals and 86 mg/kg in birds). Perchlorate was also detected in native fish, but not detected in the blood plasma of opossums and raccoons collected near impacted streams (Tan et al 2005).

Perchlorate effects have also been assessed in both aquatic and terrestrial species of ecological relevance in laboratory studies. In aquatic environments, perchlorate concentrations under 1000 mg/L did not significantly affect aquatic microbial photosynthesis, aquatic bacterial production, sediment bacterial decomposition (i.e., respiration), or bog peat bacterial carbon dioxide and methane production in freshwater or marine systems (Hines et al. 2002). Aquatic invertebrates, including the water flea (*Ceriodaphnia dubia*), tolerated 9.3 mg/L perchlorate under chronic conditions and up to 20 mg/L under acute (i.e., short-term) conditions (Dean et al. 2004). An *in vitro* study of larval lamprey thyroids demonstrated that perchlorate's MOA is the same in fish as in humans (i.e., decreased iodide uptake and production of T_4) (Manzon and Youson 2002). At concentrations greater than 10 mg/L, perchlorate had no demonstrated effects on mortality, mating or offspring of adult threespine stickleback fish (*Gasterosteus* sp.) (Hines et al. 2002). Fathead minnow (*Pimephales promelas*) embryos reared for 28 days in 1–100 mg/L perchlorate exhibited decreased whole-body T_4 levels, delayed development, decreased scale production, and altered thyroid histopathology (Crane et al. 2005). Toxicity studies in amphibians indicate that they may be sensitive to high concentrations of perchlorate in the environment during metamorphosis (Dean et al. 2004, Goleman et al. 2002, Miranda et al. 1995). Studies of terrestrial species include a few bird studies (McNabb, Jang, and Larsen 2004; McNabb 2003) and multiple laboratory animal studies (York et al. 2001a, 2001b, 2003) performed to assess potential human health effects. Ecologically relevant studies in laboratory animals have shown that perchlorate does not affect reproduction end points in rats and rabbits. Decreases in T_4 and increases in TSH demonstrated in maternal laboratory rats at doses as low as 0.0085 mg/kg/day perchlorate (York et al. 2003) would be expected to occur among wild rodent populations at similar exposures. Whether these changes would result in an ecologically relevant population end point is not clear.

Ecological toxicity of perchlorate will be important on a site-by-site risk assessment basis. At some sites, ecological interests instead of human health concerns may drive remediation efforts. Ecological risk will not be addressed further in this document.

4.3 Perchlorate Exposure

Recent developments in analytical chemistry have allowed perchlorate to be measured at low concentrations in water, soil, food, and vegetation (Section 3). These advances in chemistry allow researchers to test for perchlorate in various media to levels as low as a few parts per trillion.

To determine how humans and ecosystems may be exposed, routes of exposure must be identified. Routes of exposure to perchlorate in ecosystems are complex and not well defined in available literature; therefore, only human exposure is discussed in the remainder of this section (Section 4.3).

4.3.1 Primary Routes of Exposure

Chemicals may enter the human body in several ways, known as "routes of exposure," including ingestion, dermal (skin) absorption, and inhalation. The primary route of human exposure to perchlorate is via ingestion of perchlorate-contaminated water and/or food. Human studies have indicated that ingested perchlorate is readily and completely absorbed from the gastrointestinal tract and excreted rapidly primarily via the urine (Eichler 1929 as cited in Stanbury and Wyngaarden 1952, Durand 1938). Based on available literature, ingestion of perchlorate-contaminated drinking water is one of the major exposure routes of concern, although ingestion of contaminated food and human milk are other potential sources of exposure.

When compared to ingestion, skin absorption and inhalation of perchlorate can be considered negligible exposure pathways. The compounds most readily absorbed through the skin are primarily organic chemicals. Because perchlorate is an inorganic compound and completely ionized in water, the potential for dermal absorption of perchlorate while bathing and washing is minimal.

Perchlorate particles can be suspended in the air and can be inhaled by individuals working in areas where perchlorate is manufactured (Lamm et al. 1999). Although release of perchlorate to the atmosphere is possible during the launching of solid propellant rockets, setting off fireworks, and as a result of the open detonation of old propellant, no published data were found on levels of perchlorate in the ambient air. Since perchlorate is not volatile, inhalation exposure from domestic use of contaminated water should not pose a problem (USEPA 2002).

4.3.1.1 Drinking Water

Public water systems, monitored under the UCMR, have detected perchlorate concentrations in several drinking water sources across the United States. In California, perchlorate has been found in more than 350 of the approximately 6,700 public drinking water sources (California Department of Health Services 2005). The lower Colorado River, a major source of irrigation and drinking water for southern California, also contain levels of perchlorate. Data collected by

the Nevada Division of Environmental Protection and the Metropolitan Water District of Southern California reflect perchlorate concentrations in the lower Colorado River, downstream of Hoover Dam, at less than 4 µg/L since June of 2004 (USEPA 2004c). The Texas Commission on Environmental Quality has detected perchlorate concentrations in an area exceeding 30,000 square miles in western Texas (Jackson et al. 2003). Extensive testing of Massachusetts' public water supplies has shown several drinking water sources to have perchlorate.

4.3.1.2 Food and Agriculture

In some agricultural settings, perchlorate-contaminated groundwater or surface water is used to irrigate foodstuff crops and animal feed crops. Recent studies have investigated the presence of perchlorate in these crops.

Studies conducted by Sanchez and Krieger (2004) revealed accumulation of perchlorate takes place in some plants and is accumulated mostly in leafy greens. Studies on lettuce have shown that accumulation occurs mostly in outer leaves and not consumable portions, such as the head (Susarla et al. 1999c, Sanchez and Krieger 2004). Susarla, Wolfe, and McCutcheon (1999) reported that when lettuce was irrigated with perchlorate-contaminated water (0.2–5 mg/L), total perchlorate concentrations within the leaves, stems, and roots ranged 248–1559 mg/kg. FDA collected lettuce samples from fields or packing sheds and various lettuce types (e.g., romaine, red leaf, green leaf, iceberg) that were found to contain average perchlorate concentrations from 7.76 to 11.9 ppb. (See Table 4-1 for preliminary results from data collected in five states). Tomatoes, carrots, cantaloupe, and spinach were also sampled, but results are not available at this writing (USFDA 2004a, 2004b).

Besides foodstuff crops, perchlorate has been detected in some animal feed crops, dairy, and meat. Alfalfa, a beef cattle and milk cow feed, tested at 109–555 µg/kg for samples from the Imperial Valley and 146–668 µg/kg from Yuma (Sanchez and Krieger 2004). Perchlorate has been detected in milk. The California Department of Food and Agriculture measured perchlorate at 1.5–10.6 ppb in milk samples. Milk samples (whole, 1% fat, fat-free, and organic) collected at grocery stores in 14 states were found to contain an average perchlorate level of 5.76 ppb (USFDA 2004a, 2004b) (see Table 4-1 for preliminary results from data). In addition to these studies, information obtained by the Environmental Working Group (a private nonprofit environmental group) indicated that perchlorate in eight samples of lettuce from a California grower ranged 0.110–6.9 mg/kg (EWG 2004b), and researchers from Texas Tech University measured perchlorate concentration up to 6.4 ppb in samples of supermarket milk (Kirk et al. 2005).

Other food sources where perchlorate has been detected include those detected by the Kansas Department of Health and the Environment. Unpublished data on perchlorate contamination in meat, chicken, eggs, produce, and fish indicate the following: chicken (8 and 14.6 ng/g wet weight), eggs (<4 and 102 ng/g wet weight), and milk (4 ng/g wet weight) collected in the vicinity of a site that has contaminated groundwater ranging from <0.3 to 118 µg/L. Last, kelp analyzed by Orris et al. (2003) contained 885,000 ppb perchlorate. Since kelp is used in many different food products, these high concentrations may be of concern.

Table 4-1. Summary of FDA preliminary data from samples collected through August 2004

Item	Number of samples	LOQ* (ppb)	Mean value (ppb)	Lowest value (#) (ppb)	Highest value (#) (ppb)
Green leaf lettuce	25	1.0	10.7	1.0 (1)	27.4 (1)
Iceberg lettuce	38	1.0	7.76	NQ** (8)	71.6 (1)
Red leaf lettuce	25	1.0	11.6	NQ (2)	52.0 (1)
Romaine lettuce	40	1.0	11.9	NQ (2)	129 (1)
Milk (all varieties)	104	3.0	5.76	NQ (3)	11.3 (1)

*LOQ = limit of quantitation, **NQ = not quantifiable, ½ LOQ used in averaging.

Even though perchlorate has been found in multiple food sources at varying concentrations, FDA continues to recommend that consumers eat a balanced diet, choosing a variety of foods that are low in trans fat and saturated fat, and rich in high-fiber grains, fruits, and vegetables.

4.3.2 Secondary Routes of Exposure: Fetal and Neonatal and Infant Exposure Pathways

Secondary routes of exposure are also of significant concern because they can impact sensitive receptors. Perchlorate can pass through the placenta and enter the fetal bloodstream; the lower the dose, the greater the percentage of maternal perchlorate that passes through the placenta to reach the fetus (Clewell et al. 2003a).

Infants, which have been identified as a potentially sensitive receptor population, may also be exposed to perchlorate in human milk. In laboratory studies, perchlorate was found in higher concentrations in the milk of treated animals than was present in the serum of the treated animals (Clewell et al. 2003b). Recently, Kirk et al. (2005) measured perchlorate concentrations in 36 samples of human milk from 18 states. This exposure pathway is of concern because perchlorate may inhibit the active transport of iodide into the mammary gland (Tazebay et al. 2000). During early development, infants depend on maternal iodide present in the milk.

4.4 Perchlorate Human Health Risk Assessment

An oral RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious noncancer health effects during a lifetime. A high-confidence RfD is based on data that address all potentially critical life stages.

Although there is a standard process for risk assessment, its application on a site-specific basis can be complex. The difficulty of site characterization, the likelihood of exposure under different scenarios, the ongoing scientific debate over toxicity, and the weighting of uncertainty result in a range of different outcomes and risk evaluations. These difficulties are evident in the site-specific risk assessments for most chemicals, including perchlorate.

4.4.1 Sensitive Subpopulations

Concern for perchlorate toxicity is rooted in our common understanding of thyroid hormone imbalance as described in Section 4.1. While there is general agreement that fetal and neonatal neurodevelopment is the main end point of concern, the disagreement has occurred over what biological change constitutes a key event on which to base toxicity values. Potential key events for setting perchlorate toxicity values include inhibition of iodide uptake, alterations in thyroid hormone synthesis, or some other measurable end point.

Based on the review of available studies, the sensitive receptor of concern for perchlorate exposure is the developing fetus in a mother who is hypothyroid. It is postulated that hypothyroid pregnant women would not have sufficient compensatory mechanisms to manage reduced iodide uptake due to perchlorate competitive inhibition, although the dose-response relationship is still uncertain. Thyroid hormones are critical for both the fetus and neonate. Although the periods of development that are most sensitive to thyroid perturbations are known, our understanding is limited by lack of data on perchlorate dose-response, making it difficult to predict the potential effects of perchlorate (Howdeshell 2002).

Fetal effects associated with severe iodide deficiencies (e.g., cretinism and mental retardation) are rare in the United States. Therefore, the primary concerns regarding iodide deficiency are decreased IQ and alterations in psychomotor development. A recent study by Auso et al. (2003) indicates that in rats even short-term iodide deficiency during fetal development results in altered neuronal migration, along with aberrant response to acoustic stimuli, including seizures. However, no studies of perchlorate conducted to date have documented these types of outcomes in humans. Uncertainties in the identification of the threshold for maternal and fetal thyroid effects and their relationship to fetal brain development (Morreale de Escobar, Obregon, and Escobar del Ray 2000) complicate deriving allowable perchlorate concentrations. While fetuses of hypothyroid pregnant women are considered to be the most sensitive subpopulation, other populations of concern may include nursing infants, children, postmenopausal women, and hypothyroid individuals (Table 4-2).

Adequate dietary iodine intake may reduce the susceptibility of individuals to the effects of perchlorate exposure; however because iodine overdose can have serious adverse impacts on thyroid function, it must be emphasized that individuals should not use iodine supplements, unless specifically directed to do so by their doctor.

4.4.2 Reference Dose

To calculate an RfD, risk assessors must first select a study that demonstrates a dose-response relationship between the chemical of interest and some critical effect. The critical effect is usually an adverse effect resulting from the chemical exposure. An analysis of the study is performed to determine the dose where there is no observed adverse effect (the no observed adverse effect level [NOAEL]). In some cases, the NOAEL cannot be determined, so the lowest dose corresponding to the adverse effect is used (low observed adverse effect level [LOAEL]). The NOAEL or LOAEL is then used as the point of departure for the calculation of the RfD.

Table 4-2. Subpopulations of potential concern

Potential receptor of concern	Rationale	References
Developing fetus	Thyroid hormones necessary for normal brain development	Haddow et al. 1999, Howdeshell 2002, Heindel and Zoeller 2003, Lavado-Autric et al. 2003, Auso et al. 2003
Nursing infants	Exposure to perchlorate via human milk; brain still developing, thyroid hormones necessary for brain development	Clewell et al. 2003b, Tazebay et al. 2000
Children	Brain still developing; thyroid hormones necessary for brain development, as well as growth and metabolism	Giedd et al. 1999, Sowell et al. 1999, Thompson et al. 2000, Webster et al. 2003
Postmenopausal women	High rates of hypothyroidism	Hollowell et al. 2002, Surks et al. 2004

To calculate the RfD, uncertainty factors are used to ensure that the RfD will be adequately protective of public health. Uncertainty factors (traditionally 10 or 3) can be applied to compensate for studies that are based on subchronic (short-term) exposure, rather than chronic (long-term) exposure, studies conducted using laboratory animals, calculations based on the LOAEL, rather than the NOAEL, or database insufficiencies. The uncertainty factors are combined via multiplication, and the NOAEL (or LOAEL) is divided by the uncertainty factors to derive the RfD. Table 4-3 illustrates how the reference dose for perchlorate has changed over time, as data have accumulated. The DWEL is a nonregulatory value that is based on the assumption that 100% of perchlorate ingestion is from drinking water.

To address these differences, the National Academy of Sciences, the National Research Council (NRC) established a committee to assess the health implications of perchlorate ingestion. At the request of DoD, DOE, NASA and USEPA, the NRC committee has recently addressed a number of charge questions covering key scientific issues associated with perchlorate risk and recommended an RfD of 0.0007 mg/kg/day (NRC 2005a). The NRC findings were summarized in the "Report in Brief: Health Implications of Perchlorate Ingestion," which is available online (NRC 2005b).

The NRC report determined that the inhibition of iodide uptake is the key biochemical event, is not an adverse effect, and should be used as the basis of the risk assessment (NRC 2005a). The NRC committee considered rats to provide only qualitative information on potential adverse effects of perchlorate exposure. The committee found that human data provided a more reliable point of departure than the animal data. They used iodide inhibition as the point of departure for developing the RfD. Inhibition of iodide uptake is a more reliable and valid measure, has been unequivocally demonstrated in humans exposed to perchlorate, and is the key biochemical event that precedes all other thyroid-mediated effects of perchlorate. Using a nonadverse effect that is a precursor to any adverse effects is an especially health-protective approach to the perchlorate risk assessment (NRC 2005a).

Table 4-3. Review of proposed RfDs

	USEPA 1992	USEPA 1995	USEPA 1999	USEPA 2002	NRC 2005 USEPA IRIS
Critical study	Stanbury & Wyngaarden (1952)	Stanbury & Wyngaarden (1952)	Argus 1998 Developmental Neurotoxicity Study	Argus 2001 Effects Study	Greer 2002
Species	Human	Human	Rat	Rat	Human
Critical effect or biochemical event	Release of iodide in the thyroid due to competitive inhibition by perchlorate	Release of iodide in the thyroid due to competitive inhibition by perchlorate	Altered brain morphometry (size and shape) in rat pups	Decrease T4 levels in dams and altered brain morphometry in rat pups	Inhibition of iodide uptake in humans (key biochemical event)
NOAEL/ LOAEL, mg/kg/day	0.14	0.14	0.1	0.01	0.007*
Uncertainty factors	1000	300	100	300	10
Calculated reference dose, mg/kg/day	0.00014	0.00046	0.001	0.00003	0.0007
DWEL, ppb	4	18	32	1	24.5

*This value is a No Observed Effect Level (NOEL). It differs from the NOAEL in that it is the highest dose at which there are no statistically or biologically significant increases in the frequency or severity of any effect between the exposed populations and its appropriate control.

The committee applied a total uncertainty factor of 10 (variability among humans) to the point of departure, which was the NOEL of 0.007 mg/kg/day in humans from the Greer et al. (2002) study. One committee member felt that an additional uncertainty factor of 3 should be used for database adequacy. However, the other 14 committee members concluded that the database—which includes five human clinical studies, occupational and environmental epidemiologic studies, studies of long-term perchlorate administration to patients with hyperthyroidism, and animal toxicology studies—is sufficient. The NRC committee concluded that a reference dose of 0.0007 mg/kg body weight per day would protect the health of even the most sensitive groups of people over a lifetime of exposure (NRC 2005a).

Based on the NRC report, USEPA posted the RfD for perchlorate on the Integrated Risk Information System (IRIS) as 0.0007 mg/kg/day in February 2005. The USEPA has not yet set an MCL for perchlorate in drinking water. In lieu of this regulatory value, various entities may calculate DWELs. As described previously, the DWEL is a nonregulatory value calculated on the assumption that 100% of perchlorate ingestion is from drinking water. Its sole utility is in making rough comparisons among different reference doses. Since other sources, such as milk and food, contribute to the total perchlorate ingestion, a risk-based regulatory value should include an estimate of the relative source contribution of water. To accomplish this goal,

exposure from all sources must be accounted for, as well as exposure factors, such as water consumption, and intake of (potentially contaminated) foods. As noted by NRC, such an assessment requires policy decisions, which are beyond the scope of their document and this chapter.

4.5 Perchlorate Uncertainties and Data Gaps

There are currently many unanswered questions surrounding the prevalence of perchlorate in the environment, the possible exposures and effects, and the risk management strategies available to manage perchlorate contamination. Further information must be obtained in each of these areas to develop successful and appropriate strategies for handing perchlorate contamination now and in the future.

4.5.1 Toxicity Uncertainties and Data Gaps

While animals are useful models because scientists can conduct multigenerational exposures (which cannot be conducted in humans), it is difficult to extrapolate effects in laboratory animals to effects in humans. This is particularly true for neurological effects, since animal models may not adequately capture the complexity of the human brain.

Since iodide uptake fluctuates every day as a result of diet and other factors and the body's natural adaptive processes compensate for these fluctuations, it would be helpful to gain a better understanding of when iodide uptake inhibition by perchlorate reaches the threshold of iodide deficiency. We still need to elucidate the relationship between reduced iodide uptake with compensatory changes in thyroid regulation and an irreversible developmental effect (hormone dysregulation).

There are several confounding factors that limit the value of epidemiological studies, including gaps in our understanding of these data. Comprehensive human epidemiologic studies may help quantify effects of perchlorate in sensitive subpopulations, assuming that researchers can develop adequate controls for potentially confounding factors.

Although very high concentrations of perchlorate can cause cancer in laboratory animals (Capen 1997; York et al. 2001a), exposure to perchlorate in the environment has not been shown to cause cancer in humans, and USEPA has concluded that perchlorate is unlikely to cause thyroid cancer in humans. The laboratory animal studies are somewhat controversial. Perchlorate does not produce tumors through alteration of genetic material in animals (USEPA 2002). Tumor production in laboratory animals is thought to be dependent on dose and the physiological perturbation of the thyroid hormone feedback system (USEPA 1998). The concentrations of perchlorate required to produce tumors are far greater than the amounts encountered by human populations, even in highly contaminated industrial settings (Gibbs et al. 1998, Lamm et al. 1999).

Finally, there are numerous other compounds that can modulate thyroid hormone homeostasis (for example, see list of chemicals compiled by Howdeshell [2002]). We lack data to evaluate potential interactions with these additional compounds.

4.5.2 Exposure Uncertainties and Data Gaps

The prevalence of perchlorate in public and private drinking water supplies and in foodstuffs must be further evaluated. The results of recent sampling efforts in water and food indicate that perchlorate may be more widely prevalent than originally recognized. Additional sampling of these exposure media is ongoing. The results of such testing should be compiled and evaluated.

Since nursing infants are considered to be a potentially sensitive subpopulation, further research on measuring possible exposure to perchlorate in human milk would be a significant addition to the database. In particular, further research should focus on understanding the effects of perchlorate exposure on lactation and the iodide and perchlorate concentrations in human milk, and in particular, the concentrations of perchlorate in human milk over time.

In quantifying the scope of existing contamination, research efforts can be aimed at understanding effects of environmentally relevant concentrations and the development of appropriate risk management strategies.

4.5.3 Risk Assessment Uncertainties and Data Gaps

Uncertainties, such as dose-response extrapolation and exposure estimation, confound the risk assessment process. In general, chemical concentrations of contaminants in food and water are much lower than those used in experimental settings (using rats as models, for example). Therefore, it is always difficult to estimate the potential effects of exposure to concentrations that are much lower than those used in experiments.

The primary sources of uncertainty in estimating an RfD for perchlorate in drinking water arise from the absence of data on possible effects of exposure among populations at greatest risk of adverse effects of iodide deficiency (pregnant women and their fetuses and newborns). Therefore, to reduce the uncertainty in the understanding of human health effects associated with perchlorate exposures, NRC has recommended additional research in several areas. Some of the major research areas include studies to determine the effects in humans of chronic low-dose exposure to perchlorate and studies to determine the effects of perchlorate on sensitive subpopulations (fetuses, infants, and pregnant women). The NRC committee also recommended a clinical study to provide information on the potential chronic effects of perchlorate exposure on thyroid function. Finally, to ensure that all pregnant women have adequate iodide intake, the committee recommends that consideration be given to adding iodide to all prenatal vitamins (NRC 2005a).

4.6 Summary

There are several significant and unique challenges in identifying and managing risks associated with perchlorate. In summary:

- Perchlorate competes with iodide uptake in the thyroid; this is the only known mode of action.

- The fetus of a hypothyroid woman is considered to be the most sensitive receptor. Other sensitive receptors may include nursing infants, children, postmenopausal women, and hypothyroid individuals.
- Toxicological uncertainty exists around the question, "What perchlorate exposure level leads to an adverse effect?" or conversely, "What perchlorate exposure level shows no effect in the most sensitive population?"
- Humans can be exposed to perchlorate primarily through ingestion of contaminated water and foods. Exposure of infants to perchlorate in human milk is of concern as well.
- Currently more is known about perchlorate exposure via drinking water than via other media since water supplies have recently begun testing for perchlorate. Less is known about exposure through food, although this data gap is receiving more attention.
- Potential for impacts to other species—plants, animals, and fish—is another area for further evaluation; primary interest will be in accumulation and transmittal to humans through the food chain, but the potential for direct effects on other species should also be investigated.
- NRC recently concluded that a reference dose of 0.0007 mg/kg body weight per day would protect the health of even the most sensitive groups of people over a lifetime of exposure. USEPA adopted NRC's recommended reference dose.

5. RISK MANAGEMENT AND REGULATORY STATUS

This section briefly discusses the role of risk management strategies, presents some possible risk management actions, and discusses the current regulatory status of perchlorate. Risk management involves the evaluation of strategies to eliminate or minimize risks due to contaminants at a site.

Because of the potential risks to human health associated with perchlorate exposure, the regulatory status of perchlorate has received increasing attention in recent years. At this point, the federal government and state governments have not yet set regulatory standards for perchlorate. However, some states have adopted advisory levels for perchlorate in drinking water, and a few states are considering or are in the process of promulgating state levels. It is important to note that although the federal government may set an MCL based upon the RfD recently established by USEPA, states retain the right to set stricter state standards.

5.1 Risk Management

Risk management involves evaluation of several different factors to decide how best to eliminate or minimize risks due to contaminants at a site. Risk management typically involves either implementing remedial activities that reduce contaminant concentrations to acceptable risk-based levels (established during the risk assessment), taking other measures to prevent completion of exposure pathways, or combining these approaches. Because of site- and location-specific factors, risk management strategies may not be consistently applied across site and programmatic boundaries.

The foundation for risk management strategies is information provided in the risk assessment. Other factors evaluated as part of risk management include regulatory requirements, technical feasibility, cost, effectiveness, and public acceptance.

Risk management begins with initial evaluation of the potential and actual occurrence of a perchlorate source. Short-term response actions generally evaluate sources relative to potential or completed exposure pathways. Initial efforts by regulatory entities may include identifying likely key source areas and sampling nearby water wells to help determine the need for immediate response actions to mitigate ongoing exposures. Environmental impacts that do not pose an immediate threat still require response actions, but using the more traditional, systematic approach common to all regulatory programs.

5.1.1 Risk Management Strategies

5.1.1.1 Pollution Prevention

The best risk management approach is to prevent a chemical release before it occurs. Therefore, the regulatory agencies and the regulated community have taken steps to eliminate or minimize perchlorate releases and improve management practices. In addition, some states have initiated reporting requirements for facilities that store or manage perchlorate materials.

In some cases, it is possible to manufacture products without perchlorate. For example, some manufacturers are now marketing alternatives to perchlorate-based road flares in the form of high-visibility lighting. However, replacing perchlorate is not always possible or practical.

Proper management and storage of perchlorate can also prevent perchlorate release to the environment. Solid perchlorate may be delivered in “super-sacks” or bags and typically stored on pallets within buildings constructed with concrete floors. Perchlorate may also be supplied in drums. Steel drums containing perchlorate are stored separately from potential fuels such as wood, oil, grease, etc. and provide isolation from the environment. Perchlorate salts and solutions are very corrosive to steel and degrade fiberglass and concrete. For example, corrosion impacts to concrete and steel, at least in part, have resulted in the release of perchlorate to groundwater at the former manufacturing facility at Henderson, Nevada. Unless the storage vessels, piping, and secondary containment are corrosion resistant and monitored, leakage to the environment and groundwater contamination can occur. Storage of bags and super-sacks and pouring/transfer operations may release perchlorate in the form of dust with similar results.

Some commercial explosives manufacturing facilities in operation today are equipped to ensure zero discharge of perchlorate waste. At these facilities, all wash water is captured and used in production, and affected containers are rinsed to remove all perchlorate before being disposed. Some facilities capture and recycle all residual perchlorate into new product. Incineration at a RCRA Treatment Storage or Disposal Facility, though very expensive, is also a disposal option for any perchlorate wastes. Explosives ready for use are typically stored in magazines for safety purposes. There is little risk of release from complete and packaged explosives unless carelessness results in packaging puncture with subsequent leakage.

California requires that perchlorate facilities have an unsaturated zone monitoring program and that all existing groundwater monitoring wells in the state be available for use as early warning or sentinel wells to warn of impending threat to drinking water resources. By the end of 2005, the California Department of Toxic Substances Control will adopt regulations specifying BMPs for managing perchlorate materials and prohibiting the management of perchlorate materials after the effective date of those regulations except in compliance with the specified BMPs. The California Environmental Protection Agency will also be required to establish a statewide data base for the electronic collection of perchlorate data.

5.1.1.2 Recycling

Since the early 1990s, the armed services have been developing methods of recycling solid rocket propellant, primarily because of concerns over air emissions from open burning. See Section 2.2.1.3 for more information on recycling of solid rocket propellants.

5.1.1.3 Risk Reduction

Assuming that "no action" has been eliminated as a potential response action, potential response actions fall into two broad categories: (a) the use of engineering or institutional actions to interrupt exposure media and ingestion pathways and (b) treatment solutions to address contaminant sources that pose an ongoing threat of release and environmental degradation.

Alternative Water Supply. When perchlorate has contaminated a drinking water source, one option is to provide an alternative drinking water supply (e.g., providing bottled water or switching to different source waters). Due to the volume of water supplied to most communities, this strategy may greatly affect the infrastructure and incur some costs. In some cases other sources may not be available, or the alternative supply may have other contaminants of concern not yet identified. In some cases states have issued warnings to the public without or before ensuring an alternative water supply. This approach allows the public to decide for themselves—based on age, condition, etc.—whether there is enough risk to identify an alternative water source. However, finding an alternative water supply does not lessen the need to clean up the source and impacted groundwater areas.

Blending. Some water purveyors have traditionally blended water from different sources and with different characteristics to produce a suitable, deliverable water supply. Blending is typically conducted to ensure that water supplied to the public is below an MCL or other regulatory standard and is a strategy that has been previously used in some cases of inorganic and organic contamination. Blending may be the only available option for a water purveyor with perchlorate contamination because of significant water demands, insufficient water treatment facilities, and insufficient resources.

As a long-term strategy, blending essentially allows lower-level exposure to a larger population instead of higher exposure to a smaller population. This strategy imposes exposure to concentrations below regulatory thresholds on populations who were not originally exposed to a contaminant. From a cost standpoint, blending may require additional services or construction of a new distribution infrastructure. It is also likely that the source areas and highly impacted groundwater require cleanup.

Treatment Prior to Use. Based on the extensive volume of drinking water supplied to most areas, surface water or groundwater treatment for perchlorate contamination would be costly. Available technologies for treating perchlorate include filtration through resins or other media that remove the compound and biological treatment of perchlorate that destroys the perchlorate ion. Section 6 presents several different treatment technologies and factors and limitations for the treatment technologies.

Plume/Source Remediation. Groundwater contaminants that have moved away from the source are typically characterized as "plumes." In the event that a contaminant plume has not yet affected a drinking water supply system, treatment of the plume and its source may be one alternative for preventing exposure in the future. In the event that a contaminant plume has already affected a drinking water supply well, treating the plume and/or the source may be components of a remedy that could eventually restore the quality of the drinking water supply. Groundwater remediation technologies are addressed in Section 6.

5.2 Regulatory Status

5.2.1 Federal Status

USEPA has not yet set an MCL for perchlorate in drinking water; however, the 1999 *Interim Assessment Guidance for Perchlorate* is still in effect (USEPA 1999a). In 2003, the USEPA reaffirmed the guidance with the added suggestion to carefully consider the low end of the provisional 4–18 ppb range (USEPA 2003b). In February 2005, based on the National Academy of Science's January 2005 report (NRC 2005a), USEPA established an official RfD of 0.0007 mg/kg/day of perchlorate.

In lieu of a regulatory value, various entities may calculate DWELs. As described previously, the DWEL is a nonregulatory value calculated on the assumption that 100% of perchlorate ingestion is from drinking water. Its sole utility is in making rough comparisons among different reference doses.

5.2.2 State Status

Some states have adopted advisory levels for perchlorate in drinking water, while a few are considering or are in the process of promulgating state levels. Massachusetts and California are currently in the process of promulgating state levels. Massachusetts has recently reaffirmed its proposed level of 1 ppb, while California has proposed a level of 6 ppb. These two states, and others that are considering promulgating state levels, evaluate the same toxicological data as presented in Section 4 to determine a proposed level. It is this interpretation and evaluation of data (such as applying a different uncertainty factor or considering food sources in addition to drinking water sources of perchlorate) that results that results in different proposed numbers at the state and federal levels.

The ITRC Perchlorate Team conducted a survey in 2004 to assess the most recent and current status of state regulatory, advisory, health-based, and/or other levels for perchlorate. The results

of the survey represent a snapshot in time and will be outdated by the ongoing assessment of perchlorate toxicity data and any resulting federal standard and/or state standards.

The survey focused on perchlorate health-based goals, cleanup goals, and action levels in groundwater, soil, surface water, and drinking water and consisted of the following five questions:

- Does your state have a health-based goal for perchlorate?
- Does your state have a state-promulgated drinking water standard for perchlorate?
- Does your state have a regulatory cleanup standard or level for perchlorate in groundwater?
- Does your state have a cleanup standard or level for perchlorate in surface water?
- Does your state have cleanup levels of standards for perchlorate in soil?

Fourteen states responded to the survey directly, and additional information was obtained via telephone call (New Mexico), via e-mail (Alabama) from the Texas Interoffice Memo (November 14, 2001) discussing an interim standard for perchlorate, and the USEPA Web site (MD) (Table 5-1).

Based on the survey results, states have not yet established official promulgated perchlorate standards or cleanup levels. The results also indicate that only a few states are evaluating official drinking water standards and that at least two states, Massachusetts and California, appear to be near completion of officially establishing state standards. California has proposed an MCL of 6 ppb and Massachusetts has established a health-based goal of 1 ppb for sensitive populations.

Currently, some states are using interim action levels based on the USEPA *Interim Assessment Guidance of Perchlorate* or site-specific risk-based cleanup standards to conduct remediation activities. For example, the Superfund Record of Decision for the Aerojet facility in Rancho Cordova, California, established a discharge and cleanup standard of 4.0 ppb for perchlorate. In July 2001, USEPA Region I established a perchlorate groundwater cleanup level of 1.5 ppb for Camp Edwards at MMR in Massachusetts. At least one state has adopted usage of the reference dose in the IRIS database. This state, Texas, has modified their risk reduction rules to adopt the RfD for use in their risk based exposure limit equations.

Table 5-1. Results of perchlorate levels survey (quantities are in parts per billion)

	Health-based goal	Health-based goal under consideration	Cleanup standard for groundwater	Cleanup standard for groundwater under consideration	Cleanup standard for surface water	Cleanup standard for surface water under consideration	Drinking water standard	Drinking water standard under consideration	Soil standard
AZ	14		No		No		No		No
AL [a]	No		No		No		No		No
AR	No		No	<4[b]	No	<4[b]	No		No
CA	6		No	Under evaluation	No	Under evaluation	No	Under evaluation	No
CO	No		No		No		No		No
KS	No	4	No	4	No		No		No
MA	1[c]		No	Under development	No	Under development	No	Under development	No
MD	1								
MO	No		No		No		No		No
NM	1 [h]		No		No				No
NV	No		18[d]		18 [d]		No		No
NH	No		No		No		No		No
NJ	No		No		No		No		No
NY	No		No	Under development	No		No		No
OR	No		No		No		No		No
TX	No		17[e]		17[e]		No		14[g]
UT	No		No		No		No		No
VA	No		No		No		No		No

[a] Alabama is currently developing a program to set site-specific risk-based standards for some chemicals of concern, including perchlorate.
[b] Arkansas currently uses this number for plume definition.
[c] Massachusetts: health-based goal for sensitive populations.
[d] Nevada has adopted a provisional action level of 18 ppb in groundwater and surface water until a new national standard is set by USEPA.
[e] Texas has established an action level, based on residential land use, for drinking water (Class 1 groundwater) at 17 ppb and 1700 ppb for nondrinking water (Class 3 groundwater). Where impacted groundwater is released to surface water used/designated as drinking water sources, the 17 ppb would apply as a surrogate standard.
[g] This level is the protective level for leachate of perchlorate from soil to drinking water; human health protective level in soil (combination of inhalation, ingestion, dermal contact, and vegetable consumption pathways) is 51,000 ppb.
[h] Drinking water screening level.

The following are additional responses and information provided by a number of respondents that could not be incorporated into Table 5-1:

- California, New Hampshire, and New Mexico indicated that current cleanup standards would be health risk based and site specific.
- Oregon indicated that no guidance or rulemaking on perchlorate is anticipated in the near future, but the state continues to track developments at a national and regional level.
- MADEP is currently conducting occurrence monitoring of public water supplies to support the development of a drinking water MCL and is also developing soil and groundwater standards.
- Arkansas will adopt a national standard as soon as one is set and use the soil number that USEPA Region VI will produce.
- Nevada has adopted a provisional action level of 18 ppb in groundwater and surface water for managing characterization and remediation at the Kerr-McGee and AMPAC facilities. When a national standard is set, Nevada will adopt this new standard.
- New York indicated that a drinking water standard is being developed by New York State Department of Health.

6. REMEDIATION TECHNOLOGIES

This section surveys the current state of perchlorate remediation technologies, with a focus on proven and commercially available technologies. Emerging technologies with tested bench-scale and/or pilot-scale studies, as well as those perchlorate treatment technologies in developmental stages, are also briefly discussed. The majority of the technologies discussed have primarily been applied to groundwater contamination. However, this section includes a brief review of perchlorate remediation technologies that are applicable for remediation of perchlorate in soil. A summary of different technologies, including each technology's applied scale (i.e., bench, pilot, or full), throughput (amount by volume treated), effectiveness, and current applicability towards a specific media is provided in Appendix F. A more detailed review and discussion of perchlorate treatment technologies, including a number of case studies and associated costs, will be provided in the ITRC Perchlorate Team's technical and regulatory guidance document, currently under development.

The success of any perchlorate treatment technology depends on several factors, including perchlorate concentration, the presence and concentrations of cocontaminants, and groundwater geochemistry. In general, ion exchange is more cost-effective when perchlorate concentrations are low (<50 μg/L). In addition, common anions in groundwater, including nitrate, sulfate, and bicarbonate, compete with perchlorate for binding sites on ion exchange resins. As the concentrations of these anions increase, the cost of ion exchange for perchlorate removal tends to also increase. Alternatively, microbial perchlorate reduction is negatively impacted by specific geochemical parameters, including low pH and high TDS. High levels of cocontaminants, such as heavy metals and organic solvents, could also be anticipated to negatively impact perchlorate degradation. It is important to consider these site-specific factors when selecting treatment technologies.

6.1 Cocontaminants

Cocontaminants can have an impact on the successful remediation of perchlorate. The most common cocontaminants found at perchlorate-contaminated sites are nitrate and sulfate (Table 6-1). Nitrate concentrations in contaminated media are generally far greater than those of perchlorate, and the presence of nitrate typically interferes with efficient reduction of the perchlorate anion. However, nitrate is commonly removed along with perchlorate because most perchlorate-reducing bacteria are denitrifiers as well (Logan 2001). The presence of sulfate should not adversely impact perchlorate removal, as perchlorate is generally reduced before sulfate. However, if the redox potential is too low, sulfate may become the electron acceptor (ITRC 2002). Additionally, cocontaminants such as sulfate, nitrate, bicarbonate, carbonate, and bromide can also compete with perchlorate during the ion exchange process.

Table 6-1. A partial list of characterized perchlorate-contaminated sites with identified cocontaminants

Site	Contaminated media	Other identified contaminants
Aerojet Facility, Rancho Cordova, California	Groundwater	TCE, N-nitrosodimethylamine (NDMA), nitrate, sulfate
Aerojet Facility, San Gabriel, California[a]	Groundwater	Nitrate, TCE
Big Dalton Well Site, Los Angeles, California[a]	Groundwater	Nitrate, sulfate
La Puente, California[a]	Groundwater	NDMA, 1,4-dioxane, sulfate, VOCs
Confidential site	Groundwater	Nitrate, chlorate[b]
DoD site, West Virginia	Groundwater	Nitrate, sulfate
Edwards Air Force Base, California	Groundwater	Nitrate, sulfate
Henderson, Nevada	Groundwater	Sulfate, sodium, calcium, magnesium, nitrate, boron, hexavalent chromium, chlorate
Lawrence Livermore National Laboratory, Site 300, Livermore, California	Groundwater	VOCs, nitrate, explosive compounds
Pueblo Chemical Depot, Colorado	Soil, groundwater	HMX, RDX, nitrate

[a] These are three different plumes from the same site, San Gabriel Valley Area 2 Superfund Site, also known as the Baldwin Park Operable Unit.

[b] Chlorate may be present as a cocontaminant as well as a potential degradation product. Isotopic analyses of these surrogate chemicals associated with perchlorate may similarly provide a means of source identification and cost apportionment.

Source: Hjeresen et al. 2003.

The presence of cocontaminants at perchlorate sites also depends on facility-specific operations and historical practices. For example, the majority of major weapons system with solid propulsion, explosive devices, or pyrotechnic devices contain perchlorate compounds. At such

sites, typical cocontaminants also include volatile organic compounds (VOCs), halogenated VOCs such as trichloroethylene (TCE), solvents, and explosive compounds such as trinitrotoluene (TNT), RDX, and HMX (ITRC 2002). The presence of these compounds makes perchlorate treatment systems more difficult to design.

Because of these concerns regarding cocontaminants, all cocontaminants should be well characterized before selecting a perchlorate treatment technology. This document does not review the effects of cocontaminants in any further detail for individual treatment systems. A more detailed discussion of the impact of cocontaminants on perchlorate treatment technologies will be addressed in the ITRC Perchlorate Team's next document.

6.2 Remediation Technology Applicability Matrix

There are a variety of remediation technologies for perchlorate remediation. Some technologies are proven and commercially available, while others are still in the research and development phase. This document provides an overview of the commercially available technologies (Section 6.3) and summaries of emerging technologies still at the bench- or pilot-scale stage (Section 6.4).

To summarize the state of technology development at this point in time, a detailed list of the various remediation technologies being used for 120 different projects has been compiled and provided in Appendix F. Of these 120 projects, 51 are full-scale systems. Thirty-nine treatment units were operational at the time of the completion of this report.

6.3 Proven/Commercially Available Technologies

A variety of remediation technologies are currently commercially available and being used for perchlorate remediation. These remediation technologies fall into two broad categories, ion exchange and biological processes. The majority of these treatment technologies have been applied to remediation of groundwater; however, biological processes are also being applied to the remediation of soils.

6.3.1 Ion Exchange

Ion exchange is a reversible chemical reaction wherein an ion from solution is exchanged for a similarly charged ion attached to an immobile solid. Similar to adsorption or chemical reactions, ion exchange depends on several variables, including the presence and concentrations of competing ions.

Ion exchange is the most commonly used physical treatment process for the treatment of perchlorate-impacted groundwater. During ion exchange, perchlorate, which is a negatively charged ion (anion), is exchanged with another anion, typically chloride (Cl^-). The ion exchange medium consists of a polymer (ion exchange resin) containing a positively charged functional group (e.g., a quaternary amine, R_4N^+) with a strong preferential affinity to the perchlorate ion. The following is the primary ion exchange equilibrium reaction of perchlorate with a strong base ion exchange resin in the chloride form:

$$R_4N^+Cl^- + ClO_4^- \Leftrightarrow R_4N^+ClO_4^- + Cl^- .$$

Ion exchange is an equilibrium process, and exposing the contaminant-laden ion exchange resin to a concentrated (sodium) chloride brine can reverse the equilibrium of the reaction to the left, thus displacing the perchlorate from the resin. This equilibrium reversal is used in the regeneration of spent resin and creates a brine with relatively high perchlorate concentrations that needs to be managed further. Once the resin is reloaded with chloride, it is placed back in service, and the ion exchange cycle is repeated. Another spent-resin management option that is widely used for resins based on styrene-divinylbenzene copolymers involves removal of the ion exchange resin when loaded with perchlorate for thermal destruction by blending the resin with boiler fuel. Figure 6-1 presents a conceptual schematic of the ion exchange process showing the two main management options for perchlorate-impacted ion exchange resins.

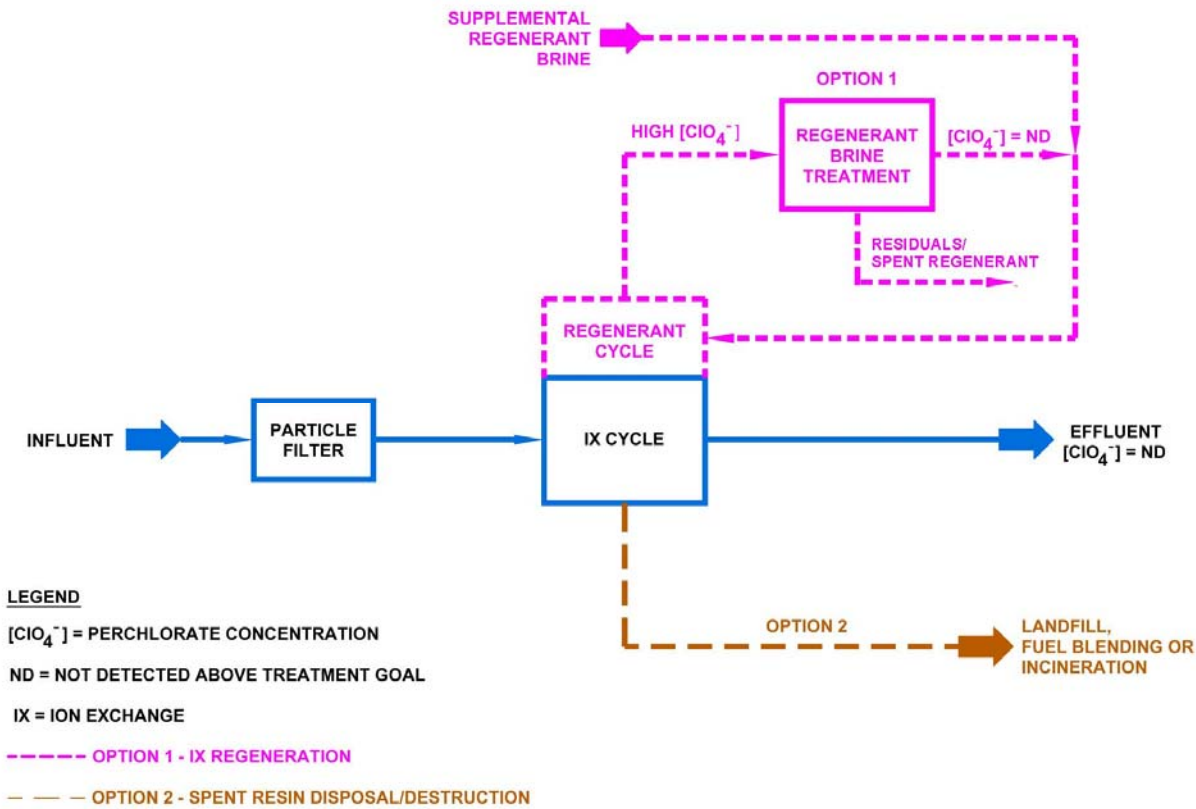

Figure 6-1. General schematic of ion exchange.

Many other anions commonly present in groundwater will compete with the perchlorate ion for this reaction. These include sulfate (SO_4^{2-}), nitrate (NO_3^-), bicarbonate (HCO_3^-), carbonate (CO_3^{2-}), and bromide (Br^-). Trace ions can also compete with the perchlorate ion for the resin surface (e.g., chlorate, bromate [BrO_3^-], arsenate, etc.). Water that contains high TDS values can significantly hinder ion exchange effectiveness and can become cost-prohibitive to treat. Interference from other anion species on the perchlorate loading of an ion exchange resin can be minimized by selecting a resin with functional groups that favor the exchange of perchlorate over other anions.

Several ion exchange equipment designs are currently employed, including fixed-bed downflow or upflow contactor systems that can be operated in either concurrent or countercurrent (service flow in the direction opposite to the regeneration), continuous moving-bed systems, and continuous multiport rotating distributor systems (e.g., Calgon Carbon's Ion SEParator [ISEP®] system). Some newer resin designs, however, take advantage of a greater selectivity for perchlorate, making it possible to operate the ion exchange unit for a protracted period of time while removing mainly perchlorate and not all of the other ions in the influent stream. Depending on the method of ion exchange system operation, the volume of the regenerant waste stream can range 2%–8% of the volume of water treated by ion exchange.

ORNL and the University of Tennessee have developed bifunctional resins that have the highest selectivity for perchlorate (CalEPA, 2004). These resins can be regenerated or removed for off-site disposal; several ompanies now market commercially available ion exchange resins. The quaternary ammonium groups combined with small alkyl groups afford these bifunctional resins high perchlorate selectivity and highly favorable exchange kinetics.

6.3.1.1 Concentrated Brine Treatment

Although regeneration of ion exchange resins is widely practiced in general, the management of the regenerant brine containing high levels of perchlorate in the presence of high chlorides and other anions poses significant challenges. The following summarizes three regenerant brine treatment alternatives: catalytic chemical reduction, ferrous chloride reduction, and biological reduction. Aside from the destruction of the perchlorate in the brine, the catalytic and ferrous iron reduction options aim to recycle the treated brine and reuse it for the regeneration of perchlorate laden resin.

Catalytic Chemical Reduction. In 1999, Calgon Carbon pilot-tested catalytic chemical reduction using ammonia as the reductant on the concentrated brine of their ion exchange system. The process was conducted under high pressure and temperature. The test results demonstrated effective destruction of perchlorate to levels below the (elevated) detection limit of 125 µg/L (Calgon, 1999). Calgon Carbon has coupled this technology with the ISEP® system to treat the concentrated ion exchange regenerant solution. The combined system is referred to as the ISEP®+ system.

Ferrous Chloride Reduction. ORNL has developed a new technology to regenerate selective ion exchange resins using a ferric chloride solution acidified with hydrochloric acid, creating a tetrachloroferrate ion ($FeCl_4^-$). The tetrachloroferrate ion displaces the perchlorate from the ion exchange resin. Desorption of the tetrachloroferrate ion from the resin takes place with water or a dilute acidic solution, so the resin becomes available again for perchlorate removal. The perchlorate-rich regenerant solution is subsequently reduced using ferrous chloride under elevated temperatures (<200°C) and/or pressures (~20 atmospheres) (Gu et al. 2001). Although this regeneration technology could be used either on or off site, it is likely that off-site regeneration will be appropriate for most low resin usage applications.

Biological Reduction. A membrane bioreactor system (MBR) is undergoing testing by Applied Research Associates for the treatment of perchlorate in the brine produced by regenerable ion exchange systems. The MBR has been successful at treating perchlorate-laden brine with TDS levels as high as 7% in the laboratory and underwent field testing in late 2004. (Section 6.3.2.1).

6.3.1.2 Spent Resin Disposal/Destruction

The vast majority of full-scale ion exchange applications for perchlorate treatment employ a once-through treatment where the perchlorate-laden (spent) resin is disposed of at an off-site location. Although landfill disposal could be considered, it is not widely used and does not eliminate the generator's ongoing liability. Instead, most spent resin management options center around thermal destruction, either via fuel blending or hazardous waste incineration.

6.3.2 Biological Processes

Perchlorate-reducing bacteria appear to be widespread in the environment, even though the presence of perchlorate is localized. This conclusion is supported by both microbial isolations and a multitude of microcosm studies showing that the addition of an appropriate electron donor (i.e., energy source) to a site sample causes perchlorate degradation without the addition of exogenous bacteria (Coates et al. 1999; Hatzinger et al. 2002; Waller, Cox, and Edwards 2004; Tan, Anderson, and Jackson 2004). That biological perchlorate reduction is occurring so widely in nature in the absence of perchlorate may reflect the similarity of the enzymatic reduction to biological denitrification and the conservation of this metabolism by microorganisms.

The biological degradation of chlorate was first observed in the 1920s and is the basis of an assay for biochemical oxygen demand (BOD) in wastewater (Bryan 1966, Logan 1998). A limited amount of research was also performed in the degradation of perchlorate as early as the 1960s (Hackenthal et al. 1964), but significant studies in this area began in only the mid-1990s concurrent with the first reports of widespread perchlorate contamination in the United States. Despite the rather short period of study, appreciable knowledge has been gained concerning the types of perchlorate-reducing bacteria, their ecology, and the pathway and kinetics of the biological reduction process.

A variety of perchlorate-reducing bacteria have been isolated, many of which are members of the newly identified genera *Dechloromonas*, *Dechlorospirillum,* and *Azospira* (formerly *Dechlorosoma*) (Achenbach et al. 2001, Xu et al. 2003). All of the bacteria isolated to date are facultative anaerobes, i.e., organisms that can grow in either the presence or the absence of oxygen, provided proper nutrients are available in the medium. Using this metabolic versatility, these organisms are capable of degrading perchlorate, chlorate, and in most cases, nitrate. For perchlorate, these bacteria use an organic substrate or, in some cases, hydrogen gas as an electron donor and use the perchlorate molecule as a terminal electron acceptor. As shown in Figure 6-2, the bacteria oxidize the organic substrate to carbon dioxide (or sometimes an intermediate) and reduce perchlorate initially to chlorate and then chlorite and finally to chloride and oxygen (Van Ginkel et al. 1996, Kengen et al. 1999). The enzyme (per)chlorate reductase is known to carry out this initial two-step reaction. A second enzyme, chlorite dismutase, subsequently disproportionates chlorite to chloride (Cl^-) and oxygen (O_2) (Coates et al. 1999).

An immunoprobe for the chlorite dismutase gene has been developed to detect perchlorate-reducing bacteria in environmental samples (O'Conner and Coates 2002).

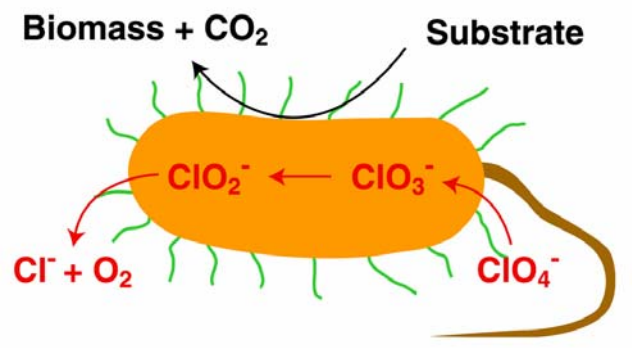

Figure 6-2. Schematic of biological reduction of perchlorate.

A variety of different electron donors have been shown to promote the biological reduction of perchlorate by individual strains and/or in environmental microcosms. These substrates include fatty acids (e.g., acetate, citrate, lactate), mixed and pure sugars (e.g., molasses, glucose), protein-rich substrates (whey, casamino acids), alcohols (e.g., ethanol), vegetable oils (Borden, Lindow, and Rodriguez 2004; Henry et al. 2003), and hydrogen gas (Logan 1998; Hunter 2002; Waller, Cox, and Edwards 2004; Zhang, Bruns, and Logan 2002; Hatzinger 2002). However, the specific substrates utilized as energy sources are strain- and site-specific.

The irony of perchlorate remediation is that despite the large numbers of microorganisms shown to be capable of reducing perchlorate and the breadth of metabolic capabilities that these microorganisms possess, perchlorate continues to persist in the environment. Thus, it remains important to develop approaches to address the large volumes of perchlorate-contaminated groundwater and soil. Biological processes offer many powerful and manageable solutions to this problem and are discussed in the following sections.

6.3.2.1 Ex Situ Bioremediation

A variety of different biological reactors, including continuous-flow stirred tank reactors (CSTRs), packed-bed reactors (PBRs), and fluidized-bed reactors (FBRs), have been tested for the ex situ bioremediation of perchlorate in water and wastewater. A recent review summarizing pilot- and full-scale bioreactor systems for perchlorate is provided by Hatzinger (2005). Figure 6-3 presents a diagram of a generalized ex situ bioremediation system. In addition, brief descriptions of these reactor designs are provided in the subsequent sections, and information concerning current status for perchlorate treatment can be found in Table 6-2.

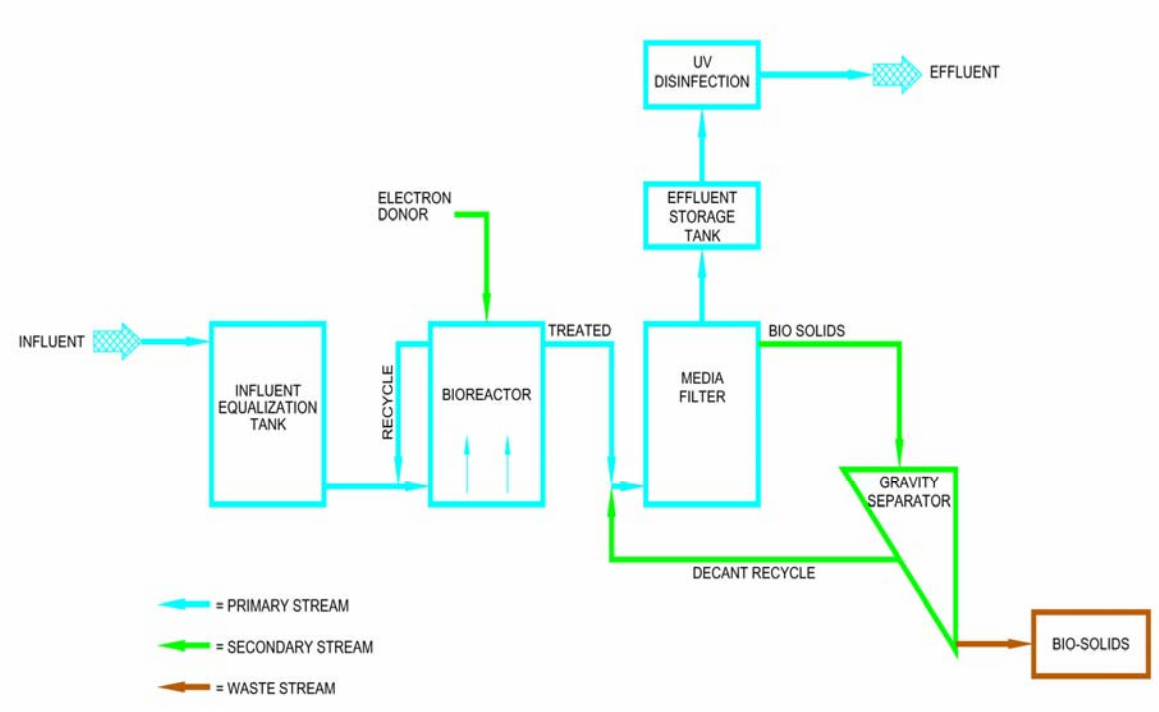

Figure 6-3. General schematic of ex situ bioremediation.

Table 6-2. Bioreactor system information

Reactor type	Description/location	Scale	Status	Perchlorate levels treated
Continuous-flow stirred tank reactors, Applied Research Associates	For treatment of hog-out[a] wastewater, Thiokol, Brigham City, Utah, using *Wolinella succinogenes* HAP-1 and desugared molasses	Originally: 1,600 and 720 gal, 2 × 1,000 gal added	Prototype 1997, expanded in 2002, currently operational	Capable of treating ~100,000 pounds per year
	For treatment of wastes from gunpowder manufacture, Hodgdon Powder Co., Kansas	2,500–5,000 gpd	Currently operational	Influent of 3,000 ppm to less than ~20 ppb (minimum reporting level [MRL])
Fluidized bed reactor, Shaw Environmental (formerly Envirogen) and U.S. Filter/Envirex Products	Treatment of both nitrate and perchlorate in groundwater, AeroJet General Corp., Rancho Cordova, California,[b] using granular activated charcoal (GAC), with ethanol	Required flow 4,000 gpm, currently 5,300 gpm	Operational since 1998	Designed to treat 8 ppm perchlorate and 1.5 ppm nitrate, currently, influent of 1,700 ppb to less than 4 ppb (MRL)
	Treatment of groundwater, Longhorn Army Ammunition Plant, Karnak, Texas,[c] using GAC, with acetic acid	50 gpm	Operational since 2001	Influent averaging 25 ppm to effluent less than 4 ppb
	Treatment of groundwater, McGregor Naval Weapons facility, McGregor, Texas,[d] using GAC, with carbon source not specified	Up to 400 gpm	Operational since 2002	Influent average of 2.3 ppm (range 0.5–5 ppm), effluent less than 4 ppb

Reactor type	Description/location	Scale	Status	Perchlorate levels treated
	Treatment of groundwater at Henderson, NV[e] (Kerr-McGee plant) using sand and GAC, with ethanol and mixed microbial population	~1000 gpm	Operational since 2004	Effluent nondetect levels <18 ppb
Packed bed reactor laboratory studies	This type of system has been pilot-tested for drinking water treatment at Castaic Lake	Up to 20 gpm	No operational units	See references
Other bioreactor designs	Treatment of drinking water at laboratory scale using a hollow-fiber membrane[f]	1.5 gpm	Pilot-scale testing	Influent initially 60 ppb, effluent going to <6 ppb
	Treatment of brine from ion exchange systems, Applied Research Associates, using membrane bioreactor technology	1 gpm	Pilot-scale testing	Influent initially 3–4 ppm, effluent going to <50 ppb reporting limit

[a] Hog-out wastewater is generated when high-pressure water is used to remove solid propellants from rockets and missiles (a process often termed "hog-out"). Initial laboratory and pilot-scale studies were performed at Tyndall Air Force Base (Pensacola, Fla.) in the early 1990s.

[b] System consists of four FBRs, 14 inches in diameter by 22 feet high. First commercial installation of FBR. System discharges overland toward the American River and has treated more than 8 billion gallons since 1998.

[c] System consists of one FBR, 5 feet in diameter by 22 feet high.

[d] Single 7.5-foot-diameter FBR. The groundwater feeding the reactor at McGregor emanates from a series of cut-off trenches installed at the site, a subset of which are also designed to promote in situ perchlorate treatment.

[e] Largest system to date, consists of eight FBRs, four sand and four GAC media. Sand and GAC reactors configured in series. Influent water initially flows through sand FBRs (removes chlorate, nitrate, and most perchlorate), then through GAC units for additional perchlorate removal. Influent concentrations were initially 2122 pounds/day, full-scale system will be ~2400 pounds/day.

[f] System is a suspended-growth reactor, using hollow-fiber membranes to supply/distribute hydrogen as substrate for microbial growth.

Continuous-Flow Stirred-Tank Reactors. The CSTR is a suspended-growth reactor (i.e., maintains biodegradative organisms in suspension) that has continuous influent and effluent flow (Figure 6-4). The use of a flow-through system differentiates these reactors from batch reactor systems, which treat specific volumes of water under static conditions. CSTRs have been applied most commonly for the treatment of commercial and domestic wastewaters. These systems are generally best suited for low-flow, high-strength waste streams.

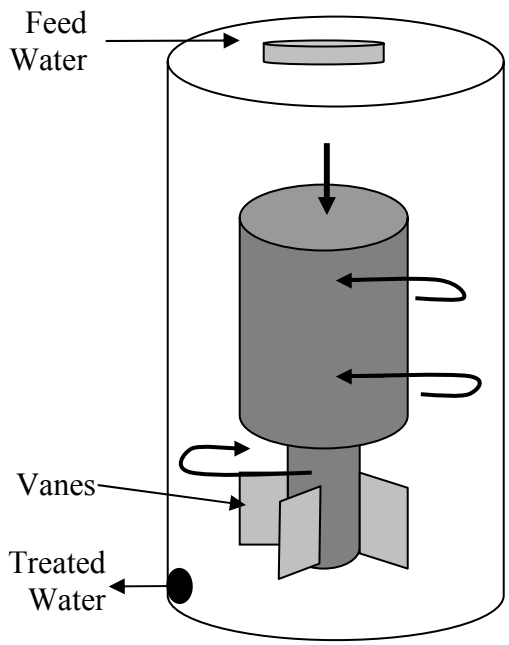

Figure 6-4. General schematic of CSTR.

Fluidized-Bed Reactors. The FBR is a fixed-film bioreactor that uses a solid media, often sand or GAC, to support microbial biofilms. FBR media is suspended or "fluidized" by the flow of water through the reactor (Figure 6-5). The up-flow velocity of water is sufficient to overcome

the gravitational force on the particles and to achieve a significant expansion (20%–30%) of the particles composing the FBR bed. The high surface area of the media within the expanded reactor bed (essentially the entire surface of the GAC or sand particles is exposed) allows high biomass densities to be achieved and maintained and subsequently reduces reactor size compared to more conventional designs. Moreover, most commercial-scale FBRs are designed with efficient biomass control devices that prevent the reactor fouling. As such, some commercial FBRs have been in operation for more than 15 years (Hatzinger 2005; Sutton and Mishra 1991; USEPA 1993; Hatzinger et al. 2000; Polk et al. 2002; Beisel, Craig, and Perlmutter 2004).

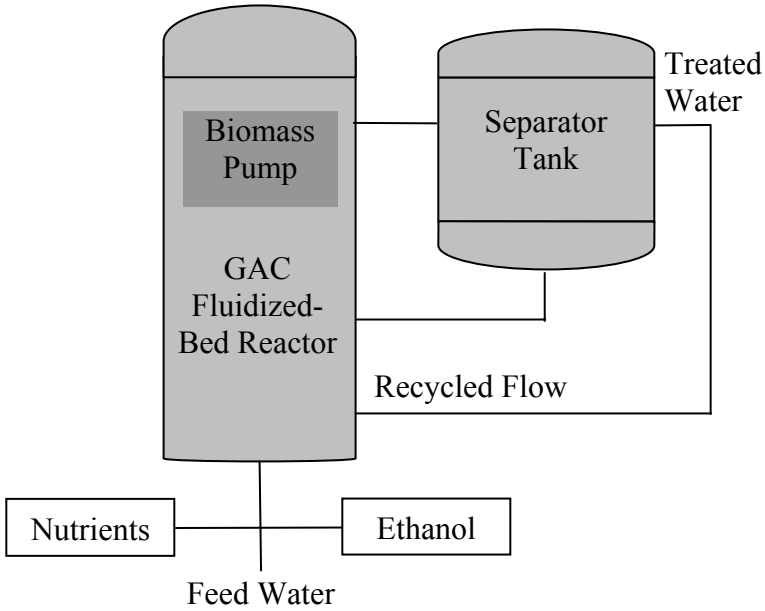

Figure 6-5. General schematic of a fluidized bed reactor.

Packed Bed Reactors. The PBR is a fixed-film bioreactor that uses a solid media to support biodegradative organisms. These organisms grow as a biofilm on or within the packing material and degrade aqueous contaminants as water moves through the reactor in either an up-flow or down-flow manner. The basic reactor consists of a vessel filled with sheet packing, coarse sand, plastic rings, or other support media, and all associated pumps and controls to set water flow and to supply necessary amendments to the water being treated. The key advantage of fixed-film systems compared to suspended-growth reactors is the ability to achieve high concentrations of biomass within the reactor, even in the presence of rapidly flowing water.

At present, there are no full-scale PBR systems treating perchlorate in groundwater or wastewater that are fully operational. However, several different researchers have evaluated PBRs for this purpose at the laboratory and the pilot scales with flow rates as high as 20 gpm. Overall, the testing has shown that this reactor design can effectively remove perchlorate and nitrate in groundwater to below the respective MRLs for these contaminants for short periods of time. However, the absence of an effective technique to control biomass within these reactors has caused questions concerning their long-term operability in the field. With time, biomass overgrowth within the PBR can cause channeling through the reactor and a subsequent loss of performance due to a subsequent shortening of the hydraulic residence time. Techniques such as periodic backwashing have been effective for controlling this problem in pilot-scale units and this technique may also be effective at full scale (Hatzinger 2005; Min et al. 2004, Xu et al. 2003, Losi et al. 2002, Hatzinger et al. 2002).

Other Bioreactor Designs. In addition to the aforementioned reactors, other biological reactor designs have been tested for specific perchlorate treatment applications, including the treatment

of perchlorate in drinking water and in ion exchange brine. These include a specialized hollow-fiber membrane reactor and a membrane bioreactor system, which is a suspended-growth reactor that uses a membrane to separate biomass from effluent water (letting effluent pass through but not bacterial solids). These systems are very different in that the hollow-fiber reactor uses a membrane to regulate hydrogen supply, while the MBR uses a membrane to retain biomass within the reactor vessel. MBRs have previously been applied at large scale for treatment of chemical manufacturing wastes and other concentrated streams, but their application for perchlorate treatment has been limited at this point. It is likely that the technology will find a niche for low-flow, high-concentration streams, such as that produced during resin regeneration (see Section 6.4).

6.3.2.2 In Situ Bioremediation

As previously noted, laboratory microcosm studies have shown that perchlorate-reducing bacteria are indigenous to many soils, sediments, surface waters, and groundwaters. Moreover, these organisms can often be stimulated to degrade perchlorate to below detection by adding a microbial growth substrate to these environments (Wu et al. 2001; Hatzinger et al. 2002; Waller, Cox, and Edwards 2004; Tan, Anderson, and Jackson 2004). There are two general strategies for delivering amendments to the contaminated groundwater—fixed biobarriers and mobile soluble amendments.

Fixed Biobarriers. Fixed biobarriers (Figure 6-6) are solid or viscous amendments emplaced across the flow path of the contaminated groundwater and allowing the contaminated groundwater to flow to, through, and past the fixed amendment. This fixed biobarrier approach can use engineered trenches or barriers containing solid-phase, slow-release substrates (Perlmutter et al. 2001) or viscous substrates emplaced cross gradient via direct-push injections (Zawtocki, Lieberman, and Birk 2004). A number of fixed biobarrier electron donors, including vegetable oil, pecan shells, chitin, Hydrogen-Release Compound (HRC™), and compost materials have been observed to support microbial reduction of perchlorate. The following are three examples of fixed biobarriers:

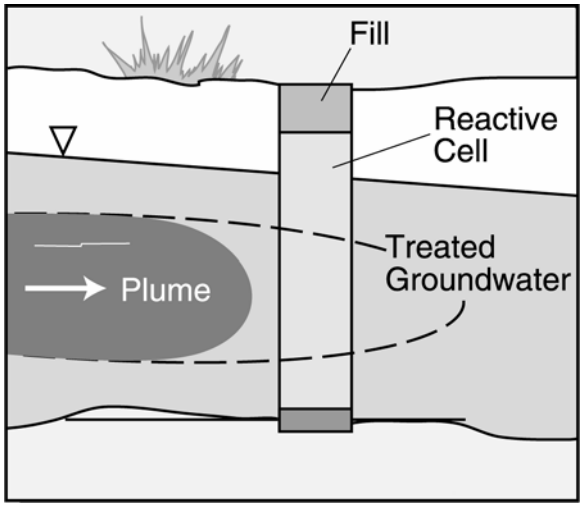

Figure 6-6. General schematic of a biobarrier.

- A barrier at the Naval Weapons Industrial Reserve Plant (NWIRP), McGregor, Texas, is the largest installation to date. It consists of a series of trenches (several thousand feet in combined length) that contain a mixture of mushroom compost, soybean oil, and wood chips as slow-release electron substrates. The shallow trenches (10–25 feet in depth) are cut into limestone and designed to capture groundwater and runoff water at the site. Influent perchlorate levels as high as 13,000 ppb have been reduced to below detection in this barrier.

- The second barrier system, installed in Mortandad Canyon at LANL, consists of the mineral apatite, a phosphate mineral, to remove various radionuclides from groundwater and a mixture of pecan shells and cottonseed as slow-release substrates for the reduction of perchlorate and nitrate.
- The third barrier example is an emulsified vegetable oil injected into a shallow, perchlorate-contaminated aquifer in Maryland to create a passive barrier (Zawtocki, Lieberman, and Birk 2004). Within 35 days of injection, perchlorate levels had declined from 9,000 μg/L to <10 μg/L within 20 feet of the barrier.

Mobile Amendments. Mobile amendment systems are characterized by injecting water-soluble amendments with low viscosity into the upgradient portion of the plume or source area and allowing that amendment to move downgradient, treating the groundwater as it moves. This technology can be implemented by direct-push injections or injection wells. Injection strategies dictate the need for passive or active treatment. Passive treatment (Figure 6-7) requires no extraction or recirculation. Active treatment (Figure 6-8) can use groundwater extraction and reinjection systems to distribute substrates in the subsurface (Hatzinger 2005; Cramer et al. 2004; Cox, McMaster, and Neville 2001) or horizontal-flow treatment wells to mix and distribute electron donor in groundwater. A variety of soluble amendments can be used, including but not limited to lactate, ethanol, citric acid, acetate, molasses, and corn syrup. Following are examples of mobile amendments.

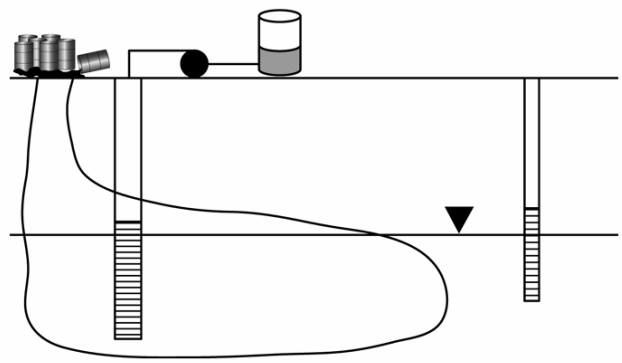

Figure 6-7. Schematic of passive in situ bioremediation.

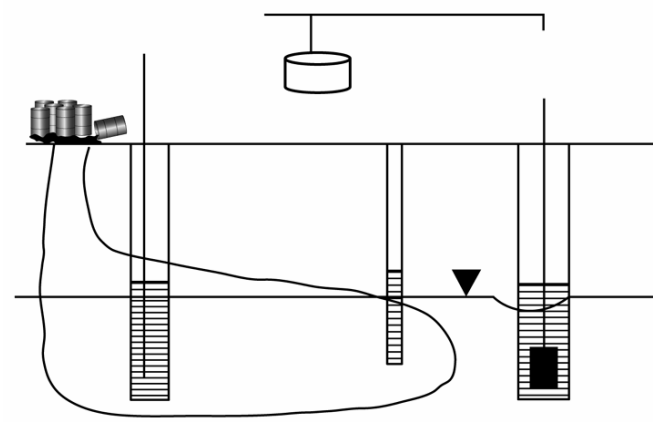

Figure 6-8. Schematic of active in situ bioremediation recirculation system.

- At Indian Head Division Naval Surface Warfare Center in Maryland, lactate was injected via injection well using the passive approach. A buffer was also added to the aquifer to increase groundwater pH and enhance the kinetics of perchlorate reduction. Over a 20-week demonstration, during which lactate was added as an electron donor, the perchlorate concentration in groundwater declined by >95% in eight of the nine monitoring wells in the field plot from an initial average of 170 mg/L, with five wells reaching <1 mg/L during the demonstration and two wells declining to below the MRL for the study (5 μg/L) during this period (Cramer et al. 2004).

- At Aerojet-General Corp. in Rancho Cordova, California, groundwater was extracted, amended with an electron donor (ethanol, lactate, and citric acid were tested), and then

reinjected to the subsurface. Several active mobile amendment studies have also been conducted at Aerojet-General, the most extensive of which consisted of a groundwater extraction/reinjection system designed to capture a perchlorate plume that is approximately 600 feet wide (Cox, McMaster, and Neville 2001). During this demonstration, ethanol was used as the electron donor. Perchlorate was reduced from 8 mg/L to <4 µg/L within 35 feet of the groundwater reinjection well. In addition, a pilot study is ongoing at Aerojet-General in which horizontal flow treatment wells have been installed to mix to distribute electron donors within a perchlorate-contaminated groundwater plume without bringing water to the surface. Citric acid is being used as the electron donor for this pilot project. This demonstration and several others have been funded by the Environmental Security Technology Certification Program (ESTCP, www.ESTCP.org).

- At the former Pacific Engineering and Production Company in Henderson, Nevada, GeoSyntech Consulting, Inc. conducted a recirculating in situ pilot study in November 2002 though May 2003. The pilot study initially included ethanol amendments, which result in mineral precipitation and well fouling. This problem was resolved by replacing ethanol with citric acid. Perchlorate concentrations were reduced from a range of 510–780 mg/L to a range of 0.6–28 mg/L.

6.3.2.3 Soil Remediation

Remediation processes for perchlorate in soil, both ex situ and in situ, have focused mainly on the application of bioremediation. Laboratory studies suggest that perchlorate-reducing bacteria are present in most surface soils and that perchlorate bioreduction can be stimulated through the addition of appropriate organic substrates to these soils (e.g., Wu et al. 2001, Hatzinger 2002). Field-scale treatment of perchlorate-contaminated soils has been performed using in situ and ex situ techniques. Insufficient food and moisture appear to be the limiting factors in stimulating bacterial reduction of perchlorate in soils.

In Situ Soil Bioremediation. In situ treatment has been tested at several sites with near-surface perchlorate contamination, including the Longhorn Army Ammunition Plant (LHAAP) in Karnack, Texas, and Aerojet-General Corporation in Sacramento, California. A variety of different carbon sources, including various types of manure, ethanol, molasses, and calcium magnesium acetate, have been tested as biological substrates. These amendments were either placed on the surface (followed by soil wetting) or dissolved directly into water prior to application. At LHAAP, for example, horse manure, chicken manure, and ethanol were tested as soil amendments in small field plots (O'Niell and Nzengung 2003). Up to 99.7% of the perchlorate in the upper 3 feet of the soil column was remediated in 10 months. Similar results were seen at Aerojet's Area 41 site, where cow manure and acetate were used as carbon sources for food.

Ex Situ Soil Bioremediation. Ex situ treatment methods have focused on treatment cells using anaerobic composting or lined treatment cells containing excavated soils. These methods have been evaluated in pilot- and/or full-scale applications. For composting applications, carbon sources, water and, in some cases, bulking agents, are blended with the contaminated soil. In a study conducted at Aerojet, perchlorate-contaminated soils were prepared in a 7-foot-diameter

by 5-foot-high compost pile on an impermeable liner. The soil was mixed with carbon amendments, wetted, then covered with a plastic tarp to prevent moisture loss and oxygen intrusion. Perchlorate levels within the compost pile were observed to decline from 23 mg/kg to less than the reporting limit for the study (0.1 mg/kg) within 7 days (Cox et al. 2000). A large-scale soil demonstration was performed at the NWIRP McGregor Area M. Approximately 1500 cubic yards of perchlorate-contaminated soil was excavated and transported to a biotreatment cell. The soil was mixed with amendments (citric acid, nitrogen, phosphorus, and soda ash as a buffer) and saturated with water. Perchlorate was reduced from an estimated average of 500 mg/kg to below the reporting limit (0.1 mg/kg).

Thermal Processes. Thermal remediation is another process investigated for the remediation of perchlorate in soils. Thermal remediation systems generally rely on volatilization or evaporation mechanisms as an integral part of the destruction process. In general, these processes can be applied to soil contaminated with perchlorate; however, because of cost, many of these should probably be considered only when perchlorate-impacted soils are mixed with other hazardous and toxic substances, such as explosives, radionuclides, or various metals (Gangopadhyay et al. 2005). Thermal destruction of perchlorate was tested at MMR and at a Thiokol facility in Utah. At both of those sites, the goal was to destroy not only perchlorate but other explosive materials as well. The MMR test was performed on soils contaminated with perchlorate at up to 100 mg/kg using a thermal desorption process operating at temperatures ranging 725°–900°F. Perchlorate was reduced to <0.001 mg/kg. Higher temperatures would be need for concentrations of perchlorate >100 mg/kg.

6.4 Emerging Processes

Previous sections of this document have given some insight into various processes and technologies that have been used effectively to remove or degrade perchlorate from natural resources. The emerging processes described in this section are all in the developmental stages. To date, the work on the emerging technologies shows great promise for implementation in areas where more traditional technologies are not readily implementable. The new approaches and processes described in this section are being investigated and tested but have yet to be applied or accepted as viable treatment approaches. The successful development and documentation of these approaches will provide remediation practitioners and regulators with additional resources for treating perchlorate contamination that will be both innovative and protective of human and environmental health.

6.4.1 Vapor-Phase Electron Donor Injection

The treatment of contaminated soil using vapor-phase electron donor injection is an emerging technology that has been applied in various ways to a number of contaminants that are amenable to reductive biodegradation processes. So far the process has been shown to be feasible for some types of high explosives (e.g., RDX), some chlorinated VOCs (e.g., perchloroethylene, TCE, and dichloroethylene), and inorganic compounds such as nitrate and perchlorate. This process involves injection of an inert gas (e.g., nitrogen) and volatile, carbon-based substrate (electron donor) to enhance in situ growth of bacteria that use the contaminant as an electron acceptor under reducing conditions in vadose zone soils. After oxygen and residual nitrate have been

depleted by aerobic and denitrifying microorganisms, reduction of perchlorate mediated by naturally occurring perchlorate-reducing bacteria usually occurs.

Vapor-phase nutrient injection confers important advantages over processes relaying on infiltration of liquids. Solutions used for infiltration tend to follow preferential pathways as they migrate downward. Use of vapor-phase amendments can result in more uniform distribution of amendments within the vadose zone relative to infiltration. Infiltration can result in leaching of perchlorate to groundwater, whereas vapor-phase injection does not use enough water to cause leaching and favors in situ destruction.

This process will be especially applicable to contaminated areas of the vadose zone that are not easily accessible. Near-surface soils that are easily accessible could be excavated and treated via an ex situ process (see Section 6.3.5). Vapor-phase injection could be applicable under buildings and paved surfaces, around active utility corridors where excavation is not practical, and at depths beyond the practical limit of excavation. This type of nutrient injection would generally not be practical for near-surface soils without the use of an impermeable cover to prevent exchange of oxygen between the atmosphere and the pore space of the soil.

Several projects have tested this type of technology. A field demonstration for treatment of RDX-contaminated soils was conducted at the DOE Pantex site (Rainwater et al. 2001). A commercially available version of a similar process was developed at Savannah River (Jackson, Tan, and Anderson 2003) and patented by the DOE and is being adapted for use in treating perchlorate-contaminated vadose zone soil at a depth of ~100 feet. Treatability studies are in process, to be followed by a pilot-scale installation. Another version of the technology is being developed by Camp, Dresser & McKee, Inc.; a funded ESTCP proposal to test this process is titled "In Situ Bioremediation of Perchlorate in Vadose Zone Soil using Gaseous Electron Donors."

6.4.2 Phytoremediation

Perchlorate remediation by plants has been investigated at a research level. This work has considered the possibility that natural plant processes, with or without the participation of soil microorganisms, may be able to remove perchlorate from the environment. Plant root system processes involving water and nutrient uptake may remove, sequester, or degrade perchlorate dissolved in soil moisture or flowing groundwater. This technology is anticipated to be most applicable to surface soil contamination, shallow groundwater contamination, or surface runoff. However, with the possibility for perchlorate accumulation in plant tissues, it is unclear whether phytoremediation technologies will provide any significant advantages compared to more traditional bioremediation approaches using substrate amendments. The rate at which the plants become established and phytoremediation treatment occurs may also be a consideration (www.hqafcee.brooks.af.mil/products/techtrans/phytorem.asp).

6.4.3 Constructed Wetlands

Constructed wetlands have been used for decades for the management and treatment of many wastewaters, including municipal wastewaters, acid mine drainage, agriculture, petrochemical

and textile industries, and storm water (Kadlec and Knight 1996, Moshiri 1994, Hammer 1990). However, constructed wetlands are increasingly being used for the remediation of groundwater or surface water impacted by industrial chemicals and wastes such as landfill leachate (Mulamoottil, McBean, and Rovers 1998) and explosives such as TNT or RDX (Best et al. 1998).

Treatment of perchlorate by constructed wetlands is a potentially effective remediation method due to the following conditions: the reducing conditions of wetland soil/sediment, the high biological activity of wetland soil/sediment in terms of microbial diversity and numbers, the availability of a variety of dissolved carbon sources, the ability of plants to uptake and transform perchlorate, and the ubiquity of bacteria which degrade perchlorate. Biological methods such as constructed wetlands treatment are particularly attractive since they cost-effectively destroy many contaminants, perchlorate included, rather than merely transferring them to another media (e.g., impacted resin or brine).

6.4.4 Nanoscale Bimetallic Particles

With diameters on the order of 100–200 nm, nanoscale bimetallic (iron [Fe]/palladium [Pd]) particles (nanoparticles) have large surface areas and surface reactivity to rapidly degrade redox-amenable contaminants such as chlorinated solvents and perchlorate. In addition, these particles can be effectively delivered to the subsurface. Laboratory research has reportedly shown that nanoscale iron particles are effective reductants and catalysts for a wide variety of contaminants, including perchlorate (Zhang 2003).

6.4.5 Titanium^{3+} Chemical Reduction

Georgetown University has developed a technique using titanous ions (3+) to chemically reduce perchlorate. Several new organic ligands have been developed that have been shown to catalyze reduction of perchlorate by titanous ions (3+) to titanium dioxide and chloride in acidic aqueous media. A preliminary patent application has been filed for this process.

6.4.6 Zero-Valent Iron Reduction under Ultraviolet Light

Gurol and Kim (2000) investigated chemical reduction of perchlorate using iron and iron oxide under various conditions. The main result of their investigation was that the addition of metallic iron (100 g/L) combined with exposing the solutions to ultraviolet light at wavelengths <185 nm achieved 77% reduction in perchlorate and an intensity of 0–9 W/cm^2. A patent (#6,531,065) was issued for this technology in 2003, and a field demonstration program is currently being planned to develop a commercial prototype. The large concentrations of iron needed to make this reaction effective, however, may cause this method to become impracticable due to the potential for fouling, which will in turn inhibit effective ultraviolet exposure.

6.4.7 Electrochemical Reduction

A bench-scale study of electrochemical reduction of perchlorate was conducted using two-chambered batch reactor systems. An ion exchange membrane separated cathodic and anodic

compartments, and electrodes consisted of titanium coated with a thin film of titanium dioxide particles. Initial perchlorate concentration ranged 50–500 mg/L. Perchlorate reduction was limited due to the competition among anions for active sites on the electrode surface, with perchlorate being less strongly adsorbed than both sulfate and chloride. The time required for ions in the water to travel to the electrode surface is a design concern in developing a practical full-scale system.

6.4.8 Capacitive Deionization

This technology, patented in 1995 by Lawrence Livermore National Laboratory, relies on the separation of ions from solution by applying an electric field between carbon-aerogel electrodes. The cations and anions are electrosorbed onto the carbon aerogel of the cathode and anode, respectively. Regeneration is accomplished by electrically discharging the electrodes and yields a stream of purified water and a concentrated reject stream similar to membrane and ion exchange processes. In the case of perchlorate removal, the concentrate solution will require further treatment (e.g., via catalytic or biological reduction) before it can be discharged. A limitation of capacitive deionization is that the sorption capacity of the carbon-aerogel anodes decreases with the size of the ion. In the case of perchlorate, a relatively large monovalent anion, the electrosorption capacity is less than the capacity for chloride (Farmer et al. 1996).

6.4.9 Reverse Osmosis

In the reverse osmosis process, the influent stream is driven, under pressure, through a semipermeable membrane that does not allow the contaminants to pass. In this case, the perchlorate is removed from the process in a concentrate or brine, which requires further treatment or destruction. The lack of ionic selectivity in the semipermeable membrane can alter the pH of the effluent stream and make it corrosive. Membrane resilience may also be a performance issue in treating perchlorate.

6.4.10 Electrodialysis

Within the electrodialysis process, water is passed through flow channels of alternating semipermeable and permeable membranes (for either anions or cations) while a direct current voltage potential field is applied across the membranes. As the influent feed flows through the flow channels between the membranes, the direct current voltage potential induces the cations to migrate towards the negatively charged anode through the cation-transfer membrane. Simultaneously, the anions migrate toward the positively charged cathode through the anion-transfer membrane. Electrodialysis also produces a contaminated brine waste by-product, the treatment or destruction of which is an important design consideration.

6.4.11 Monitored Natural Attenuation

There is extensive documentation that perchlorate is biodegradable under anaerobic conditions and can be expected to naturally attenuate in some aquifers. Currently, there is no conclusive evidence for natural attenuation of perchlorate, but studies are under way to document the rate and extent of natural attenuation at selected sites (Lieberman, Knox, and Borden 2005). Without

clear, convincing evidence for the natural attenuation of perchlorate, there may be a tendency to push for aggressive remediation approaches whenever perchlorate is detected. While aggressive remediation is warranted at some sites, there may be other sites where monitored natural attenuation is an appropriate approach.

6.4.12 Nanofiltration/Ultrafiltration

Nanofiltration and ultrafiltration are membrane treatment technologies like reverse osmosis. In these technologies, the synthetic porous material of membranes acts like a shield, preventing particles of a defined size or larger from passing through. A water pressure higher than that used with other methods of filtration then pumps water through the membrane. Membranes are classified by the size of particle that the membrane removes (AWWA 2001). These membrane filtration technologies have high energy requirements and produce brines equal to 20% of the volume of groundwater treated. The brine contains high TDS and perchlorate concentrations that require treatment or further disposal. The American Water Works Association is currently funding ongoing research to investigate the feasibility of membrane filtration technology for perchlorate removal in water sources of different quality.

6.4.13 Catalytic Gas Membrane

This emerging technology, which is in the early stages of development, is based on the fact that reduction of perchlorate by hydrogen is thermodynamically favorable. However, the reaction is kinetically very slow in dilute solutions at relevant groundwater temperatures due to the high activation energy required to initiate the reaction. Use of a proper catalyst is thus necessary to facilitate perchlorate reduction in a time frame that would be potentially useful in a water or waste stream treatment scenario. Catalytic gas membrane techniques may eventually be useful for the removal of perchlorate from water; however, convincing data are currently lacking. Work is ongoing to find and coat an effective catalyst onto the outer surface of an inorganic membrane such as stainless steel or carbon materials. The membrane system is envisioned as a tubular configuration in which hydrogen gas would be purged into system. The action exhibited by the catalyst on the membrane surface would bring about the reduction of perchlorate by hydrogen.

6.5 Technology Summary

This section briefly touched upon the current state of perchlorate remediation technologies. To date, perchlorate remediation has focused primarily on groundwater cleanup with ion exchange technology and ex situ bioremediation and on a pilot-scale in situ bioremediation. Full scale in situ bioremediation systems are likely to be implemented at specific sites by the time this document is published. A number of remediation technologies for both soil and water have been implemented at only bench and pilot scale and have yet to be used as full-scale remediation systems.

The technology and regulatory guidance document to be completed by the ITRC Perchlorate Team will discuss in detail the remediation technologies touched upon in this review and include various case studies as well as any new information since the finalization of this document.

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APPENDIX A

Acronyms

ACRONYMS

BMP	best management practice
BOD	biochemical oxygen demand
CE	capillary electrophoresis
CRREL	Cold Regions Research Engineering Laboratory
CSTR	continuous-flow stirred tank reactors
DoD	(U.S.) Department of Defense
DOE	(U.S.) Department of Energy
DQO	data quality objective
DWEL	drinking water equivalent level
ECBC	Edgewood Chemical Biological Center
ESI	electrospray ionization
ESTCP	Environmental Security Technology Certification Program
FBR	fluidized-bed reactor
FDA	(U.S.) Food and Drug Administration
GAC	granular activated carbon
HMX	high-melting-point explosive
IC	ion chromatograph(y)
IME	Institute of Makers of Explosives
IRIS	Integrated Risk Information System
ITRC	Interstate Technology & Regulatory Council
LANL	Los Alamos National Laboratory
LC	liquid chromatography
LHAAP	Longhorn Army Ammunition Plant
LOAEL	low observed adverse effect level
LOQ	limit of quantitation
m/z	mass-to-charge
MADEP	Massachusetts Department of Environmental Protection
MBR	membrane bioreactor
MCL	maximum contaminant level
MCT	matrix conductivity threshold
MIDAS	Munitions Items Disposition Action System
MMR	Massachusetts Military Reservation
MOA	mode of action
MRL	minimum reporting level
MS	mass spectrometry
MSDS	material safety data sheet
NASA	National Aeronautics and Space Administration
ND	nondetect
NDMA	N-nitrosodimethylamine
NOAEL	no observed adverse effect level
NOEL	no observed effect level
NRC	National Research Council
NWIRP	Naval Weapons Industrial Reserve Plant
OB/OD	open burn/open detonation

O&M	operation and maintenance
ORNL	Oak Ridge National Laboratory
OSW	Office of Solid Waste
PBR	packed-bed reactors
ppb	parts per billion
ppm	parts per million
QC	quality control
RCRA	Resource Conservation and Recovery Act
RDX	royal demolition explosive
RfD	reference dose
SERDP	Strategic Environmental Research and Development Program
SQM	Sociedad Quimica Y Minera De Chile S.A.
TCE	trichloroethylene
TCEQ	Texas Council on Environmental Quality
TDS	total dissolved solids
TNT	trinitrotoluene
TRH	TSH-releasing hormone
TSH	thyroid-stimulating hormone
UCMR	Unregulated Contaminant Monitoring Rule
USACE	U.S. Army Corps of Engineers
USDA	U.S. Department of Agriculture
USEPA	U.S. Environmental Protection Agency
USGS	United States Geological Survey
UXO	unexploded ordnance
VOC	volatile organic compound

APPENDIX B

Naturally Occurring Perchlorate

NATURALLY OCCURRING PERCHLORATE

Table B-1. Perchlorate in natural minerals and materials

Samples	Measured concentration		Final conc. in extract (ppb)	MDL (ppb)	Spike recov. (%)	Sample weight (kg)	Extrac-tion volume (L)	Conc. (g/Kg)
	(ppb)	Dilution factor						
Muriate potash	ND	1	ND	1		0.001	0.03	ND
Mission Chem	ND	1	ND	1		0.001	0.03	ND
Miracle Grow	ND	1	ND	1		0.001	0.03	ND
Bonemeal, Brand 1	ND	1	ND	1		0.001	0.03	ND
Bloodmeal, Brand 1	5.4	1	5.4	1		0.001	0.03	0.161
Bloodmeal, Brand 1, DUP	4.8	1	4.8	1	111%	0.001	0.03	NA
Fishmeal	9.2	1	9.2	1		0.001	0.03	0.276
Fishmeal, DUP	11.0	1	11	1	84%	0.001	0.03	NA
Miracid	ND	1	ND	1		0.001	0.03	ND
Joebesi fertilizer spikes	ND	1	ND	1		0.001	0.03	ND
Peters Pro plant food	ND	1	ND	1		0.001	0.03	ND
Potash fertilizer, Brand 1	ND	1	ND	1		0.001	0.03	ND
Potash fertilizer, Brand 1, DUP	ND	1	ND	1		0.001	0.03	ND
Great Salt Lake ppt	ND	1	ND	1		0.001	0.03	ND
Salt substitute, Brand 1	ND	1	ND	1		0.001	0.03	ND
Salt substitute, Brand 1, DUP	ND	1	ND	1		0.001	0.03	ND
Salt substitute, Brand 2	ND	1	ND	1		0.001	0.03	ND
Salt substitute, Brand 3	ND	1	ND	1		0.001	0.03	ND
Lite salt, Brand 1	ND	1	ND	1		0.001	0.03	ND
Lite salt, Brand 1	48.8	1	48.8	1	98%	0.001	0.03	NA
Triple superphosphate	ND	1	ND	1		0.001	0.03	ND
Soft rock phosphate ore	ND	1	ND	1		0.001	0.03	ND
10-10-10 fertilizer	ND	1	ND	1		0.001	0.03	ND
Urea	ND	1	ND	1		0.001	0.03	ND
10-4-10 fertilizer	ND	1	ND	1		0.001	0.03	ND
Phosphate ore 1	ND	1	ND	1		0.001	0.03	ND
Phosphate ore 2	ND	1	ND	1		0.001	0.03	ND
Phosphate ore 3	ND	1	ND	1		0.001	0.03	ND
Phosphate ore 4	ND	1	ND	1		0.001	0.03	ND
Limestone	ND	1	ND	1		0.001	0.03	ND
Potash ore 1 (Sylvite 1a)	25,000		-			0.00114	0.03	0.025
Potash ore 2 (Sylvite 1b)	3,741,000		-			0.00105	0.03	3.741
Potash ore 3 (Sylvite 2)	42,000		-			0.0114	0.03	0.042
Playa crust 1 (B43)	1,745,000		-			0.00101	0.03	1.745
Playa crust 2 (B29)	560,000		-			0.00101	0.03	0.560
Playa crust 2 (B29), DUP	489,000		-			0.00101	0.03	0.489
Hanksite 1	280,000		-			0.00116	0.03	0.280
Hanksite 1, DUP	285,000		-			0.00116	0.03	0.285
Kelp	885,000		-			0.00116	0.03	0.885

Source: Preliminary Analyses for Perchlorate in Selected Natural Materials and Their Derivative Products, USGS Open File Report 03-314 (Orris et al. 2003).

Table B-2. Perchlorate in natural minerals and materials

Sample type	Number of locations	Number of samples	Percent with CLO_4	Pending	Number with NO_3
Playas	28	57	86[a] (96)	>11	>11[++]
Soils	7	15		>12	
Soil-caliche	4	10	100	>3	All
Soil-nitrate				>9	All
Older lakebeds	3	3	100[b]	>1	2
Nitrate deposits	3	5	100	>6	All
Evaporites	19	26	27[a]	>5	Unknown
Nonhalite[c]	9	16	44[a]	>3	Unknown[d]
Halite	10	10	0	>2	NA
Related H_2O	2	3	100	1	Unknown

[a] High detection limit for some samples.
[b] All values <2 ppb.
[c] Samples other than "pure" halite, commonly mixed salts.
[d] Early samples not tested for NO_3.

Source: "Perchlorate in Natural Minerals and Materials," *USGS Quarterly Report*, April 2004 (Orris 2004).

APPENDIX C

Manufactured Perchlorate Compounds

MANUFACTURED PERCHLORATE COMPOUNDS

The vast majority of manufactured perchlorate compounds (>99% of production) consist of the following four chemical species:

- ammonium perchlorate
- sodium perchlorate
- potassium perchlorate
- perchloric acid

Other much less common, even rare, manufactured specialty perchlorate compounds (list not comprehensive) include the following:

2, 2′, 2″-terpyrine perchlorate
acetylcholine perchlorate
aluminum perchlorate, hydrated
barium perchlorate, anhydrous
barium perchlorate, hydrated
bismuthyl perchlorate monohydrate
cadmium perchlorate
ceric perchlorate, solution (perchlorato-ceric acid)
cerous perchlorate, hydrated
cesium perchlorate
chromium perchlorate, hydrated
cobalt perchlorate, hydrated
cupric perchlorate, hydrated
dysprosium perchlorate, hydrated
erbium perchlorate, hydrated
europium perchlorate, hydrated
ferric perchlorate, hydrated, yellow
ferric perchlorate, non-yellow
ferrous perchlorate
gadolinium perchlorate, hydrated
gallium perchlorate, hydrated
holmium perchlorate, hydrated
indium perchlorate, hydrated
lanthanum perchlorate, hydrated
lead perchlorate solution
lead perchlorate, trihydrate
lithium perchlorate, anhydrous
lithium perchlorate, hydrated
magnesium perchlorate, anhydrous
magnesium perchlorate, hydrated
mercuric perchlorate, trihydrate
mercurous perchlorate, hydrated
neodymium perchlorate, hydrated
nickel perchlorate, hydrated
praseodymium perchlorate, hydrated
rubidium perchlorate
samarium perchlorate, hydrated
scandium perchlorate, hydrated
silver perchlorate, anhydrous
silver perchlorate, hydrated
strontium perchlorate, hydrated
terbium perchlorate, hydrated
tetrabutylammonium perchlorate
tetraethylammonium perchlorate
tetrahexylammonium perchlorate
tetramethylammonium perchlorate
thulium perchlorate, hydrated
trimethylammonium perchlorate
ytterbium perchlorate, hydrated
yttrium perchlorate, hydrated
zinc perchlorate, hydrated
zirconyl perchlorate, hydrated

Source: GFS Chemicals, Inc. Web site. Available at www.gfschemicals.com/productcatalog/Perchlorate_Compounds.asp

APPENDIX D

Historical and Current Sources and Uses of Perchlorate

HISTORICAL AND CURRENT SOURCES AND USES OF PERCHLORATE

Table D-1. Uses of perchloric acid in 1939

Analysis	Reagent in • assaying various alkaloids, such as morphine, codeine, and cocaine; • carrying out Kjeldahl digestions for the determination of the nitrogen content of various products; • determining potash in various products by the formation of an insoluble potassium perchlorate; and • effecting electroanalysis (used for the purpose of destroying the organic matter contained in the product that is to be analyzed).
Chemical	• Oxidizing agent in making inorganic chemicals, intermediates, organic chemicals, pharmaceuticals, synthetic aromatics • Starting point in making various salts
Explosives	• Manufacture of matches • Reagent in making explosive compounds, such as the perchlorated esthers of monochlorohydrin
Metallurgical	• Ingredient of lead-plating baths (used for the purpose of facilitating the deposition of lead from baths containing lead perchlorate)
Pharmaceutical	• In compounding and dispensing practice

Source: Uses and Applications of Chemicals and Related Materials, Vol. I (Gregory 1939).

Table D-2. Uses of potassium perchlorate in 1944

Analytical	• Oxidizing agent in analytical processes • Reagent in analytical processes
Chemical	• Ingredient of catalytic mixtures used in making ammonia • Oxidizing agent in chemical processes • Starting point in making perchlorates
Explosives and matches	• Constituent of detonating compositions and flare compositions • Matchhead compositions • Perchlorate explosives—primer compositions; pyrotechnic compositions; railroad signal (fuse) compositions; and smoke-producing compounds
Fuel	• Constituent of briquetted fuel binder compositions based on such materials as coal, coke • Charcoal, lignite, bituminous dust, breeze, tar, pitch, and the like
Metallurgical	• Constituent of brazing fluxes, welding fluxes
Miscellaneous	• Constituent of chemical heating compositions
Pharmaceutical	• In compounding and dispensing practice
Photographic	• Oxidizing agent in photographic processes

Source: Uses and Applications of Chemicals and Related Materials, Vol. II (Gregory 1944).

Table D-3. Current perchlorate commercial and industrial uses

Production of matches
Air bag initiators for vehicles
Nuclear laboratories in actinide research
Chemical laboratories in analytical testing, desiccant, oxidizing agent, and digestion (perchloric acid)
Engine oil testing to determine base number (BN) ASTM D2896
Some electroplating operations
Electromachining, sodium perchlorate solution
Electropolishing operations with perchloric acid
Lithium-magnesium dioxide batteries as part of electrolyte
Rare-earth extractive metallurgy using perchloric acid
Etching brass and copper with perchloric acid
Paints and enamels
Bleaching agent to destroy dyes
Photography as flash powder
Incidental by-product in some sodium chlorate, which itself has many uses, including weed killer or herbicide and defoliant in agriculture and as chemical building block
Oxygen generators
Road flares
Ejection seats
Propellant in model rocket engines
Propellant in rockets used for research, satellite launches, and space shuttle
Some explosives in construction, mining and other uses
Fireworks
Perchloric acid production and its many uses

Table D-4. Application of perchloric acid in analytical chemistry

As a solvent for metals and alloys
As a dehydrating agent, particularly in the determination of silica in iron and steel and in cement and other silicate materials
As an oxidizing agent, especially in the determination of chromium in steel, ferrochrome, chromite, leather, and chromatized catgut
In combination with nitric acid for the destruction of organic matter, especially in preparation for the determination of calcium, arsenic, iron, copper, and other metals in such materials; also in the determination of sulfur in coal and rubber
As a solvent for sulfide ores for the determination of copper and other metals
In the separation and determination of the alkali metals, sodium, and potassium
In combination with hydrochloric acid in the separation of chromium from other metals by distillation of chromyl chloride
In the isolation of fluoride prior to its determination, by distillation as hydrofluosilicic acid
As an adjunct to increase the reduction potential of cerate salts in volumetric analysis
As a primary standard acid—perchloric acid, when distilled in a vacuum at a carefully regulated pressure of 7 mm, has exactly the composition of the dihydrate, 73.6% $HClO_4$
Indirectly in the manufacture of anhydrous magnesium perchlorate, the best of the absorbents for water in analytical work
As a strong, standard acid for the titration of bases
As the strongest of the strong acids when dissolved in anhydrous acetic acid for the titration of bases in nonaqueous solvents
Mixtures of perchloric acid dihydrate with nitric acid or sulfuric acid, or of these three acids together, are employed extensively in analytical procedures for the destruction of organic matter preparatory to the determination of metallic and nonmetallic ingredients. Such procedures include • determination of sulfur in coal, coke, and oils; • determination of iron in wine, beer, and whiskey; • determination of chromium and of iron in leather and tanning liquors; • determination of phosphorus, alkali metals, lead, and other ingredients; and • analysis of blood for calcium and of urine for lead.
Mixtures of perchloric and phosphoric acids or perchloric and sulfuric acids are superior solvents for refractory oxides, stainless steel, and other high-melting ferrous alloys, as well as ores and minerals
A solution containing perchloric acid dihydrate dissolved in acetic acid is commonly used as a standard solution for the titration of organic bases in nonaqueous solvents.

Source: GFS Chemicals, Inc. Web site. Available at www.gfschemicals.com/productcatalog/Perchlorate_Compounds.asp

Table D-5. Commercial applications of perchloric acid and perchlorates

Perchloric acid as catalyst in broad range of diverse reactions: acetylations, acylations, alkylations, chlorinations, polymerizations, esterifications, and hydrolyses
Esterifications of cellulose to produce cellulose acetate
Polymerizations of phenols with formaldehyde
Polymerization of styrene
Electrolytic solutions for the purpose of electropolishing, electromachining, and electrothining of metal parts, films, and alloys
Perchloric acid employed as electrolyte in anodization of metals to produce noncorroding surfaces
Pickling and passivation of iron and steels
Dissolving refractory substances such as titanium slags, copper-yttrium oxide, and metal fluorides
Lithium perchlorate as an electrolyte in voltaic cells and batteries involving lithium or lithiated anodes, nonaqueous solvents or polymeric films, and manganese dioxide or other transition metal oxides
In nonaqueous systems, zinc perchlorate and magnesium perchlorate serve as electrolyte for zinc and magnesium batteries, respectively
Perchlorate salts serve as electrolytes in electropolymerization reactions involving monomers such as aniline, benzidine, azulene, biphenyl, divinylbenzene, and indole
As aqueous electrolytes perchlorates are found in electrochromic devices and employed for anodic dissolution of difficultly oxidizable metals, such as lead and palladium
Perchlorate salts as dopants in plastics and polymers to impart antistatic and conductive properties
Perchlorate salts as dopants in polyvinyl chloride to improve heat stability and fire retardation characteristics
Lithium perchlorate as dopant in thin films of polymers such as polyethylene oxide, polyethylene glycol, or poly (vinylpyridine) to impart conductive properties in various electrochemical devices
Anhydrous magnesium perchlorate as a desiccant or drying agent for industrial gases and other similar applications

Source: GFS Chemicals, Inc. Web site. Available at www.gfschemicals.com/productcatalog/Perchlorate_Compounds.asp

Table D-6. Perchloric acid uses

In determining the trace metals present in oxidizable substances
As a laboratory reagent
As an oxidizing agent
For the destruction of organic matter
As a dehydrating agent
As starting material for the manufacture of pure ammonium perchlorate and in the production of high-purity metal perchlorates
As a stable reaction medium in the thermocatalytic production of chlorine dioxide
As an acetylation catalyst for cellulose and glucose
In the preparation of cellulose fibers
For fluoride determination
As an ingredient of electrolytic bath in deposition of lead
In the electropolishing of metals

Source: CHEMINFO Web site (Canadian Centre for Occupational Health and Safety 2003).

APPENDIX E

Perchlorate-Containing Materials and Activities or Industries that Use Perchlorate

PERCHLORATE-CONTAINING MATERIALS AND ACTIVITIES OR INDUSTRIES THAT USE PERCHLORATE

Note: As part of developing best management practices for perchlorate materials, which are required by AB 826 the Perchlorate Contamination Act, California Department of Toxic Substances Control compiled the following list of materials that contain perchlorate and activities or industries that use perchlorate:

- Adhesive—Steel plate bonding may contain perchlorate
- Batteries—Li-Ion[6]
- Cathodic protection systems—May contain perchlorate
- Chemistry—Analysis, desiccants, feedstock, oxidizing agent
- Chemistry—Brine separation may contain perchlorate
- Chlorate/chlorite manufacturing—May contain perchlorate
- Clandestine methamphetamine labs—May be contaminated by perchlorate from dissolving flare striker caps to obtain red phosphorus
- Cloud seeding
- Coatings—Enamel paint may contain perchlorate
- Dielectric for transformers—May contain perchlorate
- Electroplating—May contain perchlorate
- Electropolishing
- Explosives—Military
- Explosives—Geoseismic, nitrate-based may contain perchlorate
- Evaporites—May contain perchlorate
- Fertilizer—Some contain perchlorate (Bulldog Soda from Chile)
- Flares/fuses
- Gas generator—Airbag, ejection seat
- Gas generator—Aircraft oxygen
- Laboratory—Rocket motor, ordnance testing
- Laundry bleach—May contain perchlorate
- Nitric acid manufacturing—May contain perchlorate
- Pharmaceutical—Diagnosis, treatment
- Photography—Flash powder and possibly other uses, potassium
- Pool sanitizer
- Pool shock—May contain perchlorate
- Propellant—Chemical cutter
- Propellant—Ordnance (gunpowder), tracer bullets (red phosphorus) may contain perchlorate
- Propellant—Solid rocket motor, ammonium perchlorate
- Pyrotechnics (fireworks)

[6] Lithium battery types include lithium-manganese dioxide, lithium-sulfur dioxide, and lithium-thionyl chloride. The anode is composed of lithium and the cathode is composed of manganese dioxide (or sulfur dioxide, or thionyl chloride). The electrolyte of the lithium-magnesium dioxide battery is composed of an organic solvent (propylene carbonate and 1,2 dimethoxyethane) solution of lithium perchlorate. In the case of the lithium-sulfur dioxide, the electrolyte is also an organic solvent (acetonitrile) solution with lithium-bromide. Lithium-thionyl chloride batteries have a nonaqueous thionyl chloride solution containing lithium aluminum chloride. Lithium-sulfur dioxide batteries contain pressurized sulfur dioxide gas and lithium-thionyl chloride batteries contain lithium thionyl chloride which vaporizes upon exposure too air, both of which are highly toxic.

- Regenerable drying agent for gases—Magnesium
- Safety matches—May contain perchlorate
- Well drilling—Permeability aid, may contain perchlorate

Previously reported to contain perchlorate but recent research shows does not contain perchlorate:

- Aluminum refining—Aluminum electropolishing only
- Animal-fattening agent—Ice cream butterfat analysis. Feedlot contamination
- Electronic tubes—Electron tube with contaminant found on it at military base
- Leather tanning—$HClO_4$ used to digest leather samples for chromium content
- Lubricating oil additive—Antioxidants added; fluorocarbon lubricating oils compatible with perchlorate pumping
- Nuclear reactor—Nuclear warheads on rockets; uranium analytical chemistry
- Synthetic rubber—Rubber as binder in rocket motors

Source: California Department of Substances Control Web site: www.dtsc.ca.gov.

APPENDIX F

Remediation Technology Applicability Matrix

REMEDIATION TECHNOLOGY APPLICABILITY MATRIX

The Remediation Technology Applicability Matrix provides a summary of the technologies available as of December 2004. The matrix thus represents a "snapshot in time" of what technologies were being employed for the removal and treatment of perchlorate. The matrix contains information on the type of process, scale, throughput, treatment effectiveness, media, residuals, location and the vendor implementing the project. The information in this section was developed from reports, presentations, and state and federal summaries of technology developments.

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
BIOLOGICAL PROCESSES				
Ex Situ Bioremediation				
Applied Research Associates, Inc.—Custom-designed biological treatment systems.				
Thiokol, Brigham City, Utah—Full scale, operational: Continuously stirred tank reactor (CSTR) biological system has operated continuously since 12/97 to treat industrial wastewater prior to discharge to sewer to treat waste stream high in salts (>2%) and nitrate. Initial pilot-scale work was performed by the Air Force Research Laboratory at Tyndall AFB, Florida. Cost: $0.02/gal	3 gpm, ~8000 lb/month of ammonium and potassium perchlorate	>5,000 mg/L to 4–400 µg/L	Wastewater	Biological oxygen demand (BOD), total suspended solids (TSS), nitrogen, phosphorous, total organic carbon (TOC), pH, turbidity, and dissolved oxygen (DO) may need to be monitored at effluent. Requires treatment of high salt effluent.
Hodgdon Powder Company, Kansas—Full scale, operational: Wastewater containing 1,000–5,000 mg/L perchlorate and 200–4,000 mg/L nitrate/nitrite is being treated down to a method reporting limit for perchlorate of 20 µg/L. Cost: $0.02/gal	3 gpm	1,000–5,000 mg/L to <20 µg/L reporting limit (RL)	Wastewater	
American Water Works Association Research Foundation (AWWARF)–sponsored project, La Puente, California—Pilot scale, completed: Mobile system treats up to 1 gpm diluted (2%–3% salt) waste ion exchange brine containing 3–4 mg/L perchlorate and 2–3000 mg/L of nitrate.	1 gpm	3–4 mg/L to 50 µg/L RL	Wastewater (drinking water plant brine)	Sulfate builds up in brine and eventually must be disposed.
Water utility–sponsored project, La Puente, California—Pilot scale, under way: Mobile system treats up to 1 gpm concentrated (6%–7% salt) brine containing 3–4 mg/L perchlorate and 2–3000 mg/L nitrate.	0.1 gpm	3–4 mg/L to 50 µg/L RL	Wastewater (drinking water plant brine)	Sulfate builds up in brine and eventually must be disposed.

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Bench-scale testing at ARA—Bench scale: Reactor operated as both a fixed-film process and a suspended-growth CSTR process for a patented full-scale process on 5× and 10× reverse osmosis (RO) rejectate containing high total dissolved solids (TDS) and up to 10 mg/L of perchlorate.		To <20 µg/L	Wastewater (RO rejectate)	
Kerr-McGee, Henderson, Nevada—Designed: Based on treatability studies, ARA with Biothane Corporation designed an 825 gpm suspended-growth, CSTR biological treatment plant to treat 400 mg/L (~4000 lb/day) of perchlorate to below 4 µg/L. (Not selected due to higher capital costs.)	825 gpm	400 mg/L to <4 µg/L	Groundwater	
Biologically Active Carbon (BAC)/University of Illinois at Urbana–Champaign and the Metropolitan Water District of Southern California (MWDSC)—AWWARF-funded bench- and pilot-scale tests indicate that BAC filtration can effectively remove low levels of nitrate and perchlorate under anaerobic conditions with the addition of an electron donor. Nitrate reduction can also enhance perchlorate reduction kinetics, making BAC filtration particularly attractive for combined nitrate-perchlorate remediation. Carrollo Engineers conducted additional pilot testing based upon the work of the University of Illinois.				
Pilot scale			Drinking water	Biosolids
Castaic Lake Water Agency, Santa Clarita, California—Pilot scale, complete: Packed-bed bioreactor used acetic acid as electron donor. Submitted for conditional approval for use on drinking water system. Perchlorate was spiked into the influent water at a concentration of 50 ppb. Granular activated carbon (GAC) was found to be the most effective media because it allowed best growth of microorganisms and it has the potential for low-level perchlorate removal.	1.75–5.2 gpm/cubic ft	50 to <6 ppb	Drinking water	Biosolids
EcoMat Hall Reactor—This patented reactor provides an efficient circulation pattern and uses a floating porous media, Ecolink, which has a very high surface area–to–volume ratio. Ecolink is a polyurethane-based sponge that is cut into 1 cm cubes. The dense biological growth supported with this system reported to provide high efficiencies with lower reactor volumes.				
Department of Defense (DOD) facility, southern California—Commercial, completed: A 200 L capacity, two-stage biological system consisting of the Hall reactor and a deaeration chamber mounted on a 4 ft × 4 ft skid was used treat perchlorate-contaminated groundwater stored in two 20,000 gal Baker tanks. Methanol was used as the electron donor. Cost: $0.50/1000 gal.	~2 gpm	300–410 µg/L to <4 µg/L	Groundwater	Biosolids

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Pilot test—Pilot scale, planned: Funded by the California State University, San Bernadino, Office of Technology Transfer and Commercialization Initiative to be conducted in the Rialto Area.			Groundwater	
Foster Wheeler				
NASA Jet Propulsion Laboratory (JPL), Pasadena, California—Pilot-scale packed-bed bioreactor (PBR), completed: Assisted by Naval Facilities Engineering Service Center, NASA managed pilot tests conducted on several different reactors. Results as of 05/01 on the PBR indicate reactors can successfully treat low concentrations of perchlorate.	2 gpm	0.42 mg/L to <4 µg/L	Groundwater	Biosolids
NASA JPL, Pasadena, California—Pilot-scale dynamic suspended bed bioreactor (DSBR): Assisted by Naval Facilities Engineering Service Center, NASA managed pilot tests conducted on the DSBR in 2002. The DSBR was designed to provide improved flow characteristics (by using different media for bacterial attachment with less surface area and greater pore volume and allowing for limited bed flux and expansion in the reactors) than those used in the PBR above.	1 gpm	6 mg/L to <4 µg/L	Groundwater	Biosolids
Hollow-Fiber Membrane Biofilm Reactors—Patented hollow-fiber membrane biofilm reactor uses hydrogen as the electron donor to biologically degrade perchlorate. Hydrogen gas is fed to the inside of the membrane fibers, and the hydrogen diffuses through the membrane walls into the contaminated water that flows past the fibers. A biofilm on the exterior surface of hollow-fiber membranes houses microbes that act as catalysts by transferring electrons from supplied hydrogen gas to an oxidized contaminant.				
La Puente, California—Pilot scale: Northwestern University, the technology developer, teamed with Montgomery-Watson-Harza Engineers, Inc. to conduct a pilot study treating groundwater with perchlorate and nitrate initiated in 2002 and continuing through 2003. Results indicate the biofilm reactor can effectively treat 1.5 gpm to remove both perchlorate and nitrate.	1.5 gpm	60 µg/L to <6 µg/L	Drinking water	Biosolids

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
ICBM System Program Office—Demonstration of anaerobic percolating biofilters funded by Environmental Security Technology Certification Program (ESTCP).				
Hill AFB, Utah—Pilot scale, planned: Applying the principle of anaerobic perchlorate reduction in a reactor configured as a hybrid between a multimedia filter and a conventional leach-bed reactor. The system includes a contact chamber where the electron donor is added to the wastewater and a fixed-film biofilter that serves as the reactor where perchlorate biodegrades. The reactor packing consists of gravels, sand, and peat in grading sizes over the filter depth. Limestone gravel can be used to buffer the system against pH changes in low alkalinity soils. The biofilter is designed to prevent filter desiccation and oxygenation between loadings so that the anaerobic organisms remain viable.			Wastewater	
Pennsylvania State University—Anaerobic PBR filled with sand and plastic media fed with acetate and nutrients; hydrogen reactors.				
Crafton-Redlands Plume, Redlands, California—Pilot and lab scale: Funded by AWWARF, PSU is conducting anaerobic PBR tests, one with sand and one with plastic media. Initial results show both reactors with acetate and trace nutrient additions capable of reducing concentrations of 70 µg/L perchlorate to less than 4 µg/L. Prior to the pilot-scale tests, PSU conducted perchlorate degradation studies in laboratory-scale reactors evaluating both acetate-fed PBRs and hydrogen reactors.		70 µg/L reduced to <4 µg/L	Drinking water	
Shaw (Envirogen)/U.S. Filter–Envirex fluidized-bed reactors (FBR) with GAC media—Typically, ethanol or acetic acid is used as the electron donor.				
Aerojet, Rancho Cordova, California—Full scale, operational: Four FBRs with GAC media and ethanol feed as the food source have been in operation since 1998. The system was designed to treat 8 mg/L of perchlorate with a perchlorate loading of 44 lb/day per 1000 cubic ft of reactor volume. Total throughput design capacity of 4000 gpm, but processing 5300 gpm as of 10/03. The Aerojet System is based on pilot-scale laboratory testing using a 30-gpm FBR developed by U.S. Filter and Envirogen. The pilot-scale FBR also successfully reduced high concentrations of chlorate (480 mg/L) and nitrate (20 mg/L).	5300 gpm	Can reliably treat relatively high or low concentrations to below the 4 µg/L detection limit (DL)	Groundwater, wastewater, surface water, drinking water	Biosolids that slough off the FBR are trapped in the sand filters, which are periodically backwashed. Biosolids from filters and backwash are discharged to the sanitary sewer.

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Longhorn Army Ammunition Plant (LHAAP), Texas—Full scale, operational: FBR with carbon media and acetic acid/nutrient additions treats groundwater with perchlorate concentrations up to 35 mg/L to below 5 µg/L. Acetic acid and nutrient additions. $650K capital cost, $25K operation and maintenance (O&M) cost.	35 gpm	35 µg/L to <5 µg/L	Groundwater	
NASA, JPL, Pasadena, California—Pilot scale, completed: Pilot test completed with FBR using native "JPL bacteria" and ethanol as the food source.	5 gpm	350–770 µg/L to <4 µg/L	Groundwater	Elevated natural chloride levels required a variance for reinjection.
NASA, JPL, Pasadena, California—Full scale, under way: In the source zone of Operating Unit 1. Influent perchlorate concentration is 7–15 ppm.	250 gpm		Groundwater	
Kerr McGee facility, Nevada—Full scale: FBR system with four sand-media primary reactors and four carbon-media secondary reactors will replace the single-pass ion exchange resin systems. The primary reactors biodegrade the high chlorate and nitrate concentrations to allow the secondary reactors to treat the perchlorate. Denatured alcohol will be used as the electron donor. The system is currently in start-up mode and is expected to treat a blended influent from the three well fields averaging 350 ppm perchlorate.	900 gpm	350 ppm to <18 ppb permit limit for discharge; limit may be >18 ppb due to high concentrations of TDS and sulfate concentrations that result in higher RLs.	Groundwater, surface water	
Massachusetts Military Reservation, Massachusetts (MMR)—Laboratory/pilot scale, completed: FBR to treat perchlorate and RDX with different electron donors. Influent concentrations were perchlorate 100 µg/L, RDX 200 µg/L, HMX 20 µg/L, and nitrate 8 mg/L.		100 µg/L perchlorate to <4 µg/L with acetic acid as electron donor	Groundwater	
Naval Weapons Industrial Reserve Plant (NWIRP), McGregor, Texas—Full scale, operational: FBR system using acetate as electron donor, treating blended influent from collection/biobarrier trenches averaging 1–2 ppm perchlorate.	400 gpm	2000 µg/L to <4 ppb RL	Groundwater, surface water (seeps)	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
In Situ Bioremediation				
Arcadis—Injection of corn syrup or other carbon source as the electron donor to promote biodegradation of perchlorate.				
NASA, JPL, Pasadena, California—Pilot test, completed: Conducted in 2003 to evaluate use of in situ bioremediation to reduce perchlorate concentrations in the source area. Instead of molasses, corn syrup was used as the electron donor because it does not contain significant amounts of sulfur and nitrogen (sulfur creates potential for hydrogen sulfide formation; bacteria preferentially degrade the added nitrogen before perchlorate contamination.		Up to 90% reduction	Groundwater	Conversion to a reducing environment can potentially mobilize some metals such as Mn and Fe.
GET B, Aerojet, California—Pilot test, completed: Corn syrup was injected into two aquifers upgradient of existing extraction wells in an effort to remove perchlorate through biodegradation prior to the extraction wells. Significant reduction of perchlorate occurred near the extraction wells. However, mechanical difficulties in delivering the corn syrup in an efficient and consistent manner helped lead to less of a reduction than anticipated. Perchlorate was not reduced to concentrations (<4 µg/L) that would eliminate the need for aboveground perchlorate removal.			Groundwater	
Ensafe, Inc.—Groundwater collection trench constructed with composting materials, cotton seed meal, and cotton seed.				
Area M, NWIRP, McGregor, Texas—Full scale, operational: Industrial area using 25 ft deep, 30 inch wide trench. Water is run through ex-situ bioreactor for polishing.		100–13,000 µg/L to <4 µg/L	Groundwater, surface water (seeps)	
Area F, NWIRP, McGregor, Texas—Pilot scale, operational: Industrial areas using 12 ft deep, 30 inch wide trenches with composting materials, wood chips, acetic acid, and vegetable oil.		From 100s of ppb to very low ppb levels	Groundwater, surface water (seeps)	
Area S, NWIRP, McGregor, Texas—Full scale, operational: Industrial area using 30 inch wide trench with composting materials, wood chips and vegetable oil.	3500 ft of trenching	From the 100s of ppb to very low ppb levels	Groundwater, surface water (seeps)	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
GeoSyntec Consultants—Delivery of soluble electron donors via groundwater recirculation systems and active biobarriers. Typically groundwater is extracted, amended with an electron donor, and reinjected to the aquifer to promote in situ treatment.				
Area 20, Aerojet, Sacramento, California—Pilot scale, completed: Conducted to accelerate in situ bioremediation of perchlorate in a deep contaminated aquifer ~70 ft thick and extending to 100 ft below ground surface. Groundwater was extracted, amended with electron donor (acetate, lactate), and reinjected upgradient to promote biodegradation of perchlorate (12,000 µg/L) and trichloroethene (TCE, 2 mg/L). Included a donor delivery well, an extraction well, and two monitoring wells. One-time bioaugmentation of the test cell with a TCE-degrading microbial consortia (KB-1) was required to achieve TCE dechlorination to ethene.		12,000 µg/L perchlorate reduced to <4 µg/L within 15 ft of donor delivery well in ~50 days; remained below detection through end of study (~250 days). TCE reduced to <5 µg/L through reductive dechlorination to ethene.	Groundwater	
Area 20, Aerojet, Sacramento, California—Pilot scale, completed: A follow-on test was conducted to demonstrate a single-pass active biobarrier. The project created a 600 ft wide biologically active zone across the groundwater plume using two groundwater extraction wells and a single centralized electron donor delivery/recharge well. Ethanol was used as the electron donor. Chlorine dioxide was used to control biofouling of the injection well. Funded by DOD's Strategic Environmental Research and Development Program (SERDP).	20 gpm	8,000 µg/L perchlorate reduced to <4 µg/L in downgradient monitoring wells within ~20 days; remained below detection through end of study (120 days). TCE reduced to <5 µg/L through reductive dechlorination to ethene.	Groundwater	Dissolved Mn and Fe concentrations exceeded secondary maximum contaminant levels (MCLs) due to creation of reducing conditions. This issue is expected with all in situ bioremediation projects, but most projects do not measure these constituents.

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
GET D, Aerojet, Sacramento, California—Pilot scale, completed: An existing groundwater extraction and treatment system for volatile organic compounds (VOCs) required retrofit to treat perchlorate (250 µg/L). Ethanol was added to the effluent from the treatment system, and the effluent was recharged to the aquifer to promote in situ bioremediation of the perchlorate. Perchlorate was effectively removed to less than 4 µg/L a short distance (25–75 ft) downgradient from the extraction well. Chlorine dioxide was used to control biofouling of the injection well.	150 gpm	250 µg/L perchlorate reduced to <4 µg/L in downgradient monitoring wells within 30 days, and remained below detection through end of the study.	Groundwater	When concentration of electron donor addition was balanced with stoichiometric demand posed by oxygen, nitrate, and perchlorate in recharge water, perchlorate reduction occurred without mobilization of dissolved Mn and Fe above secondary MCLs.
AMPAC (formerly Pepcon) facility, Nevada—Pilot scale, completed: A 6-month in situ biological treatment pilot project in the hot spot area of the plum was completed in 5/03. Groundwater was recirculated at rate of 10 gpm between an injection and extraction well located 100 ft apart in line with groundwater flow. A number of electron donors were tested. The electron donor was switched from ethanol to citrate after 3 months to correct mineral precipitation problems. The groundwater has high TDS (3000–5000 ppm) with high concentrations of nitrates and chlorates that are preferentially biodegraded over perchlorate.	10 gpm	After 160 days, perchlorate concentrations of 600,000 µg/L were reduced to <2 µg/L at the downgradient performance monitoring well 50 ft from injection well.	Groundwater	
Former rocket testing facility, Nevada—Pilot scale, completed: Groundwater recirculation system was implemented to treat a source of perchlorate to groundwater. Groundwater was extracted, amended with citric acid, and reinjected to subsurface to treat the remaining source. No biofouling control was required for this application.	5 gpm	540 µg/L to <4 µg/L within 4 months. Concentrations have not rebounded in 6 months following bioremediation.	Groundwater	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
WNN, Aerojet, Sacramento, California—Pilot scale, completed: A large-scale test of in situ bioremediation using a 900 ft wide active biobarrier was conducted to generate site-specific data in support of a Feasibility Study. The biobarrier employed two groundwater extraction wells and a single centralized electron donor delivery/recharge well. Ethanol was used as the electron donor. Chlorine dioxide was used to control biofouling of the injection well.	60 gpm	3000 µg/L) to <4 µg/L in downgradient monitoring wells within 14 days; remained below detection through end of study (~200 days).	Groundwater	Production of dissolved Mn and Fe controlled by balancing electron donor addition versus demand.
LHAAP, Karnack, Texas—Pilot scale, in progress: A demonstration of in situ bioremediation of perchlorate impacted groundwater using a semipassive approach to electron donor (sodium lactate) addition. The biobarrier uses periodic (e.g., semiannual) bulk additions of electron donors to create a biologically active zone across the perchlorate plume to prevent migration. Funded by DOD's ESTCP.		1000 µg/L concentrations significantly reduced, in most downgradient wells down to <4 µg/L. Additional electron donor injections planned to improve biobarrier effectiveness in very heterogeneous aquifer.	Groundwater	
NIROP, Magna, Utah—Interim remedial measure: An active in situ biobarrier where groundwater is captured, amended with an optimized concentration (based on stoichiometric needs) of electron donors, and recharged to the aquifer to promote in situ perchlorate reduction (and hence perchlorate migration control). This approach allows for addition of a controlled and optimized amount of electron donor and therefore has minimal adverse impact on secondary groundwater quality. Funded by DOD's ESTCP.	100 gpm		Groundwater	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Groundwater Barrier Trench—Joint DOD/ESTCP–funded project.				
Pilot scale, planned: The objective is to evaluate the efficiency and design criteria of a permeable mulch biowall to degrade perchlorate in groundwater. The demonstration will evaluate critical design parameters such as biowall composition and contaminant residence time that are required to successfully implement this technology on a broader scale.			Groundwater	
Los Alamos National Laboratory (LANL)—A multilayered permeable reactive barrier (PRB) incorporates a sequence of four reactive media layers to immobilize or destroy a suite of contaminants present in alluvial groundwater, including Sr-90; Pu-238, -239, -240; Am-241; perchlorate; and nitrate. The four sequential media cells consist of gravel-sized scoria, apatite, pecan shells and cottonseed with an admixture of gravel (biobarrier), and limestone.				
LANL, Mortandad Canyon, New Mexico—Full scale, operational: PRB was installed in 02/03 to demonstrate in situ treatment of contaminants within alluvial and deeper perched groundwater. The 27 ft deep by 20 ft wide by 20 ft long PRB was designed with a 10-year lifetime and 1-day residence time within the biobarrier. Preliminary results indicate that both nitrate and perchlorate are being reduced by microbial activity. After the PRB was installed, drought conditions lowered the groundwater table to below the bedrock-alluvium interface and hence below the bottom of the PRB. A meaningful evaluation of PRB effectiveness has thus been delayed until groundwater levels recover to normal levels. Cost to install: $900K.		Field data indicate nondetectable levels (2 ppb) in wells within biobarrier, but this is residual water in bedrock under alluvium; 20 ppb was detected in residual groundwater in upgradient monitor well.	Groundwater	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Shaw—Injection of lactate and carbonate/bicarbonate amended water into aquifer.				
Naval Surface Warfare Center, Indian Head, Maryland—Pilot scale, completed: Site required the addition of the carbonate/bicarbonate buffer due to low pH. After 20 weeks, eight of nine wells had >95% reduction, with two wells down to the RL. Funded by DOD's SERDP and Navy.		170,000 µg/L to <4 µg/L	Groundwater	
Aerojet, California—Pilot scale, under way: An innovative, recirculating well technology developed at Stanford University will be evaluated for electron donor addition and mixing. This horizontal-flow treatment well technology was chosen for this application because it is anticipated to be the most effective and inexpensive method for applying electron donor to deep aquifers contaminated with perchlorate. Funded by DOD's ESTCP.			Groundwater	
Whittaker Bermite Facility, Santa Clarita, California—Pilot scale, planned: A groundwater recirculation system will be installed to distribute and mix electron donor with perchlorate-contaminated groundwater in a shallow, alluvial aquifer. This system will create a wide capture zone for the contaminated water, provide hydraulic control within the test region, and facilitate modification of the aquifer geochemistry to promote perchlorate biodegradation. Funded by Army Corps of Engineers.			Groundwater	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Solutions-IES—Biologically active permeable barrier: injection of emulsified soybean oil product (EOS®) as the electron donor to promote biodegradation of perchlorate. The emulsion is prepared using soybean oil, food-grade surfactants, and vitamins (commercially available as EOS) and then distributed throughout the treatment zone using temporary injection wells to create a permeable reactive biologically active barrier.				
Northern Maryland—Pilot scale, under way: This ESTCP-funded project is investigating an innovative, low-cost approach for distributing and immobilizing a water-miscible emulsion with a controlled droplet size as the biodegradable organic substrate in a perchlorate- and 1,1,1-trichloroethane (TCA)-contaminated aquifer. The aquifer contains elevated concentrations of perchlorate (~10,000 mg/L) and TCA (~23,000 mg/L) released from a closed lagoon. The test barrier is 60 ft long and 10 ft deep in the contaminated, saturated, shallow aquifer. A portion of the oil becomes trapped within the soil pores, leaving a residual oil phase to support long-term anaerobic biodegradation of the perchlorate. This approach provides good contact between the slowly biodegradable organic substrate (oil), the perchlorate, and TCA and substantially reduces initial capital costs with virtually no long-term (O&M) costs.		Within 1 month, rapid, complete, and sustained removal of perchlorate (<0.004 mg/L) traversing the treatment barrier and no rebound downgradient of the contact zone. Within 68 days of contact with the substrate, TCA concentrations decreased by 95% in monitor wells up to 20 ft downgradient with increasing concentrations of biological daughter products.	Groundwater	
Phytoremediation				
GeoSyntec Consultants				
Rocket manufacturing facility, California—Pilot scale, completed: An engineered planting of Sudan grass was constructed to prevent perchlorate in VOC treatment system effluent from reentering groundwater. Sudan grass has a high water-uptake capability. Perchlorate concentrations in infiltrating water declined during the test as a result of biodegradation in the rhizosphere and possibly reduction within plant tissues.	7 acres		Wastewater (from VOC treatment plant)	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Salt cedar trees—These trees are known to mine salt from the water. Stalks of the plant in the Las Vegas Wash picked up significant concentrations of perchlorate per gram of tissue.				
Research			Groundwater	
University of Georgia and Iowa—Performed in conjunction with the Air Force Research Laboratory and LHAAP.				
California—Pilot scale, completed: Rhizodegradation and enzymatic degradation in leaves has been observed in different plant species. Species tested include French tarragon and cottonwood. Current research focuses on enhancing rhizodegradation over slower enzymatic degradation pathway, which can allow for accumulation of perchlorate in plant tissues.			Groundwater	
Willow trees—In bench-scale tests, willows successfully treated water contaminated with both perchlorate and TCE. Rhizodegradation accounted for most of the removal of perchlorate with little uptake into the plant. Plant uptake might be significant with high-nitrate environments (a competing terminal-electron acceptor).				
Bench scale			Groundwater	
Constructed Wetlands				
Containerized Wetlands, Lawrence Livermore National Laboratory (LLNL)—Engineered use of plants to assimilate or degrade nitrate and perchlorate in water via the interaction of the contaminant with plant roots and their associated rhizosphere microorganisms. System consists of fiberglass tanks in series, containing coarse, aquarium-grade gravel and native wetland plants, such as bulrushes (*Scripus*), cattails (*Typha*), and sedges (*Carex*).				
Pilot study, completed: A containerized wetland system designed to remove nitrate and perchlorate from groundwater was tested over a 7-month period.		Removal of nitrate (as NO_3 to <4 mg/L) and perchlorate (to <4 µg/L)	Groundwater, surface water	BOD, TSS, nitrogen, phosphorous, TOC, pH, turbidity, DO may need to be monitored at effluent.

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Simulated Wetland Drum—Work performed by the University of Georgia in conjunction with the Air Force Research Laboratory.				
Laboratory study, completed: The system consists of a 55 gal drum filled with sand and potting mix. One drum was planted with native wetland plants, such as cattails (*Typha*), duckweed (*Spirodela*), and parrot feather (*Myriophyllum*). The media quickly developed reducing conditions, and drums containing wetland plants showed the highest removal rates for perchlorate (half-lives ~1.5–4 days).		250 mg/L perchlorate to ? µg/L	Groundwater, surface water	BOD, TSS, nitrogen, phosphorous, TOC, pH, turbidity, DO may need to be monitored at effluent.
Soil Bioremediation				
CDM—In situ bioremediation of vadose zone soil. Funded by DOD's ESTCP.				
Gaseous Electron Donor Injection Technology (GEDIT)—Pilot scale, planned in location to be determined: Patent-pending technology for treatment of perchlorate injects gaseous electron donors into soil using injection wells in combination with optional soil vapor extraction wells. These electron donors can include hydrogen/carbon dioxide or VOCs such as methanol, ethanol, butanol, acetic acid, ethyl acetate, and butyl acetate.			Soil	
Earth Tech/Geosyntec—Ex situ anaerobic composting				
Edwards AFB, California—Feasibility study, completed: A pilot study of anaerobic composting of perchlorate soils was conducted in 55 gal drums. Objectives were to reduce the perchlorate concentrations in soil below the residential primary remediation goal (PRG) of 7.8 mg/kg by using horse stable compost as the electron donor.	130 cubic yd	Up to 57 mg/kg to <7.8 mg/kg	Soil	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Ensafe, Inc.—Anaerobic landfarming in lined, flooded cell.				
NWIRP, McGregor, Texas—Full scale, completed: Perchlorate-contaminated soil was excavated; transported to a biotreatment cell; mixed with amendments (citric acid, nitrogen, phosphorus, and soda ash as a buffer) in a 40 cubic yd roll-off container; and placed in the treatment cell lined with 30 mil high-density polyethylene (HDPE). The soil was saturated as it was placed in the cell, and more water was added to maintain at least 2 inches of water above the soil to foster anaerobic conditions.	1500 cubic yd	500,000 µg/kg average to <100 µg/kg RL	Soil	
Environmental Alliance/Geosyntec—Ex situ anaerobic composting.				
Rocket manufacturing facility, Arkansas—Full scale, completed: Ex situ anaerobic composting was employed to treat 1500 cubic yd of soil containing perchlorate. Mulch and hay were used as electron donors.	1500 cubic yd	100 mg/kg average to <0.01 mg/kg in 12 months	Soil	
ENSR/Geosyntec—Ex situ anaerobic composting.				
Rocket manufacturing facility, San Jose, California—Full scale, completed: Pilot test to confirm the ability to reduce perchlorate concentrations to below a site-specific cleanup level of 0.02 mg/kg. Methyl soyate and acetate used as electron donors.	500 cubic yd	No data yet	Soil	
GeoSyntec Consultants—Ex situ and in situ anaerobic degradation.				
Ex situ anaerobic composting Area 41, Aerojet, Sacramento, California—Pilot scale, complete: Composting of soils from former perchlorate burn area. Two ~10 cubic yd piles treated. Degradation half-life was 1–2 days. Cost: $65/cubic yd.	20 cubic yd	23 mg/kg average to <0.1 mg/kg in 14 days	Soil	
Ex situ anaerobic composting Rocket manufacturing facility, San Jose, California—Full scale, completed: Treated soil adjacent to a grinder station. Horse stable compost used as electron donor. Cost: $45/cubic yd.	200 cubic yd	175 mg/kg to <1 mg/kg within 90 days	Soil	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Ex situ anaerobic composting Former road flare manufacturing facility, Santa Clara County, California—Full scale, completed: Acetate and citric acid used as electron donors. Cost: $50/cubic yd.	1000 cubic yd	7 mg/kg to <0.1 mg/kg within 90 days	Soil	
In situ anaerobic composting Area 41, Aerojet, Sacramento, California—Pilot-/full-scale, completed: Based on pilot test above, project was modified to perform the same function without excavating the soils. Cow manure and calcium magnesium acetate was applied directly over the hot spots of perchlorate with the addition of moisture. Pilot was successful and turned into full scale. Unique site characteristics allowed penetration of the electron donor to the full depth of the soil column (2–3 ft soil overlying bedrock). Cost: $25/cubic yd.	65 hot spots over 550 acres	450 mg/kg average to 1.4 mg/kg average; 96.4% average perchlorate reduction	Soil	
In situ soil and groundwater treatment Former road flare manufacturing facility, Santa Clara County, California—Full scale, under way: Through infiltration of electron donors (acetate and citric acid) to a depth of 16 ft (average water table elevation).	40,000 cubic yd	No data yet	Soil	
In situ soil and groundwater treatment Hogout Facility, Aerojet, Sacramento, California—Pilot scale, under way: The goal is to bioremediate perchlorate in a 35 ft vadose zone sequence using a combination of technologies—a radial biobarrier for groundwater extraction and infiltration flushing of vadose zone. Using oleate and calcium magnesium acetate as electron donors to treat perchlorate being flushed from vadose zone at a major source of perchlorate in soil and groundwater.		No data yet	Soil, groundwater	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
GeoTrans—In situ soil washing.				
Inactive Rancho Cordova Test Site, Aerojet, Sacramento, California—Pilot scale, under way: Soil washing using ethanol-blended water injected into a recharge well was attempted to bioremediate a 120 ft thick vadose zone. Results to date have not been successful.		Variable	Soil	
MWH/Geosyntec—Combined in situ and ex situ bioremediation.				
Boeing, Santa Susana Field Laboratory, Ventura Co., California—Full scale, under way: A combined in situ/ex situ bioremediation remedy is treating soils to a depth of 3 ft in three production areas by mixing with an electron donor (acetate) to promote in situ bioremediation of perchlorate in surface soils. Soils excavated from other areas have been subsequently mixed with electron donor (methyl soyate) and placed over top of the amended in situ soils to combine in situ and ex situ treatment.	20,000 cubic yd in situ, 8000 cubic yd ex situ	No data yet	Soil	
Naval Surface Warfare Center/Shaw—In situ bioremediation of vadose zone soil. Funded by DOD's ESTCP.				
Pilot scale, planned: Objective is to demonstrate and validate treatment of perchlorate in vadose zone soils through two approaches aimed at bioremediation and flushing via the infiltration of liquid electron donor. First, an engineered infiltration gallery will be designed to deliver and distribute the electron donor to perchlorate-impacted vadose zone soils. In conjunction with the infiltration gallery, an injection well may be used to supply donor to deeper vadose zone soils. The second approach will use a simple soil-mixing and watering approach, wherein donor agents are mixed with the upper 2–3 feet of the soil column and then watered regularly to deliver donor agents to contaminated vadose zone soils. Both liquid and solid donor amendments will be evaluated in the second approach. For both approaches, the most effective electron donor will be determined using site-specific column studies.			Soil	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Planteco and University of Georgia—In situ biological treatment of perchlorate-contaminated soil.				
LHAAP, Texas—Pilot scale, completed: Laboratory testing indicated that soils containing 300 mg/kg could be treated to nondetectable levels in less than 9 days using chicken manure, horse manure, and ethanol as carbon sources. Perchlorate reduced to below RL after 10 months to 30 inches, with varied levels of reduction in the deeper layers. Perchlorate concentrations in the wettest cells had decreased to nondetectable levels. Estimated cost: $25–50/cubic yd.	110 square ft	6700 µg/kg to <40 µg/kg RL in first 30 inches	Soil	
LHAAP, Texas—Pilot scale, completed: The site was subdivided into three sections. Approximately 2/3 of the southern section of the 1-acre plot was treated with 600 cubic yd of mushroom compost. The northeast 1/6 was treated with 125 cubic yd of cow manure compost only. The northwest 1/6 was treated with 125 cubic yd of cow manure compost and then with perchlorate-degrading bacteria. An irrigation system was used to mobilize the nutrient amendments into the vadose and saturated zones, and tensiometers were installed to monitor moisture content in the site soils.	1 acre	80% reduction in mass	Soil	
Soil Composting				
Pueblo Army Depot, Colorado—Full scale: Performed to remediate soils contaminated with explosives (HMX and RDX) and now known to also be contaminated with perchlorate. Analyses are under way to assess the effectiveness of the process in reducing perchlorate concentrations.			Soil	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
PHYSICAL PROCESSES				
Conventional Ion Exchange Resins				
Calgon ISEP® (Ion SEParator), Continuous Anion Exchange and Regeneration—System includes multiple (20–30) anion exchange columns mounted on a turntable attached to a rotating multiport valve. During a rotation, each resin cell is subjected to a cycle of adsorption, regeneration (with an NaCl solution) or elution, and one or two rinse steps.				
La Puente Valley County Water District, California—Full scale, operational: Designed to treat 2500 gpm with 600 µg/L perchlorate; began operating 02/00. Uses Purolite A 850, strong base anion, acrylic, Type 1 gel resin and operates 19 hours/day to control the perchlorate plume in the San Gabriel Groundwater Basin. Capital cost = $2 million; operating cost = $145/acre-ft.	2500 gpm	~200 µg/L to <4 µg/L	Drinking water	Concentrated brine potentially containing nitrate, sulfate, and perchlorate requires treatment or disposal.
Kerr-McGee, Henderson, Nevada—Full scale, operational: Perchlorate destruction module started in 03/02 and operated for about 6 months to treat extracted groundwater from Athens Road Well Field and Las Vegas Wash seep area. Actual flow rates varied 200–560 gpm. Maintenance problems were caused by high TDS, hardness, and sulfate. Operation discontinued due to corrosion in heat exchangers.	450 gpm	80–100 mg/L to <2 mg/L (DL, ion-specific electrode)	Groundwater	
Big Dalton Well, Baldwin Park, California—Pilot scale, completed: Study initiated in 5/98; brine produced was 0.75% of the inflow.	4.3 gpm	18–76 µg/L to <4 µg/L.	Drinking water	
San Gabriel Valley Water Company, El Monte, California—Full scale, planned: B6 well site; system built, first phase of start-up under way; expected operational by 02/04.	7800 gpm		Drinking water	
Valley County Water District, Baldwin Park, California—Full scale, planned: Under construction, start-up 01/04.	7800 gpm		Drinking water	
City of Pasadena, California—Full scale, proposed: 3500–5000 gpm system proposed at existing wells next to JPL site; planning stage.	7000 gpm		Drinking water	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Calgon Anion Exchange—Fixed-bed nonregenerable anion exchange resin treatment.				
California Domestic Water Company, Whittier, California—Full scale, operational: Start-up 7/02. Cost: $125/acre ft.	5000 gpm	<14 µg/L to <4 µg/L	Drinking water	Perchlorate-laden resin requires disposal.
Tippecanoe Treatment Facility, City of Riverside, California—Full scale, operational: Start-up 12/02.	5000 gpm	Distribution system 6.4 ppb average in 2001 to 4.6 ppb average in 2002	Drinking water	
Gage 51-1 Treatment Facility, City of Riverside, California—Full scale, operational: Start-up 05/03.	2000 gpm	<60 µg/L to <? µg/L	Drinking water	
West San Bernadino Water District, Rialto, California—Full scale, operational: Start-up 05/03.	2000 gpm		Drinking water	
City of Monterey Park, Delta Treatment Plant, Well 12 (San Gabriel GW basin—Full scale, planned: System constructed and tested, awaiting permit, expected operational 01/04.	4050 gpm		Drinking water	Perchlorate-laden resin requires disposal.
B5 Site, San Gabriel Valley Water Company, El Monte, California—Full scale, planned: Under construction, start-up 04/04.	7800 gpm		Drinking water	
Kerr-McGee facility, Nevada. Full scale, operational: Once-through ion exchange system to treat captured surface water in the seep area has been ongoing since 11/99. Groundwater in seep area has been pumped and treated since 10/01. The initial four-well extraction system was expanded to nine wells in 03/03. Pumping rates varied 300–600 gpm 10/02–03/03.	>300 gpm	Influent averages ~30 ppm. Combined with effluent from ion exchange system, effluent varies <0.5–2 ppm and averages 1.3 ppm.	Surface water, groundwater	
NWIRP, McGregor, Texas—Full scale, completed: Modular system was brought in to treat a blended influent from the collection/biobarrier trenches averaging 1–2 ppm perchlorate. System was replaced by a biological FBR.	200 gpm?	2000 µg/L to < 4 ppb RL	Groundwater, surface water (seeps)	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Loma Linda, California—Full scale, planned: Single-pass ion exchange treatment; start-up planned spring 2004.	2000 gpm		Drinking water	
Kerr McGee facility, Nevada—Full scale, operational: A single-pass ion exchange system was installed to replace the Calgon ISEP system and to allow continuous treatment of the extracted groundwater from the Athens Road wells. Continuous operation since 10/03.	850 gpm	Influent varies 200–300 ppm. Combined with effluent from ion exchange system, effluent varies <0.5–2 ppm and averages 1.3 ppm.	Groundwater	
Ion Exchange—Originally designed for nitrate removal, anion exchange system achieves perchlorate removal.				
City of Pomona, California—Full scale, operational.	10,000 gpm		Drinking water	Concentrated brine potentially containing nitrate, sulfate, and perchlorate requires treatment or disposal?
U.S. Filter Anion Exchange—Fixed-bed nonregenerable anion exchange resin treatment.				
Aerojet, California—Full scale, operational: Sacramento GET D facility.	1000 gpm	200 ppb to <4 ppb	Groundwater	Perchlorate-laden resin requires disposal.
Aerojet, California—Full scale, operational: Sacramento GET B facility.	2000 gpm	50 ppb to <4 ppb	Groundwater	
Aerojet and Boeing (formerly McDonald Douglas), Sacramento, California—Full scale, operational.	800 gpm	250 ppb to <4 ppb	Groundwater	
City of Morgan Hill, California—Full scale, operational: Two wells: Nordstrom well operating; Tennant well installed. Perchlorate plume due to Olin Corp. manufacture of road flares.	800 gpm	<10 ppb to <4 ppb	Drinking water	
West Valley Water Co., West San Bernadino, California—Full scale, operational: Start-up 05/03.	2000 gpm	<10 ppb to <4 ppb	Drinking water	
City of Rialto, California—Full scale, operational: Start-up 08/03.	2000 gpm	<10 ppb to <4 ppb	Drinking water	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
City of Colton, California—Full scale, operational: Start-up 08/03.	3500 gpm	<10 ppb to <4 ppb	Drinking water	
Fontana Union Water Co., Fontana, California—Full scale, operational: System being loaded with resin as of 12/19/03; operational by 01/04.	5000 gpm	15 ppb to <4 ppb	Drinking water	Perchlorate-laden resin requires disposal.
West San Martin Water Co., California—Full scale, operational.	800 gpm	17 ppb to <4 ppb	Drinking water	
Selective Ion Exchange Resins				
Applied Research Associates, Inc.—ESTCP-funded selective resin demonstration.				
Redstone AAP—Pilot scale, planned: A perchlorate-selective ion exchange resin and ferrate ion displacement regeneration technique will be demonstrated with a skid-mounted, field demonstration unit. Multiple, ion-exchange-column regenerations will be performed using this resin and regeneration technique that can reduce effluent volume to 0.1%–0.2% of state-of-the-art ion exchange processes. Biological and thermal effluent treatment techniques will be demonstrated that enable discharge or reuse of the spent regeneration solution. A low-cost, prototype field monitor capable of online, real-time, perchlorate analysis to <1 ppb will also be demonstrated.			Groundwater	Perchlorate-laden resin requires disposal.
Carrollo Engineers, Inc.				
Castaic Lake Water Agency, Santa Clarita, California—Pilot scale, completed: Study on three single-use resins: USF 9708, USF 9710, and CalResin #2. Influent feed water concentration was spiked to approximately 50 ppb perchlorate. All the resins removed perchlorate, with breakthrough occurring at 25,000 bed volumes for USF 9708; 72,000 bed volumes for USF 9710; and 76,000 bed volumes for CalResin #2.		50 ppb to <1 ppb		
SYBRON IONAC SR-7 Anion Exchange Resin, LLNL—Commercially available regenerable nitrate selective anion exchange resin manufactured by Sybron; resin is effective for perchlorate, whose ion exchange properties are similar to nitrate's. In these systems, anion exchange is part of a treatment train, preceded with biological treatment to remove nitrate and followed with GAC to remove TCE.				
LLNL, Building 815 SR-7—Full scale, operational: Start-up 07/00; regenerant flow rate 0.25–0.5 gpm/cubic ft.	1400 gpd	10 µg/L to <4 µg/L	Groundwater?	Perchlorate-laden resin requires disposal.

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
LLNL, Building 830-DISS—Full scale, operational: Start-up 11/00; regenerant flow rate 0.25–0.5 gpm/cubic ft.	5000 gpd	10 µg/L to <4 µg/L	Groundwater?	
LLNL, Building 854-PRX—Full scale, operational: Start-up 09/00; regenerant flow rate 0.25–0.5 gpm/cubic ft.	1000 gpd	7.2 µg/L to <4 µg/L	Groundwater?	
Oak Ridge National Laboratory (ORNL) and University of Tennessee Purolite A-530E Bifunctional Resin—Bifunctional anion exchange resins highly selective for perchlorate consist of quaternary ammonium groups with large (C6) and small (C2) alkyl groups resulting in high selectivity and good exchange kinetics. The technology has been licensed to Purolite to develop a commercial version of the resin. Difficulty with regeneration of bifunctional resins has limited their use. ORNL has patented a process using a ferric chloride-hydrochloric acid displacement technique to regenerate bifunctional and other selective anion-exchange resins. Lab studies indicate a high recovery of ion-exchange sites can be achieved with the regenerant solution without affecting the resin's performance after repeated cycles.				
ORNL lab studies demonstrating D3696 resin (aka Purolite A-530E) to remove perchlorate.			Groundwater	Perchlorate-laden resin requires disposal.
Stringfellow Site, Riverside Co., California—Full scale, planned: A system to treat the downgradient "toe" of the perchlorate plume (~30 µg/L) began continuous operation in 12/03. The system consists of two 10-cubic-ft beds in series and can treat perchlorate to below the 4-ppb DL. The highly selective resin is expected to last several months before change-out is required. On-site regeneration was not an option because of location in a residential area which required a low profile and minimal operational requirements. High TDS, including sulfates (~200 mg/L) and nitrates (~70 mg/L) makes use of nonselective anion exchange resins problematic for this application due to frequent regeneration or change-outs and no brine disposal options. Significant concentrations of tetrahydrafuran and methyl ethyl ketone were detected during system start-up but not in subsequent sampling. The source of these contaminants is unclear (may be from the resin system) as these compounds are not normally found in groundwater plume at this location.	25 gpm	30 ppb to <4 ppb	Groundwater	Perchlorate-laden resin requires disposal.

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Site 285, Edwards AFB, California—Full scale, under way: The system, including a chemical regeneration process and destruction module, became operational in the spring of 2003 and has removed 32 lb of perchlorate from approximately 9 million gal of water processed through 06/04. Destruction module is expected to become operational in summer 2004.	35 gpm	300 µg/L to <4 µg/L	Groundwater	
Castaic Lake—Pilot scale, completed: Five-month pilot plant study (Kennedy-Jenks), three wells	300 gpm	to <4 µg/L	Groundwater?	
Purolite A-520E Anion Exchange Resin—Commercially available nitrate selective anion exchange resin manufactured by Purolite; effective for perchlorate, whose ion exchange properties are similar to nitrate's. Reported by ORNL as one of the best nitrate-selective resins; higher affinity for nitrates over sulfates.				
Paducah Gaseous Diffusion Plant—Lab study to treat pertechnetate.			Groundwater?	Perchlorate-laden resin requires disposal.
ORNL comparison study for bifunctional resins—Lab study.			Groundwater	
Rohm and Haas Corporation Amberlite PWA2 Perchlorate Selective Resin—A proprietary perchlorate-selective resin that is NSF 61–certified for potable use. Amberlite PWA2 is a nonregenerable resin for "load and toss" applications.				
Aerojet, Sacramento, California—Full scale, operational.	2000 gpm	50 ppb to <4 ppb	Drinking water	Perchlorate-laden resin requires disposal.
Lincoln Avenue, Altadena, California—Full scale, operational.	2000 gpm	20 ppb to <6 ppb	Drinking water	
Rohm and Haas Corporation Amberlite PWA 555 Nitrate Selective Resin—Commercially available nitrate selective anion exchange resin is effective for perchlorate, whose ion exchange properties are similar to nitrate's.				
W. San Martin Colony and County wells, California—Full scale, operational.	1000 gpm	15 ppb to <4 ppb	Drinking water	Perchlorate-laden resin requires disposal.
Selective strong-base anion exchange resin				
Site 9, Vandenberg AFB, California—Pilot scale, operational: System consists of two 560 gal tanks, each containing ~42 cubic ft of a selective strong-base anion resin; associated interconnection and process piping, and instruments and controls. Columns are arranged in series (lead-lag configuration) and installed inside a double-contained treatment pad. Cost: $81K/year for O&M.		204 µg/L to <4 µg/L	Groundwater	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Tailored Granular Activated Carbon/GAC				
Granular Activated Carbon				
Crafton-Redlands Plume, City of Redlands, California—Full scale, operational: System installed to treat VOC contamination for drinking water supply later found effective to treat low concentrations of perchlorate. In 09/01, the Department of Health Services issued a domestic water supply permit amendment to the City of Redlands Municipal Utilities Department to operate the Texas Street GAC facility to remove perchlorate in the domestic water supply system. Penn State University is using 4 of the 24 GAC vessels at the same facility for additional studies, looking at enhancing GAC performance by preloading with iron organic complex and regenerating with reducing solution.		Influent concentration of 60–138 µg/L perchlorate; GAC bed regenerated every 6 weeks for perchlorate treatment vs. the 8 months required for treatment of VOCs.	Drinking water	GAC loaded with perchlorate and potentially other compounds requires treatment or disposal.
Site 133, Edwards AFB, California—Full scale, operational: Liquid-phase GAC system. Three 2000 lb carbon canisters in series, constructed in 05/01 to remove VOCs, are now treating 92 µg/L perchlorate as a cocontaminant; U.S. Filter has conducted bench-scale testing of modified carbon to treat perchlorate at the treatment system effluent.	100 gpm	Influent concentration of 92 µg/L perchlorate; 09/03 report indicates system not effective for perchlorate.	Drinking water	
City of Monterey Park, Well 5, California—Full-scale, planned. Coconut carbon to treat low levels.			Drinking water	
Penn State University, Tailored GAC—Preloaded with quaternary ammonium compounds				
Crafton-Redlands Plume, City of Redlands, California—Pilot scale, completed: A number of different quaternary ammonium compounds have been pilot tested using rapid, small-scale columns. Results concluded that for Redlands water, commercially available GAC can be tailored to extend the service life for perchlorate from 1 month to 2.5 years.	2.65 mL bed volume	60–140 µg/L to <6 µg/L	Drinking water	Tailored GAC loaded with perchlorate and potentially other compounds requires treatment or disposal.

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Crafton-Redlands Plume, City of Redlands, California—Full scale, under way: Testing began in the spring 2004 to last 6–9 months. Results after 6 weeks of operation have treated 7100 bed volumes of water with no breakthrough of perchlorate, which averaged 49 ppb at the influent.		49 µg/L average to 6 µg/L	Drinking water	
MMR, Cape Cod, Massachusetts—Pilot scale testing of tailored GAC				
Reverse Osmosis				
Reverse Osmosis (RO)—Water is forced through a semipermeable membrane. RO has been used to treat various water sources to remove high concentrations of total dissolved salts. Although performance data is not available, RO would also be expected to effectively remove perchlorate ions. Unselective removal of dissolved ions results in a more corrosive, lower pH effluent. Degradation of the membrane in treating perchlorate may be a concern.				
NASA, JPL, Pasadena, California—Bench scale: A laboratory treatability study was performed to assess the effectiveness of RO to remove perchlorate from groundwater. A thin film composite and a cellulose acetate membrane were tested. In both tests, 80% of influent stream was recovered as permeate and 20% as rejectate. High energy requirements due to operating pressures required.		Influent 800 µg/L, thin film permeate 12–16 µg/L, thin film rejectate 3600 µg/L, cellulose acetate permeate 680 µg/L, cellulose acetate rejectate 1600 µg/L	Groundwater	Effluent (rejectate) brine production (TDS, perchlorate) can be equal to 20% of influent flow rate and require further treatment or disposal.
Electrodialysis				
Electrodialysis—Water is passed through channels of alternating semipermeable and permeable membranes (to either anions or cations), while being exposed to an electrical field.				
Magna Water Co., Utah—Pilot scale, completed: An electrodialysis reversal pilot unit (Ionics Aquamite III) was installed at an uncontaminated well with high TDS (1300 mg/L) and silica (80 mg/L) and operated continuously for 4 days to evaluate perchlorate removal effectiveness. Extracted groundwater feed to the pilot unit was dosed to 130 µg/L perchlorate. Cost: $1.10–1.50/1000 gal	7.4 gpm	Stabilized in the low 70% range; higher rates (94%) possible with a four-stage system	Drinking water?	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
CHEMICAL PROCESSES				
Concentrated Brine Treatment				
Calgon Carbon ISEP™ System Perchlorate and Nitrate Destruction Module (PNDM)—A catalytic chemical reduction process for treating perchlorate and nitrate ions in the waste regeneration brine. A hydrogen source (ammonium) is added as a reductant, and perchlorate is reduced to chloride ($ClO_4^- + 8e^- + 8H^+ \rightarrow Cl^- + 4H_2O$). The system operates at 250ºC and is relatively energy intensive.				
NASA, JPL Pasadena, California—Pilot scale, completed: Seven-month study conducted 1998–99 on groundwater with 1200-µg/L perchlorate and high concentrations of nitrate and sulfate. PNDM effectively reduced the perchlorate and nitrate present in regeneration brine waste, while >96% of sulfate was removed. Treated regenerant stream was recycled to effectively regenerate the resin. Overall process waste from the system was about 0.16% of the feed volume. O&M costs are estimated at about two times the cost of a comparable biological treatment unit.	<2 gpm	1200 µg/L to <4 µg/L; nitrates and sulfates removed to acceptably low levels	Wastewater (brine from water treatment plant)	A small concentrated brine (sulfate buildup) waste stream requires treatment or disposal.
Kerr-McGee, Henderson, Nevada—Full scale, operational: System started up in 03/02 and operated for about 6 months to treat extracted groundwater from the Athens Road Well Field and the Las Vegas Wash seep area. Actual flow rates varied 200–560 gpm. Maintenance problems were caused by high TDS, hardness, and sulfate. Operation was discontinued due to corrosion in the heat exchangers.	450 gpm	80–100 mg/L to <2 mg/L (DL, ion-specific electrode)	Wastewater (brine from water treatment plant)	
ORNL Chemical Reduction of Perchlorate $FeCl_3$-HCl Regenerant Solutions—Perchlorate in $FeCl_3$-HCl regenerant solutions is degraded using ferrous iron and/or nontoxic organic reducing agents (patent pending). While perchlorate is reduced, ferrous (Fe^{2+}) ions are oxidized to ferric (Fe^{3+}) ions, which replenish or "regenerate" the $FeCl_3$-HCl solution.				
Site 285, Edwards AFB, California—Full scale, under way: Bifunctional resin treatment system including a chemical regeneration process and destruction module, is under way. Destruction module became operational in fall 2004. Destruction of perchlorate to chloride and water required up to 1-hour residence time in pilot testing.	35 gpm	50 µg/L to <5 µg/L	Wastewater (brine from water treatment plant)	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Nanoscale Bimetallic Particles				
Lehigh University—Nanoscale bimetallic particles (Fe/Pd, 99.9% Fe) are being investigated for their possible use as remediation technology. Nanoparticles feature large surface area and extremely high surface reactivity.				
In lab research, nanoscale zero-valent iron particles degraded perchlorate to chloride after a lag period at an estimated rate of 1.2 mg/L-day.			Groundwater?	
Ozone Peroxide				
AWWARF-Funded Study				
In "Removal of Perchlorate and Bromate in Conventional Ozone/GAC Systems," investigators explored water quality conditions under which ozone/GAC and other advanced oxidation processes (AOPs) may result in by-products that donate electrons sufficiently to facilitate destruction of perchlorate. Results indicated that perchlorate ions exchanged to some extent onto the GAC, but that abiotic reduction of perchlorate did not occur under these conditions. Since perchlorate solutions in water cannot be reduced by strong common reductants, it is unlikely that AOPs would be successful unless the kinetic barrier to reduction can be overcome.			Drinking water	
Titanium				
Titanium +3 Chemical Reduction, Georgetown University				
A technique using titanous ions (3+) to chemically reduce perchlorate. Several new organic ligands have been developed that have been shown to catalyze reduction of perchlorate by titanous ions (3+) ions to titanium dioxide and chloride in acidic aqueous media. A preliminary patent application has been filed.			Wastewater	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
UV/Zero-Valent Iron				
UV Light/Zero-Valent Iron Reduction—Lab studies (Gurol and Kim 2000) indicate that perchlorate can be reduced by iron (FeO) under anoxic conditions and that UV light can accelerate the reaction rate to levels for practical application. Patent #6,531,065 was issued March 11, 2003. The patent also covers use of the iron metal with a catalyst and with phosphoric acid.				
Pilot test, planned: Funded by the California State University, San Bernadino, Office of Technology Transfer and Commercialization Initiative to be conducted in the Rialto Area.		77% reduction in perchlorate concentration in laboratory study	Drinking water	
Electrochemical				
Capacitive Deionization, Carbon Aerogel, LLNL—Influent water containing salts enters space between two carbon-aerogel electrodes; electrostatic field forces ions into aerogel, where they are held, and purified water leaves the space between the electrodes. CDI systems potentially use 10–20 times less energy per gallon and achieve the same results as a convention electrodialysis or RO system.				
LLNL patented the carbon aerogel capacitive deionization technology in 1995 and has licensed the technology for commercialization to CDT Systems, Inc. (formerly FarWest Group, Inc.), based in Tucson, Arizona. CDT Systems, Inc. has a proposal to install a system to clean up brackish water at the municipal water treatment plant in Carlsbad, California.			Wastewater? Drinking water?	
Capacitive Deionization, Flow-Through Capacitor, Biosource, Inc.—Made up of alternating electrodes of porous activated carbon. With small-voltage applications, dissolved salts in the water moving through the capacitor are attracted to the high surface area carbon and removed. Once the capacitor is fully charged, the electrodes are shorted to regenerate the capacitor, causing absorbed contaminants to be released as a small volume of concentrated liquid waste.				
Research and development: Covered by a number of U.S. patents. Biosource, Inc. indicated in May 2004 that it had recently been awarded a contract to develop water purification technology for military use and that it will be used in Iraq.			Drinking water?	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Electrochemical Reduction—Clarkson University, City of Redlands and City of Riverside, California (AWWARF-funded).				
Bench-scale study of electrochemical reduction of perchlorate used two-chambered batch reactor systems. Cathodic and anodic compartments were separated by an ion exchange membrane, and electrodes consisted of titanium coated with a thin film of titanium dioxide particles. Initial perchlorate concentration ranged 50–500 mg/L. Perchlorate reduction was limited due to the competition among anions for active sites on the electrode surface, with perchlorate less strongly adsorbed than both sulfate and chloride. The time required for ions in the water to travel to the electrode surface is a design problem in developing a practical full-scale system.			Drinking water	
THERMAL PROCESSES				
Applied Research Associates, Integrated Thermal Treatment Process—Perchlorate in regenerant brine is thermally decomposed at elevated temperature and pressure with the addition of reducing agents and promoters. Concentration of the brine with reverse osmosis would be necessary to make the process cost-effective. A patent application is pending.				
Laboratory research, completed.			Wastewater (brine from water treatment plant)	
Environmental Chemical Corp., Burlingame, California, Thermal Treatment Unit—Dry, perchlorate-contaminated soils were thermally destroyed in bench tests in 10 minutes at 775ºF in a laboratory-scale rotary kiln. Temperatures required in the full-scale unit were higher (up to 950ºF) depending on moisture evaporation requirements at a fixed total residence time of 10 minutes.				
MMR, Cape Cod, Massachusetts—Bench and full scale, under way: In full production mode, summer 2004.	40 tons/hour	To <4 ppb (µg/kg)	Soil	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
General Atomics, Super Critical Water Oxidation—Supercritical water sustains combustion and oxidation reactions because it mixes well with oxygen and with nonpolar organic compounds. Reductions, such as those necessary to destroy the perchlorate ion, also take place.				
Thiokol, Brigham City, Utah—Bench scale, completed: The concentration of ammonium perchlorate in CYH is 10.8%. During optimization testing, destruction removal efficiencies of 99.9% were achieved. The critical point of water is 374.2ºC and 22.1 Mpa. Costs are expected to be high due to high temperature and pressure.	Up to 800 lb of CYH propellant	99.9% DRE	Wastewater	
EMERGING PROCESSES				
Monitored Natural Attenuation (MNA)				
Solutions IES—A long-term process using groundwater monitoring to evaluate and track the natural degradation of perchlorate. Preliminary evidence suggests that conditions similar to those promoting denitrification may be appropriate for perchlorate MNA. These include anaerobic conditions along with depleted concentrations of oxygen and nitrate. However, at this time there is a little or no evidence of perchlorate natural attenuation at field sites as few studies have investigated this process.				
Pilot-scale, under way: ESTCP-funded project to identify perchlorate sites, monitor site conditions over an extended period, and seek commonality in conditions from sites where perchlorate appears to be controlled compared to locales where is it continuing to migrate unabated. This effort will help develop a protocol that will be useful to regulators and the public, providing the needed assurances that this approach is protective of human and environmental health.			Groundwater	

Technology & Vendor Name/Projects	Throughput	Treatment Effectiveness	Media	Residuals
Iodide Addition				
U.S. Air Force and U.S. Geological Survey—The remediation of perchlorate-contaminated wetlands using potassium iodide or elemental iodine addition to the water.				
Laboratory: Results indicate this maybe a promising method, requiring only a small amount of iodide to counteract significantly higher concentrations of perchlorate (as little as 10 ppb iodide can offset the effects of up to 50 ppm perchlorate). Additional testing at the pilot and field scale needs to be performed, as well as determining logistics and physical form of iodide application, effects on other wetland species, and stability and potential side effects of iodide addition.			Surface water	
Nanofiltration/Microfiltration				
Nanofiltration/Ultrafiltration—A partially permeable membrane is used to preferentially separate different fluids or ions. Nanofiltration generally works for particle sizes over 10 angstroms (10^{-10} m), rejecting selected salts (typically divalent). Ultrafiltration is a selective fractionation process using pressures up to 145 psi. It concentrates suspended solids and solutes with high molecular weights. Ultrafiltration process typically removes particles in the 0.002–0.1 micron range.				
AWWARF-funded studies: Nanofiltration passes more water at lower operating pressure than RO systems and thus requires less energy to perform the separation. Based on the size of the perchlorate ion, about 3.5 angstroms, nanofiltration may not prove to be effective for perchlorate removal. Ultrafiltration targets compounds that are larger than those removed by nanofiltration; thus, ultrafiltration is not expected to effectively remove perchlorate. High energy requirements due to operating pressures.			Drinking water	Effluent brine production (TDS, perchlorate) can equal 20% of influent flow rate and require further treatment or disposal.
Catalytic Gas Membrane				
University of Delaware				
Catalytic hydrogen membrane—Research				

APPENDIX G

Perchlorate Team Contacts, Fact Sheet, and Product List

PERCHLORATE TEAM CONTACTS

Sara Arav-Piper, Co-Team Leader
NV Division of Environmental Protection
702-486-2868
spiper@ndep.nv.gov

Laurie Racca, Co-Team Leader
CA Dept. of Toxic Substances Control
916-255-3668
lracca@dtsc.ca.gov

Stacey Kingsbury, ITRC Program Advisor
Sky Research
540-961-9132
Stacey.kingsbury@skyresearch.com

Richard Albright
DC Department of Health
202-535-2283
richard.albright@dc.gov

Brian Ambrose
DuPont Corp. Remediation Group
302-992-5869
brian.ambrose@usa.dupont.com

Caroline (Cal) Baier-Anderson
University of Maryland
410-706-1767
cbaie001@umaryland.edu

Keith Bailey
Kerr-McGee Shared Services
405-270-3651
kbailey@kmg.com

Jean Balent
Technology Innovation Program
EPA
703-603-9924
balent.jean@epa.gov

Joshua Barber
EPA
703-603-0265
barber.joshua@epa.gov

Bob Barnwell
ADEM
334-271-7746
bbarnwell@adem.state.al.us

Erica Becvar
HQ AFCEE / TDE
210-536-4314
erica.becvar@brooks.af.mil

Bradley Call
US Army Corps of Engineers
916-557-6649
bradley.a.call@usace.army.mil

Sandip Chattopadhyay
Battelle
614-424-3661
chattopadhyays@battelle.org

Jay Clausen
ERDC / CRREL
603-646-4597
jay.l.clausen@erdc.usace.army.mil

David O. Cook
Kleinfelder, Inc.
916-366-1701
dcook@kleinfelder.com

Charles G. Coyle
US Army Corps of Engineers
402-697-2578
charles.g.coyle@usace.army.mil

Michael Crain
US Army Corps of Engineers
402-697-2657
michael.e.crain@usace.army.mil

Geoffrey D. Cullison
Operational Environmental Readiness & Planning Branch
Chief of Naval Operations
703-602-5329
geoffrey.cullison@navy.mil

Annette Cusher
Arkansas Dept. of Environmental Quality
501-682-0841
cusher@adeq.state.ar.us

Shana R. Dalton
US Army Corps of Engineers, ERDC
402-444-4317
shana.r.dalton@nwo02.usace.army.mil

Susan Flanagan
Institute of Makers of Explosives (IME)
202-429-9280
sjflanagan@ime.org

Kimberly Gates
US Navy NFESC
805-982-1656
kimberly.gates@navy.mil

Bill Guarini
Shaw Environmental
609-895-5384
william.guarini@shawgrp.com

Paul Hadley
CA Dept. of Toxic Substances Control
916-324-3823
phadley@dtsc.ca.gov

Mark Hampton
US Army Environmental Center
410-436-6852
mark.hampton2@us.army.mil

Bryan Harre
NFESC
805-982-1795
bryan.harre@navy.mil

Lornette D. Harvey
GA Environmental Protection Division
404-656-2833
lornette_harvey@dnr.state.ga.us

T.R. Hathaway
Human & Ecological Risk Division
California EPA
916-255-6636
lazytr1@aol.com

Paul Hatzinger
Shaw Environmental
609-895-5356
paul.hatzinger@shawgrp.com

Keith Hoddinott
USACHPPM
410-436-5209
keith.hoddinott@amedd.army.mil

Rose Knox
MA Dept. of Environmental Protection
617-556-1026
rosemary.knox@state.ma.us

Limesand Kurt
KS Dept. of Health & Environment
785-296-1671
klimesan@kdhe.state.ks.us

Katharine Kurtz
Navy Environmental Health Center
757-953-0944
kurtzk@nehc.med.navy.mil

M. Tony Lieberman
Solutions-IES
919-873-1060
tlieberman@solutions-ies.com

R. Lee Lippincott
NJ Dept. of Environmental Protection
609-984-4899
lee.lippincott@dep.state.nj.us

Paul Locke
MA Dept. of Environmental Protection
617-556-1160
Paul.Locke@state.ma.us

Mark E. Losi
Center for Environmental Microbiology
949-756-7516
mlosi@biocem.com

Alexander MacDonald
CA Water Resources Control Board
California - Region 5
916-464-4625
amacdonald@waterboards.ca.gov

Malinowski Mark
Dept. of Toxic Substances Control
California EPA
916-255-3717
mmalinow@dtsc.ca.gov

Heidi Maupin
Navy Environmental Health Center
757-953-0947
maupinh@nehc.med.navy.mil

Christopher Maurer
State of Washington Dept. Of Ecology
360-407-7223
cmau461@ecy.wa.gov

Richard Newill
BEM Systems, Inc.
602-266-2011
rnewill@bemsys.com

Eric Nuttall
University of New Mexico
505-277-6112
nuttall@unm.edu

Dee O'Neill
Columbia Analytical Services, Inc.
360-577-7222
doneill@caslab.com

Ian T. Osgerby
US Army Corps of Engineers
978-318-8631
ian.t.osgerby@usace.army.mil

Gail L. Pringle
Naval Facilities Engineering Service Center
805-982-1411
gail.pringle@navy.mil

Matt Rhoades
Golder Associates
303-980-0540
matt_rhoades@golder.com

Rey Rodriguez
H2O-R1 Consulting Engineers, Inc.
626-852-1235
reyrh2or2@aol.com

Supalak (Sue) Rogers
TCEQ
512-239-6213
srogers@tceq.state.tx.us

Blaine Rowley
Office of Cleanup Technologies
US Department of Energy
301-903-2777
blaine.rowley@em.doe.gov

Lenny Siegel
Center for Public Environmental Oversight
650-961-8918
lsiegel@cpeo.org

David R. Smith
Shieldalloy Metallurgical Corporation
856-692-4201
dsmith@shieldalloy.com

Betty A. Strietelmeier
Los Alamos National Laboratory
505-665-9986
bastriet@lanl.gov

Clayton Trumpolt
CO Dept. of Public Health and Environment
303-692-3460
clayton.trumpolt@state.co.us

Harry Van Den Berg
ARCADIS
714-278-0992
hvandenberg@arcadis-us.com

Deborah Dixon Walker
US Army Corps of Engineers
256-895-1796
deborah.d.walker@hnd01.usace.army.mil

Allen Wolfenden
CA Dept. of Toxics Substances Control
916-255-6540
awolfend@dtsc.ca.gov

Children's Environmental Health Network

September 18, 2009

Water Docket
Environmental Protection Agency
Mailcode 2822T
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Re: Docket ID No. **EPA-HQ-OW-2009-0297**

Submitted via www.regulations.gov

The Children's Environmental Health Network (the Network) appreciates the opportunity to comment on the importance of regulating perchlorate in drinking water. We wish to associate ourselves with the comments submitted by Clean Water Action, the Center for Public Environmental Oversight et al on this topic.

The Network is a national organization whose mission is to promote a healthy environment and to protect the fetus and the child from environmental health hazards. The Network's Board and committee members include internationally-recognized experts in children's environmental health science and policy who serve on key Federal advisory panels and scientific boards. We recognize that children, in our society, have unique moral standing. The Children's Environmental Health Network was created to promote the incorporation of basic pediatric facts such as these in policy and practice:

- Children's bodies and behaviors differ from adults. In general, they are more vulnerable than adults to toxic chemicals.
- Children are growing. Pound for pound, children eat more food, drink more water and breathe more air than adults. Thus, they are likely to be more exposed to substances in their environment than are adults. Children have higher metabolic rates than adults and are different from adults in how their bodies absorb, detoxify and excrete toxicants.
- Children's systems, including their nervous, reproductive, digestive, respiratory and immune systems, are developing. This process of development creates periods of vulnerability when toxic exposures may result in irreversible damage when the same exposure to a mature system may result in little or no damage.

CHILDREN'S ENVIRONMENTAL HEALTH NETWORK
110 Maryland Avenue NE, Suite 505
Washington, DC 20002
202.543.4033 202.543.8797 www.cehn.org cehn@cehn.org

- Children behave differently than adults, leading to a different pattern of exposures to the world around them. For example, they exhibit hand-to-mouth behavior, ingesting whatever substances may be on their hands, toys, household items, and floors. Children play and live in a different space than do adults. For example, very young children spend hours close to the ground where there may be more exposure to toxicants in dust, soil, and carpets as well as low-lying vapors such as radon, mercury vapor or pesticides.
- Children have a longer life expectancy than adults; thus they have more time to develop diseases with long latency periods that may be triggered by early environmental exposures, such as cancer or Parkinson's disease.

Clear, sound science underlies these principles. A solid consensus in the scientific community supports these concepts.

The world in which today's children live has changed tremendously from that of previous generations. There has been a phenomenal increase in the substances to which children are exposed. According to the EPA, more than 83,000 industrial chemicals are currently produced or imported into the United States. Thousands of chemicals are ubiquitous in our environment worldwide. Traces of hundreds of chemicals are found in all humans and animals. Every day, children are exposed to a mix of chemicals, most of them untested for their effects on developing systems. Many of these chemicals are readily passed across the placenta to the fetus, to the infant via breast milk, or via toys and other children's products. Many of these chemicals are also ingested in food and water. Many also are absorbed by children through the lungs by respiration of contaminated air.

The Network believes that the potential health impacts from exposure to perchlorate through drinking water are significant and that they warrant prompt regulation to protect public health and safety. Setting a drinking water standard will provide the U.S. Environmental Protection Agency (EPA) with a "meaningful opportunity for health risk reduction for persons served by public water systems".

Consequently, **EPA should move as quickly as possible to establish a more protective reference dose for perchlorate** and then to promulgate a maximum contaminant level (MCL) for perchlorate that is no higher than one part per billion (ppb). We base this view on the scope of the contamination in drinking water supplies, exposure of the American population through other pathways, including food, and the most recent scientific studies that demonstrate serious health threats, even at low levels, to a larger portion of the population than previously recognized. These studies are based upon a much larger exposure data set than the studies upon which the current reference dose, and thus the entire regulatory regime, is based.

Perchlorate has been found in more than 400 drinking water sources in 26 states, potentially affecting tens of millions of people. EPA's own data say that nearly 17 million people receive their water from public water systems where perchlorate has been found at levels exceeding 4 ppb. Were sampling routinely conducted with a detection limit of 1 ppb, that number would be much higher—particularly considering the estimated 20 million people in the Southwest who receive drinking water from the Colorado River.

In responding to this threat, EPA must set a drinking water standard for perchlorate that protects the most vulnerable subpopulations, particularly pregnant women, fetuses, infants, and small children. By interfering with the thyroid's ability to take up iodide, perchlorate can suppress the development of thyroid hormones critical to growth, development, and metabolism. This puts fetuses and children at particular risk for learning and behavioral disabilities; impaired gait, vision, and hearing; and even mental retardation. Exposure calculations must therefore consider the ingestion rates for these populations, and the reference dose should consider the particular vulnerabilities of these age groups. EPA should also include in its calculations low birth weight babies, and underweight infants as these populations may be extremely vulnerable.

EPA must also consider other exposure pathways and additional contaminants in the environment that impact thyroid function when establishing the MCL. Studies of perchlorate levels in food, including breast milk, show that the population is exposed through multiple pathways in addition to contaminated drinking water. EPA should determine potential aggregate exposures based on a broad range of contamination levels, and not just the mean, which was the basis for current estimates. While data have also demonstrated a particular threat to the significant number of individuals, especially women of child bearing age, who are iodide deficient, the current modeling does not include this threat.

Given this widespread problem (CDC estimates up to 30% of women do not get sufficient dietary iodide), it is critical to take into consideration the potential for exposure to other thyroid-active agents. Consequently, EPA must consider the cumulative impact of perchlorate, other substances in the environment that inhibit the uptake of iodide by the thyroid, and inadequate supplies of iodide in American diets, all of which makes a stringent drinking water standard necessary to be truly health protective.

Moreover, a 1 ppb or lower MCL is supported by the most recent comprehensive studies, and these should be central to EPA's analysis. The industry-supported Greer study, which serves as the basis for EPA's current reference dose as well as California's current 6 ppb standard, consisted of a 14-day study of 37 healthy adults. In more recent years, Blount et al analyzed a nationally representative sample of 2299 U.S. residents, and they have documented anti-thyroid effects in a large population of women exposed to perchlorate at concentrations far lower than levels previously shown to have such effects. This study and subsequent data clearly justify promulgation of an even more protective MCL. It should be noted that California's Office of Environmental Health Hazard Assessment is in the process of reevaluating its Public Health Goal, on which the state MCL is based.

Finally, we wish to discourage EPA from again referring the perchlorate assessment to the National Research Council (of the National Academies of Sciences) for further review. A referral would delay the process without a great deal of additional review.

A perchlorate drinking water standard of no higher than 1 ppb would protect a large share of the American population currently at risk. Given the scope of the perchlorate contamination nationally, the multiple exposure pathways and other environmental contaminants impacting thyroid function and development, and the data demonstrating a serious health threat to a significant part of the country's population, EPA is obligated to establish such a drinking water standard. We applaud the agency's consideration of how to move forward to regulate this contaminant and urge you to take steps to establish a protective MCL as soon as possible.

Sincerely,

Nsedu O. Witherspoon, MPH
Executive Director

NATURAL RESOURCES DEFENSE COUNCIL
THE EARTH'S BEST DEFENSE

September 19, 2009

U.S. Environmental Protection Agency
Office of Water Docket (Mailcode: 2822T)
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Submitted via www.regulations.gov

Comments from the NATURAL RESOURCES DEFENSE COUNCIL

on the Drinking Water: Perchlorate Supplemental Request for Comments

Docket EPA-HQ-OW-2009-0297
Federal Register / Vol. 74, No. 159/ Wednesday, August 19, 2009

SUMMARY

On August 19, 2009, the U.S. Environmental Protection Agency (EPA) issued a Federal Register (FR) notice[1] requesting comments on additional approaches to analyzing data related to its perchlorate preliminary determination as detailed in its October 10, 2008 FR Notice.[2] In that previous notice, EPA made a preliminary regulatory determination not to set a health-protective standard for perchlorate in drinking water.[3] It stated, "The Agency has determined that a national primary drinking water regulation (NPDWR) for perchlorate would not present 'a meaningful opportunity for health risk reduction for persons served by public water systems.'" EPA also proposed a health reference level (HRL) of 15 parts per billion (ppb) as the maximum contamination level of perchlorate that could be in drinking water and still keep daily human consumption levels from exceeding the reference dose (RfD) of 0.7 µg/kg/day.

In response to the October 10, 2008 FR notice, NRDC provided comments to EPA concluding that EPA's determination was legally flawed. EPA must regulate a contaminant if it may have an adverse effect on human health, if it is known to occur (or there is a substantial likelihood that the contaminant will occur) in public water systems with a frequency and at levels of public health concern; and if its regulation would present a meaningful opportunity for health risk reduction for persons served by public water systems.[4] For perchlorate, each of these three requirements are met, and therefore, underscore the need for EPA to regulate its presence in drinking water. First, EPA's preliminary regulatory determination acknowledges that perchlorate may adversely affect human health.[5] Second, as explained in more detail below, despite EPA's contention, perchlorate is known to contaminate the drinking water systems serving millions of people at levels where adverse human health effects occur. And third, setting an appropriately stringent MCL will lead to lower levels of perchlorate ingested by hundreds of thousands of infants, children, and pregnant women, thereby offering a concrete and meaningful reduction in human health risks.

The U.S. population is about 300 million people with about 6.8%, or 20 million, under 5 years old. Therefore, based on EPA estimates that 16.6 million people are served by public water system with at least one detection of perchlorate over 4 ppb, there are, therefore, likely more than one million children in each year of life (from zero to five) who may be exposed to perchlorate levels that may adversely affect their health.[6] Thus, the evidentiary record does not support EPA's proposed determination. Rather, the evidentiary record makes clear that regulating these exposures *do* represent "a meaningful opportunity for health risk reduction for persons served by public water systems."

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[1] 74 Fed. Reg. 41883 (August 19, 2009).
[2] 73 Fed. Reg. 60262 (October 10, 2008).
[3] *Id*.
[4] 42 U.S.C. §300g-1(b)(1)(A).
[5] 73 Fed. Reg. 60275 (Oct. 10, 2008).
[6] This value is derived by multiplying 16.6 million by 0.068. Please see below for further explanation about the appropriate perchlorate level to set for the health reference level.

Based upon the evidence in the record, as discussed in greater detail below, NRDC urges EPA to reverse course, and set a national primary drinking water standard for perchlorate that is protective of sensitive sub-populations. EPA should not set a HRL at 15 ppb; rather, given the most current data available, NRDC believes that to truly protect the public health, EPA should set an enforceable maximum contaminant level (MCL) as authorized by the Safe Drinking Water Act below 1 ppb.

REGULATORY BACKGROUND

In 1974, Congress enacted the federal Safe Drinking Water Act (SDWA) to protect the public health from contaminated drinking water supplies by regulating public drinking water systems. The SDWA was amended in 1986 and 1994, and requires EPA, *inter alia,* to publish national primary drinking water regulations, which must include both non-enforceable, health-based Maximum Contaminant Level Goals (MCLGs) and enforceable Maximum Contaminant Levels (MCLs).[7] The MCLG must be set "at the level at which no known or anticipated adverse effects on the health of persons occur and which allows for an adequate margin of safety."[8] In contrast, the MCL, the maximum level of a regulated contaminant that any particular covered public water system may deliver to any user, must be set "as close to the maximum contaminant level goal as is feasible."[9] SDWA requires EPA to set a national primary drinking water standard when it determines for a contaminant that:

> (i) the contaminant may have an adverse effect on the health of persons; (ii) the contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and (iii) in the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems.[10]

SDWA also requires EPA to establish a "contaminant candidate list" (CCL) identifying a list of contaminants, not yet regulated by the Agency, which are known or anticipated to occur in drinking water and which may require regulation.[11] Every five years, EPA must determine whether or not to regulate five of the contaminants that appear on the CCL.[12]

In March, 1998, EPA's first CCL included perchlorate, but the Agency did not choose to make any determination about whether to regulate the contaminant. In February, 2005, EPA announced its second CCL, CCL2, on which perchlorate appeared again. As a

[7] 42 U.S.C. §300g-1(a)(1).
[8] 42 U.S.C. §300g-1(b)(4)(A).
[9] 42 U.S.C. §300g-1(b)(4)(B).
[10] 42 U.S.C. §300g-1(b)(1)(A).
[11] 42 U.S.C. §300g-1(b)(1)(B).
[12] *Id.*

result of its status as a candidate contaminant, EPA subsequently announced its preliminary determination not to regulate perchlorate in October, 2008.

A reference dose (RfD) is an estimate of the daily exposure to an agent over a full lifetime that is "likely to be without an appreciable risk of deleterious effects" for the human population, including sensitive subgroups.[13] The RfD is not an enforceable regulatory standard; it can be used with exposure information to set clean up levels. In 2005, the National Research Council (NRC) of the National Academies of Science recommended an RfD for daily intake of perchlorate that it considered to be an acceptable level of exposure of 0.7 µg/kg/day.[14] EPA adopted this RfD and posted on its public database, the Integrated Risk Information System (IRIS) in February 2005.[15] While IRIS values are not regulations *per se*, they are used by both state and federal regulators and by the international community for a range of environmental health regulation and management purposes. For example, the information can be used in combination with exposure data to set cleanup levels at hazardous waste sites, or to set exposure standards for air, water, soil, and food. Thus, the accuracy, credibility, and timeliness of IRIS assessments have real world consequences for human health.

In simple terms, the HRL is the maximum contamination level of perchlorate that could be in drinking water, and still keep daily human consumption levels from exceeding the RfD of 0.7 µg/kg/day. It is not an enforceable standard. EPA reports that for pregnant women, exposure to perchlorate from food is 0.263 µg/kg/day at the 90th percentile (based on data from a national food survey), representing nearly 38% of the RfD, thus leaving an RSC (Relative Source Contribution) for water of 62%.[16] This is equivalent to 0.437 µg/kg/day from water, assuming an average body weight of 70 kg, and a daily water consumption of 2 L (90th percentile adult water consumption). That is, 0.437 µg x 70 kg body wt. = 30.6 µg perchlorate in 2 liters (the daily consumption amount). This is 15 µg/L, or 15 ppb, the originally proposed HRL.

The RfD for perchlorate and perchlorate salts of 0.7 µg/kg body weight/day is based on a human volunteer study, Greer et al, 2002.[17] The RfD is for oral exposure, including food and water, and is based on radioactive iodide uptake inhibition (RAIU) in the thyroid as the critical effect. The IRIS assessment of perchlorate explains that "The point of departure is based on a non-statistically significant mean 1.8% (standard error of the mean 8.3%) decline in RAIU in healthy adults following two weeks exposure to a daily perchlorate dose of 0.7 µg/kg/day. An intraspecies uncertainty factor of 10 is applied to

[13] EPA Integrated Risk Information System (IRIS) Glossary of terms. http://www.epa.gov/ncea/iris/help_gloss.htm#r
[14] NRC. 2005. Health Implications of Perchlorate Ingestion. National Research Council of the National Academies. National Academies Press, Washington, D.C.
[15] EPA IRIS assessment of perchlorate. http://www.epa.gov/NCEA/iris/subst/1007.htm
[16] 73 Fed Reg at 60276
[17] Greer, M.A., Goodman, G., Pleuss, R.C., Greer, S.E. 2002. Health effect assessment for environmental perchlorate contamination: The dose response for inhibition of thyroidal radioiodide uptake in humans. Environ. Health Perspect. 110:927-937.

protect the most sensitive population, the fetuses of pregnant women who might have hypothyroidism or iodide deficiency. Dose is given as perchlorate anion."[18]

The RfD adopted by EPA has been widely criticized as inadequately protective by state scientific experts[19] and by EPA's own Children's Health Protection Advisory Committee,[20] and no longer reflects the best available data.[21] [22] However, even when basing its decision upon this unacceptably high RfD, EPA's preliminary determination not to regulate perchlorate would still expose hundreds of thousands of children and infants to unsafe levels of perchlorate.

NRDC strongly objected to EPA's preliminary determination not to regulate perchlorate because the conclusions are not based on a comprehensive review of the best available science (as explained in more detail below) and are not supported by the PBPK model findings, or by EPA's expert scientific advisors on the Children's Health Protection Advisory Committee.[23] In fact, drinking water that is contaminated with perchlorate at the proposed HRL of 15 ppb would leave infants and young children exposed to excessive and unsafe levels of this toxic chemical.

HISTORY OF DELAY

EPA had evidence in the 1980's that perchlorate was leaching from military dumpsites into groundwater, as documented in a 1985 interagency letter from EPA to the Centers for Disease Control and Prevention (CDC) reporting on levels as high as 300-800 ppb "potentially affecting 32,000 to 42,000 households."[24] EPA set a provisional RfD of 0.0001 mg/kg/day in 1992; this would have been equivalent to an MCL of 3.5 ppb in water, presuming an adult average body weight and daily water consumption, and presuming no other sources of perchlorate.[25] It has been 17 years since that provisional

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[18] EPA. IRIS database. Perchlorate and perchlorate salts. http://www.epa.gov/ncea/iris/subst/1007.htm#revhis

[19] Ginsberg G and D Rice. The NAS perchlorate review: questions remain about the perchlorate RfD. Environ Health Perspect. 2005 Sept; 113(9):1117-9. Erratum in: Environ Health Perspect. 2005 Nov; 113(11):A732.

[20] Letter from Melanie Marty to Administrator Johnson regarding Preliminary Regulatory Determination on Perchlorate (November 3, 2008, PDF) http://yosemite.epa.gov/ochp/ochpweb.nsf/content/perchlorateletter.htm/$file/PerchlorateLetter.pdf

[21] EN Pearce, AM. Leung, BC Blount, HR Bazrafshan, X He, S Pino, L Valentin-Blasini, and LE Braverman, 2007. Breast milk iodine and perchlorate concentrations in lactating Boston-area women. J Clin Endocrinol Metab. 92(5):1673-7.

[22] Letter from Melanie Marty to Administrator Johnson regarding Preliminary Regulatory Determination on Perchlorate (November 3, 2008, PDF) http://yosemite.epa.gov/ochp/ochpweb.nsf/content/perchlorateletter.htm/$file/PerchlorateLetter.pdf

[23] Letter from Melanie Marty to Administrator Johnson regarding Preliminary Regulatory Determination on Perchlorate (November 3, 2008, PDF) http://yosemite.epa.gov/ochp/ochpweb.nsf/content/perchlorateletter.htm/$file/PerchlorateLetter.pdf

[24] As documented in: Sass J. U.S. Department of Defense and White House working together to avoid cleanup and liability for perchlorate pollution. Int J Occup Environ Health. 2004. Jul-Sep;10(3):330-4.

[25] As documented in: Sass J. U.S. Department of Defense and White House working together to avoid cleanup and liability for perchlorate pollution. Int J Occup Environ Health. 2004. Jul-Sep;10(3):330-4.

RfD, and in that time the science supporting that RfD has grown significantly stronger, along with public concern and Agency interest. Moreover, the RfD now finalized is 0.7 µg/kg/day, not dramatically different from the provisional RfD 17 years ago, given the extremely lengthy delay.

EPA's progress on this assessment has been extensively and repeatedly reviewed by the interagency panel that was created in 1998 as a partnership between EPA, the U.S. Department of Defense , and other federal agencies to review perchlorate issues.

In 2002, EPA issued an External Review Draft that recommended a limit of 1 ppb in drinking water. This was sent to the NRC for review in 2004, which resulted in the recommended oral RfD of 0.0007 mg/kg/day, adopted by EPA in 2005.

REQUEST FOR COMMENT ON NRC REVIEW

NRDC Response: *Further Review by NRC Not Warranted*

After over 17 years of accumulated science (documented above), two EPA toxicological reviews (1998, 2002), and a lengthy NRC review (2004), it is past time for EPA to take effective regulatory action to protect people's health by preventing exposure to perchlorate. Therefore, NRDC supports the Agency's belief that further review by the NRC would create an unnecessary delay without adding anything to the scientific rigor of the Agency's determination.

NRDC would likely support the Agency if it requested a review by its Scientific Advisory Board, since it would be more rapid and less costly than an NAS review, while providing scientific oversight.

REQUEST FOR COMMENTS ON ALTERNATIVE APPROACHES

a. Using the PBPK model to evaluate the relative sensitivity of life stages to perchlorate exposure in drinking water

NRDC Response: *The PBPK model can be used to evaluate life stage sensitivity, and it provides evidence that at the proposed HRL of 15 ppb, infants and young children will have a perchlorate intake that exceeds the reference dose.*

The EPA scientific staff evaluated the application of the PBPK model, particularly as it applies to sensitive life-stages. [26] On October 2, 2008, EPA issued the staff report on this evaluation, which identifies some very troubling findings, including evidence that consuming water contaminated at the HRL of 15 µg/L (or ppb) would lead to bottle-fed infants exceeding the RfD by 5-fold and young children exceeding the RfD by 2.8-fold,

[26] EPA Office of Research and Development. Inhibition of the sodium-iodide symporter by perchlorate: An evaluation of lifestage sensitivity using physiologically-based pharmacokinetic (PBPK) modeling. Preliminary Draft. October 2, 2008. EPA/600/R-08/106A. Docket ID No. EPA-HQ-OW-2008-0692-0076.

based on average food contamination rates, average body weights, and 90th percentile water consumption rates for each age group.[27] Specifically, the PBPK model predicts that the RfD is exceeded for infants and children at the originally proposed HRL of 15 ppb, at 90th percentile water intake. (See Table 1 below). The table also identifies the magnitude by which the RfD is exceeded at EPA's originally proposed HRL of 15 ppb.

Table 1: Perchlorate intake from water at 15 ppb, with and without food intake, at 90th percentile water intake (L/day)

	Perchlorate intake from only water	Perchlorate intake from food and water	Extent by which RfD is exceeded for food and water[28]
Breast-fed infant, 7 d	1.36	1.59	2.3-fold
Breast-fed infant, 60 d	1.27	1.48	2.1-fold
Bottle-fed infant, 7 d	3.53	3.87	5.6-fold
Bottle-fed infant, 60 d	3.42	3.74	5.3-fold
Child, 6-12 mos	1.68	1.96	2.8-fold
Child, 1-2 yr	0.84	1.21	1.7-fold

These perchlorate intake values were also reported in the October 10, 2008 FR notice in Table 8.[29] Note that the overwhelming majority of perchlorate for these age groups comes from water or breast milk, and not from solid food. These data, generated from the PBPK model predictions, provide substantial scientific support for the conclusion that infants (both breast- and bottle-fed) and young children would exceed the RfD if their dietary water were contaminated with perchlorate at the originally proposed HRL of 15 ppb.

Despite these conclusions, EPA announced its preliminary determination not to regulate perchlorate in drinking water. Although that FR notice did report the staff conclusions, it contradicted them by concluding that "EPA believes drinking water with perchlorate concentrations at or below the HRL of 15 µg/L is protective of all subpopulations."[30] EPA failed to provide any data to support its conclusion, which is contradicted by the results of PBPK modeling as reported by staff experts and in the preliminary determination. [31]

EPA tried to support its conclusions that a 15 ppb HRL is safe by avoiding reference to the RfD, and instead referring to the level of inhibition of radioactive iodide uptake (RAIU) on which the NRC report (NRC, 2005) based its recommended RfD.[32] EPA

[27] EPA Office of Research and Development. Inhibition of the sodium-iodide symporter by perchlorate: An evaluation of lifestage sensitivity using physiologically-based pharmacokinetic (PBPK) modeling. Preliminary Draft. Table 4. October 2, 2008. EPA/600/R-08/106A. Docket ID No. EPA-HQ-OW-2008-0692-0076.
[28] This value is taken by dividing the perchlorate intake by the RfD. For e.g., 1.59/0.7 = 2.27.
[29] 73 Fed. Reg. at 62078.
[30] *Id.* at 60280
[31] EPA Office of Research and Development. Inhibition of the sodium-iodide symporter by perchlorate: An evaluation of lifestage sensitivity using physiologically-based pharmacokinetic (PBPK) modeling. Preliminary Draft. October 2, 2008. EPA/600/R-08/106A. Docket ID No. EPA-HQ-OW-2008-0692-0076.
[32] 73 Fed. Reg. at 60277.

cannot shift its evaluation of acceptable exposure estimates to a discrete biological endpoint that leads to exceedances of the RfD.

b. Utility of the PBPK model for predicting the impact of different perchlorate drinking water concentrations on sensitive life stages to inform the HRL

NRDC Response: *The PBPK model can predict the impacts of perchlorate water contamination on different life stages; it predicts that sensitive populations are not protected by the proposed HRL*

As detailed in our response above, the EPA staff report issued on October 2, 2008, describes findings from the PBPK model that consuming water that was contaminated at the HRL of 15 µg/L would lead to bottle-fed infants exceeding the reference dose by 5-fold and young children exceeding the reference dose by 2.8-fold, based on average food contamination rates, average body weights, and 90th percentile water consumption rates for each age group. [33]

These findings from the PBPK model analysis are supported by other published studies. A related study estimated perchlorate doses that correspond to urinary perchlorate excretion (hereinafter referred to as "Blount (2007)"). [34] Calculating doses based on urinary excretion is feasible because perchlorate is not metabolized and has a short half-life of approximately 8 hours.[35] Blount (2007) showed that the adjusted geometric mean for perchlorate exposure in women was 0.059 µg/kg-day, and the 95th percentile exposure was 0.215 µg/kg-day. This means that the adverse effects of decreased serum T4 and increased TSH in women with low dietary iodide (that is, urinary iodide below 100 µg/L) described by Blount (2006) are occurring at perchlorate exposures below the RfD of 0.7 µg/kg-day. [36] As such, the proposed HRL of 15 ppb will not protect sensitive subpopulations.

An extensive literature review and health assessment by Ginsburg et al.[37] published since the NRC review found that "drinking-water perchlorate must be < 6.9 µg/L to keep the median, and < 1.3 µg/L to keep the 90th-percentile nursing infant exposure below the

[33] EPA Office of Research and Development. Inhibition of the sodium-iodide symporter by perchlorate: An evaluation of lifestage sensitivity using physiologically-based pharmacokinetic (PBPK) modeling. Preliminary Draft. October 2, 2008. Table 4. EPA/600/R-08/106A. Docket ID No. EPA-HQ-OW-2008-0692-0076.
[34] Blount BC, Valentin-Blasini L, Osterloh JD, Mauldin JP, Pirkle JL. Perchlorate exposure of the US Population, 2001-2002. J Expo Sci Environ Epidemiol. 2007 Jul;17(4):400-7. Epub 2006 Oct 18.
[35] Ibid.
[36] Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L, Caldwell KL. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. Environ Health Perspect. 2006 Dec;114(12):1865-71.
[37] GL Ginsburg, DB Hattis, RT Zoeller, and DC Rice. 2007. Evaluation of the U.S. EPA/OSWER preliminary remediation goal for perchlorate in groundwater: Focus on exposure to nursing infants. Environ Health Perspect. 115(3):361-369. http://www.ehponline.org/members/2006/9533/9533.html

RfD." [38] Based on both exposure and toxicity information, and data on sensitive populations, the proposed HRL of 15 ppb, which is more than twice as high as the limit proposed by Ginsberg et al, will leave significant portions of the population at risk.

c. Using the PBPK modeling analysis to inform the regulatory determination for perchlorate that is different from those described in the October, 2008 FR notice

NRDC response: *The PBPK model may be used to derive a science-based adjustment factor; the model support an adjustment factor of at least 15-fold to inform the regulatory determination for perchlorate.*

EPA normally uses a 10-fold default uncertainty factor to adjust for variations among individuals, called the intraspecies factor, when the Agency lacks adequate data to calculate variability between individuals. EPA used this 10-fold intraspecies factor for its perchlorate hazard assessment on its IRIS database: "*An intraspecies uncertainty factor of 10 is applied to protect the most sensitive population, the fetuses of pregnant women who might have hypothyroidism or iodide deficiency.*" [39] The Agency has adopted the practice of describing the default 10-fold intraspecies factor as being comprised of the product of two 3-fold factors, one for pharmacokinetic variability, and the other for pharmacodynamic variability.[40] Pharmacokinetics describes the way that a compound such as perchlorate moves through the body, including its absorption, distribution, metabolism and excretion. In contrast, pharmacodynamics describes what the compound does in the body, including depressing, stimulating, irritating, or killing cells or systems.

According to the IRIS glossary of terms, a physiologically based pharmacokinetic (PBPK) model estimates the dose of a compound to a target organ or tissue by calculating the rate of absorption in the body, the distribution among target organs, the metabolism of the compound, and the excretion of the compound.[41] In other words, the PBPK model, by definition and design, estimates the pharmacokinetics of a compound.

The data from EPA's staff report shows that EPA's reliance on a default uncertainty factor of 10 *underestimates* the variability between fetuses and adults. The Executive Summary of the staff report states that "at a perchlorate dose of 7 µg/kg-day, the percent RAIU inhibition predicted by the model for the near-term fetus is 5-fold greater than the average adult….The same analysis predicts percent RAIU inhibition approximately 1-2 fold higher for the breast-fed and bottle-fed infant (7-60 days) than for the average adult."[42] More specifically, for perchlorate, the variability between a near-term fetus (40

[38] GL Ginsburg, DB Hattis, RT Zoeller, and DC Rice. 2007. Evaluation of the U.S. EPA/OSWER preliminary remediation goal for perchlorate in groundwater: Focus on exposure to nursing infants. Environ Health Perspect. 115(3):361-369.
[39] EPA. IRIS database. Perchlorate and perchlorate salts. http://www.epa.gov/ncea/iris/subst/1007.htm#revhis
[40] US EPA. Office of the Science Advisor: Staff Paper, Risk Assessment Principles & Practices. Page 69, Section 4.3.2. EPA/100-B-04/001. March, 2004. http://www.epa.gov/osa/pdfs/ratf-final.pdf
[41] IRIS Glossary. Physiologically Based Pharmacokinetic (PBPK) Model. http://www.epa.gov/ncea/iris/help_gloss.htm#p
[42] *See* EPA Staff Paper, Executive Summary, p. 4 and Table 3; *see also* 73 Fed. Reg. 60278.

weeks gestation) and an adult is 5.3-fold. Therefore, the PBPK model supports a pharmacokinetic adjustment factor of at least 5-fold.

The Agency has no information from the PBPK model, or from other data, to develop an intraspecies uncertainty factor for pharmacodynamic variability, particularly between adults and sensitive lifestages. Therefore, EPA should retain a factor of at least 3-fold or more to adjust for pharmacodynamic uncertainty, consistent with its current practice.

To be consistent with EPA policy and practice, EPA should use a total intraspecies uncertainty factor of 15-fold, rather than 10 fold. Based on the data from the PBPK model to support a pharmacokinetic intraspecies variability factor of 5, and the lack of pharmacodynamic data to support a default factor of 3, the use of a 15-fold uncertainty factor is supported by the available data.

RESPONSE TO REQUEST FOR COMMENTS ON THE HRL

In simple terms, the HRL is the maximum tolerable amount of perchlorate that could be in drinking water, considering that perchlorate is also in food, and still keep daily consumption levels from exceeding the RfD. The 2008 proposed HRL of 15 ppb was calculated as follows: For all populations, including pregnant women, EPA determined that the RfD is 0.7 µg/kg/day. This value is posted on the IRIS database based on recommendations from a committee of the NRC. EPA reports that for pregnant women, exposure to perchlorate from food is 0.263 µg/kg/day at the 90th percentile (based on data from a national food survey), representing nearly 38% of the RfD, thus leaving an relative source contribution (RSC) for water of 62%.[43] This is equivalent to 0.437 µg/kg/day from water, assuming an average body weight of 70 kg, and a daily water consumption of 2 L (90th percentile adult water consumption). That is, 0.437 µg x 70 kg body wt. = 30.6 µg perchlorate in 2 L (the daily consumption amount). This is 15 µg/L, or 15 ppb, the HRL proposed in the October 2008 FR notice.

a. Whether alternative HRLs take into account specific and appropriate exposure values for all potentially sensitive life stages

NRDC response: *It is appropriate for the HRL to account for an infant's body weight, an infant's dietary intake and relative source contribution from water, and other contaminants that share a common mode of toxicity to perchlorate.*

A bodyweight assumption appropriate for an adult female does not protect fetuses, infants or children. For example, infants consume almost six times more water (and therefore contaminants) than adults, on average, in proportion to their body weight. Therefore, it would not be appropriate to use an adult body weight when converting a reference dose into a drinking water standard that is protective of infants and children.

Many infants are breastfed for at least part of their first year of life, and perchlorate from both water and food does enter breast milk. Therefore, the appropriate choice for the

[43] 73 Fed. Reg. at 60276)

breastfeeding scenario is to use an RSC value that reflects perchlorate the mother is taking in through food and drinking water since she is the source for the infant's breast milk.

Other contaminants are known to also interfere with iodide uptake via a similar or identical mechanism. For example, the widespread water contaminant, nitrate has a shared mechanism of action as does the chemical thiocyanate, found in cigarette smoke and in some foods. [44] There is some indication in the CDC data analyzed by Blount et al. that nitrate may be a factor in the modulation of thyroid hormone status. An independent analysis by OEHHA staff found an interaction between perchlorate and thiocyanate exposure and tobacco smoke exposure on thyroid hormone. It is also known that perchlorate and thiocyanate are found in breast milk.[45]

b. On which of the alternative HRLs in Table 2 would be appropriate against which to compare levels of perchlorate in public water systems

NRDC response: *A level of perchlorate below 1 ppb is required to adequately protect vulnerable newborn babies and their recommended sole source of nutrition, breast milk.*

In June 2006, the State of Massachusetts Department of Environmental Protection (MA DEP) and its scientific advisors (MA DEP/DPH Advisory Committee) "unanimously concluded that [the RfD] did not fully account for the uncertainties surrounding science's understanding of perchlorate toxicity and exposures."[46] Following recommendations from their scientific experts, MA DEP finalized an enforceable perchlorate Maximum Contaminant Level for drinking water and a perchlorate Cleanup Standard of 2 ppb based on a review and assessment of all data available at the time. Likely because the Blount (2006) data were not yet available, the MA DEP drinking water and cleanup standards failed to consider the special exposure patterns of infants born to low-iodide women, whom we now know are among the most at-risk population based on both high exposure and vulnerability to permanent and severe neurological impacts. Therefore, an MCL must be below 1 ppb to be truly health protective.

Data shows that perchlorate is actively transported into mammary epithelial cells by the sodium iodide symporter (NIS), resulting in an accumulation of perchlorate in breast milk.[47] [48] These data suggest that perchlorate may not only inhibit iodide accumulation in maternal milk but also would be transferred in breast milk to the nursing infant where

[44] Ginsberg G and D Rice. The NAS perchlorate review: questions remain about the perchlorate RfD. Environ Health Perspect. 2005 Sept; 113(9):1117-9. Erratum in: Environ Health Perspect. 2005 Nov; 113(11):A732.
[45] Kirk, AB, Dyke JV, Martin, CF, Dasgupta PK. 2007. Temporal patterns in perchlorate, thiocyanate, and iodide excretion in human milk. Envrion Health Perspect.115(2):182-6.
[46] MA DEP, "Update To 'Perchlorate Toxicological Profile And Health Assessment'" March 2006, page xii.
[47] Dohan, O, C Portulano, C. Basquin, A Reyna-Noyra, LM Amzel, and N Carrasco. 2007. The Na+/I- symporter (NIS) mediates electroneutral active transport of the environmental pollutant perchlorate. PNAS 104(51):20250-20255.
[48] Dasgupta, P. K., Kirk, A. B., Dyke, J. V., and Ohira, S.-I. (2008). Intake of Iodine and Perchlorate and Excretion in Human Milk. *Environ. Sci. Technol.* **42**, 8115-8121.

it would be predicted to inhibit iodide uptake in the infant's thyroid gland. The NIS also is found in the placenta and based on this new research it seems likely that perchlorate is actively transported across the placenta. Because the fetus and developing infant require adequate iodide for thyroid hormone function, any determination of a safe level of exposure to perchlorate should take into account this mode of action for perchlorate toxicity.

c. On the most appropriate data to estimate alternative HRLs

NRDC response: *The CDC (2006/2007) data represent the best available data.*

The derivation of a health-based standard for perchlorate should reflect the best available data, including published data collected and analyzed by the CDC and described by Blount et al (2006) and Blount et al (2007).[49] The CDC data have the following significant advantages over the Greer et al data used by EPA:

1. Although the CDC data are from a cross-sectional analysis, because the survey includes a large number of individuals, the variability represents random error, not bias, and the data are likely to be representative of chronic perchlorate exposure;
2. The number of individuals included in the CDC study are sufficient for the specific analysis of a sensitive subpopulation defined as women with low iodine intake;
3. A benchmark dose (BMD) analysis of perchlorate-related modulation of serum thyroid hormone concentrations is feasible; and
4. Perchlorate exposures, as measured by urinary perchlorate concentration, corresponding to the benchmark dose low (BMDL) can be converted to an estimated dose in mg/kg-day, that can be used as the point of departure for the derivation of both the MCL and HRL.

From Blount et al (2006) we know that the mean for total serum T4 concentrations in women is 8.27 µg/dL and the 25th percentile of perchlorate exposure (equivalent to 1.6 ppb perchlorate in urine) is associated with a 10% drop in total serum T4 in women with low iodine intake.[50] Importantly, the unique physiology of pregnancy and interactions between the mother and fetus make both especially susceptible to the harmful effects of perchlorate; maternal T4 is the only source of thyroid hormone for the fetus in the first trimester.

[49] Blount BC, Valentin-Blasini L, Osterloh JD, Mauldin JP, Pirkle JL. Perchlorate exposure of the US Population, 2001-2002. J Expo Sci Environ Epidemiol. 2007 Jul;17(4):400-7. Epub 2006 Oct 18. Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L, Caldwell KL. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. Environ Health Perspect. 2006 Dec;114(12):1865-71.

[50] Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L, Caldwell KL. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. Environ Health Perspect. 2006 Dec;114(12):1865-71.

Blount et al (2007) established that for women with low iodine intake (defined by the World Health Organization as urinary iodine < 100 µg/L),[51] very low levels of perchlorate exposure were associated with decreased serum T4 and increased serum TSH; the CDC estimates that 36% of U.S. women have iodine intakes in this range. For iodine-sufficient women (defined as urinary iodine ≥ 100 µg/L), perchlorate exposure was associated with increased TSH. Increased TSH is an indicator that the body is attempting to compensate for a decrease in thyroid hormone production, and is clinically considered to be a more sensitive marker of subtle thyroid alteration than depressed levels of serum T4. When predicting changes in serum TSH with increasing perchlorate exposures, women with low iodine intake and TSH levels on the high end of the normal range (> 3.11 IU/L) appeared to be the most sensitive group. In this group, any increase in urinary perchlorate predicted an increase in TSH that was consistently more than twice the predicted increase in TSH for women with low iodine levels and median TSH levels. For unknown reasons, perchlorate was not associated with T4 or TSH levels in men. The observed changes in serum T4 and TSH in women are consistent with our understanding of how thyroid hormones are regulated in the body, and with the mechanism of toxicity of perchlorate.

Importantly, the extremely low levels of perchlorate were associated with thyroid hormone disruptions – and the magnitude of these disruptions. The CDC researchers found that if a low iodine woman started with perchlorate exposure corresponding to 0.19 ppb in urine (the minimum level found), and then ingested enough perchlorate through food and/or drinking water to raise her urinary perchlorate level to 2.9 ppb (the median level found), her T4 levels would drop by 13%.[52] Similarly, if her urinary perchlorate level increased to 5.2 ppb (the 75th percentile exposure), her T4 levels would drop by 16%. The maximum level of perchlorate exposure found was 100 ppb, which translated into a 29% decline in T4.

d. On the merits of the approach EPA used to derive HRLs

NRDC response: *The Greer data no longer represent the best available data.*

Because the dose-response relationship used to determine the RfD is derived exclusively from the Greer et al study, the HRL also is dependent on the Greer et al study to determine the maximum allowable level of drinking water contamination.

The Greer et al study [53] reported on study results from intentional dosing of a small population (N=37) of healthy men and women, for only two weeks. That is, the study cannot represent realistic chronic exposure scenarios, and it cannot be considered

[51] World Health Organization (WHO). 1994. Indicators for assessing iodine deficiency disorders and their control through salt iodization. WHO/NUT/94.7. Geneva: WHO/International Council for the Control of Iodine Deficiency Disorders.
[52] The drop in T4 predicted to be 1.06 µg/dL; the percentage decrease is calculated as compared to the average T4 level found in the CDC study (8.27 µg/dL).
[53] Greer MA, G Goodman, RC Pleus, and SE Greer. 2002. Health effects assessment for environmental perchlorate contamination: the dose-response for inhibition of thyroidal radioiodine uptake in humans. Environ Health Perspect 110:927–937.

representative of the U.S. population including infants and children. Moreover, the study lacked measurements of iodine status that is now known to be a critical variable. Other significant weaknesses with the Greer study included the fact that the low dose group contained only seven participants including only six women. Use of these limited data to calculate a regulatory trigger level has been widely criticized as inadequate by state scientific experts[54] and by EPA's own Children's Health Protection Advisory Committee,[55] and no longer reflects the best available data.[56] [57] Despite these limitations, careful analysis of the Greer data reveal clear evidence of perchlorate toxicity in the low-dose group; three subjects showed no perchlorate effect, but four subjects in the low-dose group had a measurable decrease in iodide uptake commensurate with perchlorate exposure.[58] Because the study authors relied on averaged data rather than individual data, the more sensitive individuals in the study group were obscured

The short duration of the Greer study, only 14 days, mean that the cumulative effects of longer-term exposure are not accounted for. A study in rats found greater perchlorate toxicity to the thyroid from 90-day exposure than from 14-day exposure (Springborn Laboratories 1998), suggesting that cumulative exposure may cause significant systemic injury that is not detectable in a short-term study. Although one sub-chronic (six month) human study with 13 volunteers has been promoted by industry as indicating that humans adapt to long-term exposure (Braverman et al. 2006[59]) this study was unlikely to have adequate statistical power to detect an effect because it failed to consider the widely-recognized vulnerable populations, including infants, children, and women with low dietary iodide. The Blount (2006) study showed that these populations are much more vulnerable to perchlorate toxicity than the average population; women are more sensitive than men, iodine-deficient (urinary iodide below 100 µg/L) women are more sensitive than iodine-sufficient women, and iodine-deficient women with TSH levels on the high end of the normal range are even more sensitive than other iodine-deficient women.[60] Other human studies suffer from the same limitations as the Greer study. For example, a

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[54] Ginsberg G and D Rice. The NAS perchlorate review: questions remain about the perchlorate RfD. Environ Health Perspect. 2005 Sept; 113(9):1117-9. Erratum in: Environ Health Perspect. 2005 Nov; 113(11):A732.

[55] Letter from Melanie Marty to Administrator Johnson regarding Preliminary Regulatory Determination on Perchlorate (November 3, 2008, PDF) http://yosemite.epa.gov/ochp/ochpweb.nsf/content/perchlorateletter.htm/$file/PerchlorateLetter.pdf

[56] EN Pearce, AM. Leung, BC Blount, HR Bazrafshan, X He, S Pino, L Valentin-Blasini, and LE Braverman, 2007. Breast milk iodine and perchlorate concentrations in lactating Boston-area women. J Clin Endocrinol Metab. 92(5):1673-7.

[57] Letter from Melanie Marty to Administrator Johnson regarding Preliminary Regulatory Determination on Perchlorate (November 3, 2008, PDF) http://yosemite.epa.gov/ochp/ochpweb.nsf/content/perchlorateletter.htm/$file/PerchlorateLetter.pdf

[58] For a complete analysis of the NAS review of perchlorate, see: Ginsberg G and D Rice. The NAS perchlorate review: questions remain about the perchlorate RfD. Environ Health Perspect. 2005 Sept; 113(9):1117-9. Erratum in: Environ Health Perspect. 2005 Nov; 113(11):A732.

[59] Braverman LE, EN Pearce, X He, S Pino, M Seeley, B Beck, B Magnani, BC Blount, and A Firek. 2006. Effects of six months of daily low-dose perchlorate exposure on thyroid function in healthy volunteers. J Clin Endocrinol Metab. Jul; 91(7):2721-4. Epub 2006 Apr 24.

[60] Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L, Caldwell KL. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. Environ Health Perspect. 2006 Dec;114(12):1865-71.

study of chronically perchlorate-exposed pregnant women in Chile[61] that also failed to find an effect of perchlorate exposure had only three iodine-deficient female subjects out of 183 in total.

REQUEST FOR COMMENT ON ALTERNATIVE APPROACHES

a. On the use of a Baysian model to estimate number of public water systems.

NRDC response: *NRDC has no opinion on this.*

b. On the use of US Census data to estimate portions of the population that are in the sensitive life stage at any one time

NRDC response: *Yes, the U.S. Census data is appropriate for this use.*

Yes, EPA should use the U.S. census data. The U.S. census is mandated by the U.S. Constitution, and is conducted every 10 years, with the next one planned for 2010. These data are used by Congress, as well as governments at the local, state, and tribal level to make important decisions about setting priorities, providing services, disbursing funds, and even distributing Congressional seats.[62] The census data are widely recognized to be reliable, credible, and useful.

There is a valid concern that these data under-represent certain populations, such as certain ethnic minorities, who may be "unregistered" for census purposes. This may be relevant to the use of these data for this perchlorate assessment, because the children of ethnic minorities may not be fully represented. If anything, these data would underestimate the number of children under 1 year old.

c. On how the Agency should account for the variation of perchlorate levels over time, based on estimating the number of systems, entry points and sampling.

NRDC Response: *If EPA plans to consider the low-end estimate of the population exposed, it must develop a justifiable estimate.*

As part of the occurrence analysis, EPA attempted a high-end and a low-end estimate of the population exposed to perchlorate from contaminated drinking water. The high-end estimate, which is the population served by a system with a contaminated entry-point is an appropriate point to use. However, EPA did not employ the best method to estimate population exposure for the low-end estimate. For systems with multiple entry points, EPA estimated an equal proportion of the population was served by each entry point. However, EPA acknowledged that "[t]his approach may provide either an overestimate or an underestimate of the population served by the affected entry point" but failed to

[61] Téllez RT, PM Chacón, CR Abarca, BC Blount, CB Van Landingham, KS Crump and JP Gibbs. 2005. Long-term environmental exposure to perchlorate through drinking water and thyroid function during pregnancy and the neonatal period. Thyroid 15(9):963–975.
[62] *See e.g.* http://2010.census.gov/2010census/

provide any reasonable uncertainty analysis. An uncertainty analysis is a mathematical measure of the "goodness" of the result, and therefore our confidence in it. With such an analysis it is impossible to determine the fitness of the value as a basis for making regulatory decisions related to health protection or scientific quality. Therefore, EPA cannot justify using this estimate to model the occurrence of and exposure to perchlorate in drinking water.

There are two problems with assuming that every entry point equally serves a population. First, it is possible that one entry point could serve a large majority of the population and other entry points serve many fewer. Basing the estimate on the proportion of the flow rate of water sent to the system by a given entry point would provide a more accurate representation of the population exposed. Second, having a detection at one entry point does not preclude the possibility that other entry points in the system are also contaminated. For example, one groundwater source may distribute water to multiple wells which separately contribute water to a system. Therefore, assuming that one contaminated entry point contributes equally to the flow of the entire distribution system is a weak way to estimate the population exposed. Because EPA can neither determine whether this estimation is an overestimate or an underestimate, or provide an analysis of the uncertainty, it should not be used as part of the regulatory determination for perchlorate.

NRDC Response: *Estimating the water systems with at least one entry point with a sample above the detection limit is appropriate for the perchlorate regulatory determination.*

The perchlorate monitoring program was not designed to specifically detect high levels of perchlorate. While we are not aware of evidence that there are large fluctuations of perchlorate levels in groundwater, detecting perchlorate in drinking water is a signal of a bigger, not smaller, contamination problem. When sporadic sampling is conducted in a system – such as taking a single quarterly or semi-annual sample – detections of contamination are a reflection of a widespread problem. It much more likely that a monitoring program would miss detections and particularly elevated spikes, rather than catch them. Much like searching for a needle in a haystack,if you find one, it is likely because there are many more; however if you don't find one, that does not mean there are none. Therefore, each finding of contamination in monitoring data should be treated seriously, as if it is representative of a widespread problem.

NRDC Response: *Only Massachusetts has finalized a drinking water standard for perchlorate; California and New Jersey have not.*

As noted in the Federal Register notice, one commenter incorrectly suggests that the population exposed would be capped because of regulatory limits in Massachusetts, California, and New Jersey. As a matter of fact, only Massachusetts has promulgated an MCL of 2 ppb for perchlorate in drinking water. California has set an unenforceable

public health goal of 6 ppb.[63] New Jersey has proposed, but has not finalized, an enforceable standard of 5 ppb.[64]

ADDITIONAL COMMENTS

Regulating Perchlorate Represents a Meaningful Opportunity for Health Risk Reduction

NRDC notes that there is enough information for the Agency to make a final regulatory determination to promulgate a national primary drinking water standard for perchlorate. The evidence about the impact of perchlorate contaminated drinking water shows that it satisfies the requirements for promulgating a drinking water standard under the Safe Drinking Water Act: (1) perchlorate is know to have an adverse effect on the health of persons; (2) perchlorate is known to occur in public water systems with a frequency and at levels of public health concern, and (3) regulating perchlorate presents a meaningful opportunity for health risk reduction for persons served by public water systems. Therefore, EPA should set an MCL for perchlorate, rather than focus on setting an HRL.

In its October 10, 2008 preliminary determination not to regulate perchlorate, EPA acknowledged that perchlorate could have an adverse effect on human health.[65] Second, based on just quarterly or semi-annual sampling along, EPA showed that 4 percent of drinking water systems have detections of perchlorate over 4 ppb. As explained in further detail below, this occurrence exposes hundreds of thousands of pregnant women, children, and infants to dangerous levels of perchlorate, giving rise to a public health concern.

In October, 2008, EPA determined that up to 28,000 pregnant women would be exposed to more than 15 ppb of perchlorate. However, at that time, EPA stated that reducing the risk that 28,000 pregnant women would be exposed to perchlorate would not provide a meaningful opportunity to reduce health risks.

What that October 2008 announcement failed to explain is that EPA's own staff experts have provided data to show that at the proposed HRL of 15 ppb, infants and children would consume perchlorate on a daily basis that exceeded the reference dose.

As explained above, EPA's proposed model shows that there are over one million children under 5 years old who would exceed the daily reference dose; this is likely an underestimate of the highly exposed.

As noted above, NRDC believes that any amount of perchlorate in drinking water over 1 ppb may have adverse health impacts on vulnerable populations, meaning EPA's estimate

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[63] California Office of Environmental Health Hazard Assessment, Public Health Goal for Perchlorate. See e.g. http://oehha.ca.gov/public_info/facts/Perchloratefacts.html.
[64] New Jersey Department of Environmental Protection, New Jersey Register, March 16, 2009 http://www.state.nj.us/dep//rules/notices/031609a.html
[65] 73 Fed. Ref. at 60275.

of the number of pregnant women who would be exposed to excessive perchlorate would be much higher than 28,000. In fact, based on EPA's estimate, over 200,000 pregnant women could be exposed to perchlorate contamination over 4 ppb (the maximum detection limit identified in EPA's estimates). As such, by any measure, a regulation that could protect up to over 200,000 pregnant women and a million children and infants would give rise to a meaningful opportunity to protect public health.

A Final MCL Below 1 ppb is Both Technologically and Economically Feasible

U.S. EPA's Method 314 approved ion chromatography detection protocol, for example, routinely detects perchlorate pollution at levels of 0.2ppb and the State of Massachusetts has established a 'reportable concentrations level for perchlorate of 2 ppb. [66,67] Ion exchange technology is able to treat perchlorate contamination to levels considerably below 1 ppb. Treatment systems operating on perchlorate-impacted wells owned by Aquarion Water Company in Massachusetts, for example, treat wells to below 1 ppb.[68]

Economically, the cost of complying with a perchlorate MCL less than 1 ppb for the City of Rialto – one of the most impacted water systems in California – for example will be zero after cleanup costs are recovered from identified responsible parties. A complete economic feasibility study should also include an analysis of the costs associated with healthcare and lost work resulting from illnesses associated with perchlorate contaminated water.

CONCLUSION

EPA should amend its preliminary determination on perchlorate. EPA should determine to promulgate a national primary drinking water standard for perchlorate, to protect public health. Existing data on perchlorate exposure and effects, especially on vulnerable subpopulations, demonstrates that setting a national primary drinking water standard for perchlorate would provide a meaningful opportunity for health risk reduction. EPA is therefore required to set such a standard under the Safe Drinking Water Act.

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[66] Thorne, Philip G. Field Screening Method for Perchlorate in Water and Soil, ERDC/CRREL Technical Report 04-8, 36 pp, Apr 2004.
[67] "Final Changes to the Massachusetts Contingency Plan –310 CMR 40.0000," downloaded from http://www.mass.gov/dep/cleanup/laws/perchlorate-310CMR40-07282006.pdf, November 2 2006.
[68] "US Filter Recovery Services," downloaded from www.usfilter.com, November 2 2006.

Furthermore, a maximum contaminant level below 1 ppb would afford reasonable protections to the health of the susceptible populations of pregnant women and breast-fed infants. However, even if EPA proceeds with its determination not to regulate perchlorate and instead finalizes an HRL, that level must be adjusted to account for the actual data from the PBPK model showing that hundreds of thousands of infants would exceed the safe daily perchlorate intake levels at the proposed HRL.

These comments are respectfully submitted for your consideration,

Jennifer Sass, Ph.D.
Mae Wu, JD

Protecting, maintaining and improving the health of all Minnesotans

October 8, 2009

Response to U.S. EPA, Drinking Water: Perchlorate Supplemental Request for Comments Docket ID No: EPA-HQ-OW-2009-0297

The approach taken by the Minnesota Department of Health (MDH) to develop health-protective guidelines for groundwater is consistent with alternative approaches considered by the U.S. EPA in the development of a drinking water guideline for perchlorate. The approach used by MDH to develop health risk limits (HRLs) for drinking water are much more aligned with the process outlined by the EPA in the August 19, 2009 Federal Register announcement than the process described in the December 2008 Perchlorate Interim Drinking Water Health Advisory report.

MDH supports EPA's August 2009 re-evaluation of the process used to develop drinking water guidelines for perchlorate. The previous approach used by the EPA in Interim Health Advisory Report was inconsistent with EPA risk assessment guidance. The use of the PBPK model appeared to be used to justify perchlorate exposure in infants and young children at levels above the RfD, an approach we would not endorse as health protective. Additionally, MDH was concerned by the lack of consideration of life stage sensitivities in the interim report, especially the absence of appropriate intake rates that were protective of sensitive subpopulations.

Our comments include a discussion about how MDH accounts for life-stages sensitivities when developing HRLs and how our approach compares with the alternative approaches EPA is considering for developing a perchlorate drinking water guideline. We have also included an example of how MDH would calculate a HRL for perchlorate using EPA's RfD of 0.0007 mg/kg-day and comments comparing the MDH drinking water guidelines and the alternative HRLs that EPA is considering (listed in Table 2, section III.B-3 of the Federal Register announcement).

Note: If this were a chemical review conducted by MDH, we would independently review the toxicological literature to derive our own RfD, which may not result in the same RfD adopted by EPA for perchlorate.

Section III, B-4.a – Request for comments about appropriate exposure values that consider sensitive life stages

Intake Rates

MDH strongly supports EPA's reconsideration to use life-stage specific, high end (95th percentile) drinking water intake rates in the development of alternative HRLs. This is consistent with the approach used by MDH and EPA's recommendation to evaluate exposures

that are shorter than chronic durations to account for higher intake rates than can occur during shorter periods (EPA, 2002). Additionally, MDH agrees with EPA's approach to use appropriate and relevant body weights for sensitive individuals when calculating intake rates.

To account for lower body weights and higher water intake rates by infants and young children during acute and short-term exposure durations, MDH uses an intake rate of 0.289 L/kg-day, based on the 95th percentile intake for an infant up to 3-months (EPA 2004 & EPA 2008a). The subchronic intake rate we use is 0.077 L/kg-day based on the time-weighted average of the 95th percentile intake from birth up to 8 years of age. The chronic intake rate used by MDH is 0.043 L/kg-day and is based on the time-weighted-average of the 95th percentile intake over approximately 70 years.

Relative Source Contribution (RSC)
MDH acknowledges the extensive national database of perchlorate exposure information that includes perchlorate concentrations found in food and beverages as well as biomonitoring data. We understand EPA's use of the NHANES biomonitoring data to estimate the 90th percentile food dose for pregnant women leading to the derivation of the drinking water RSC. For infants and young children, EPA states that the RSC is based on the central tendency dietary perchlorate exposure derived from FDA's Total Diet Study. MDH does wonder whether an RSC based on average dietary perchlorate exposure will protect individuals who have higher dietary doses. However, EPA's RSC for children 12-months and younger (0.59) based on the central tendency exposure is not much higher than the default RSC used by MDH for infants (0.5).

MDH uses 0.2 as the relative source contribution (RSC) default value for volatile chemicals for all exposure durations. However, for non-volatile chemicals, an RSC of 0.5 is used for acute and short-term exposure durations and 0.2 is used for subchronic and chronic exposure durations.

Section III, B-4.b - Request for comments on the alternative HRLs in Table 2 and which would be an appropriate guideline

The formula used by MDH to calculate a non-cancer health protective drinking water guideline is:

$$\text{Non-cancer Guideline}_{duration} = (\text{RfD}_{duration} \times \text{RSC} \times 1000) / \text{Intake Rate}_{duration}$$

In the table below (Table 1) you will find the range of perchlorate concentrations in drinking water that MDH would derive based on our standard intake rates and relative source contributions described above for multiple exposure durations (acute, short-term, subchronic, and chronic). The drinking water concentrations derived below are for comparison purposes only and do no reflect current MDH guidance.

Table 1. MDH drinking water guidelines compared to EPA HRLs for perchlorate.

Life Stage*	**MDH RSC**	**MDH Intake Rate (IR) [L/kg-day]**	**MDH health based drinking water guideline [µg/L]**	**Corresponding EPA HRL(s)** [µg/L]**
Less than 1 month	0.5	0.289	1	2
1 to 3 months	0.5	0.289	1	2
3 months to 8 years	0.2	0.077	2	3-9
> 10% of a lifetime (pregnant women)***	0.2	0.043	3	13

Assuming RfD = 0.0007 mg/kg-day, Conversion Factor = 1000 µg/mg

*We adjusted the life stages used by MDH to conform to EPA's life stages listed in Table 2, section III.B-3 of the Federal Register announcement, however normally, MDH categorizes health guidelines by exposure durations as outlined in EPA's Reference Dose Process guidance (EPA, 2002).
**MDH does not calculate guidlines for each life stage listed in Table 2, section III.B-3 so we only included EPA HRLs that correspond to the life stages we consider at MDH. The EPA HRLs that were most appropriate for comparison were the ones calculated using the 95th percentile intake rates.
*** We felt a chronic MDH guideline provided the most appropriate comparison to EPA's HRL for pregnant women. The EPA HRL is higher than the MDH guideline because MDH used our default RSC of 0.2 and EPA used an RSC of 0.62.

Using the MDH HRL approach to calculate theoretical perchlorate drinking water guidelines resulted in a range of perchlorate concentrations of 1-3 µg/L which account for all life stages and sensitive subpopulations. Based on these concentrations, it is likely we would select 1 µg/L as the guideline to ensure the most sensitive individuals are protected. The EPA HRL of 2 µg/L for infants less than 3-months old is much more comparable to the MDH guideline than the interim HRL of 15 µg/L.

Section III, B-4.d Request for comments on the merits of the approach to derive HRLs for sensitive life stages based on the RfD combined the life stage specific exposure data

MDH agrees with the approach of developing HRLs based on the RfD combined with life stage specific exposure data. When developing an HRL, MDH conducts an independent review of the toxicological literature to develop an RfD and calculates a drinking water guideline using intake rates and relative source contributions that are protective of life-stage sensitivities.

MDH commends the alternative approaches described in the EPA Drinking Water: Perchlorate Supplemental Request for Comments announcement. They show that EPA is seriously weighing all life stages and highly exposed sensitive subpopulations in the development of a perchlorate HRL.

Thank you for the opportunity to comment. Please contact Kate Sande (651-201-4902) kate.sande@state.mn.us) with the Health Risk Assessment Section in the Environmental Health Division if you have any questions concerning these comments.

Attachment: References

References

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Docket: EPA-HQ-OW-2009-0297
Drinking Water: Perchlorate Supplemental Request for Comments

Comment On: EPA-HQ-OW-2009-0297-0001
Drinking Water: Perchlorate Supplemental Request for Comments

Document: EPA-HQ-OW-2009-0297-0204
Comment submitted by Peggi Sturmfels, New Jersey Environmental Federation

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Submitter Information

General Comment

I am a program organizer for NJ Environmental Federation as well as a mom and grandmother.
My deep concern about perchlorate in our waterways is growing. Particularly in regards to NJ which is now becoming a superfort by combining FT Dix, Mcquire Air Force Base and Lakehurst Navel Air Station. As a results, military air traffic has increased from 8000 to 80,000 over Centerl Jersey, which is home to the headwaters of the Metedeconk and Toms River and the Kirkwood Cohansey aquifer that supply most of the drinking water for central and South Jersey. Added to that, this area is less than 50 miles in any direction from a major commercial airport.
Setting standards for perchlorate at one part per billion is the only reasonable action that can be taken protect the children and residents of this area. Sadly you may be too late.

- END -

COMMONWEALTH OF MASSACHUSETTS
EXECUTIVE OFFICE OF ENERGY & ENVIRONMENTAL AFFAIRS
DEPARTMENT OF ENVIRONMENTAL PROTECTION
ONE WINTER STREET, BOSTON, MA 02108 617-292-5500

DEVAL L. PATRICK
Governor

TIMOTHY P. MURRAY
Lieutenant Governor

IAN A. BOWLES
Secretary

LAURIE BURT
Commissioner

September 17, 2009

Docket ID No. **EPA-HQ-OW-2009-0297**
Drinking Water: Perchlorate Supplemental Request for Comments
U.S. Environmental Protection Agency

We highly commend the U.S. Environmental Protection Agency's (EPA) decision to reconsider its approach to analyzing scientific data related to perchlorate in drinking water. The Wednesday, August 19, 2009 Federal Register announcement includes a summary of the major comments EPA received regarding its October 10, 2008 preliminary regulatory determination to not regulate perchlorate in drinking water. This includes comments on why the proposed 15 ppb health advisory is not protective of children's health. These comments provide a strong basis for EPA's appropriate decision to consider a broader range of alternatives for interpreting the health data, the level of health concern, the frequency of occurrence of perchlorate in drinking water, and the opportunity for health risk reduction through a national primary drinking water standard. The Commonwealth of Massachusetts' Department of Environmental Protection (MassDEP) is pleased to provide comments on several of the issues that are the focus of this Federal Register announcement and is available to further consult with you or answer any questions you may have on our comments. Our comments are organized by issues described in specific sections of the Federal Register.

Section II: Background

MassDEP supports EPA's opinion that further review by the National Research Council (NRC) will delay regulatory decision-making and supports EPA's current plan to publish alternative approaches to interpreting the data on perchlorate and to consider public comments towards making a regulatory decision on perchlorate in drinking water.

Section III Alternative Approaches to Analyzing Scientific Data Related to Perchlorate in Drinking Water

For a number of reasons we do not believe that sodium iodide symporter (NIS) inhibition predictions based on Physiologically-Based Pharmacokinetic (PBPK) modeling should, at this time, be relied upon to establish or justify a perchlorate reference dose (RfD) nor to evaluate relative sensitivities between life-stages. Although the PBPK model previously relied upon, but now under reconsideration by EPA, provides a valuable exploratory research tool and is a potentially useful predictor of perchlorate distribution and NIS effects in the adult, it is highly uncertain regarding the fetal and neonatal life-stages of most concern and may not reflect perchlorate effects on thyroid function. Our view on this issue is based on the following observations:

1) In response to peer review comments on the PBPK models, EPA noted that "the models have not been specifically parameterized to describe hypothyroid or iodine deficient individuals." In other words the model does not take into account responses in those with insufficient iodine intakes, the very group of most concern with respect to perchlorate exposures. In other documents EPA has also noted that the PBPK model did not account for within group variability in pharmacokinetics; uncertainty in several model parameters, including fetal and neonatal values derived from rodent models, and differences in adaptive responses. Although peer reviewer comments recommended that a much more robust uncertainty analysis be preformed on the model, EPA concluded that this was beyond the scope of the current effort and would be difficult to conduct due to data gaps. However, such an assessment is critical to determining the ultimate usefulness of the model predictions.

2) The perchlorate associated thyroid hormone alterations reported in Blount et al. 2006 and Steinmaus et al. 2007 in women with urinary iodine < 100 µg/L highlight some of these uncertainties, as they suggest that either the model estimates of iodide uptake inhibition (IUI) at low perchlorate intake levels are inaccurate; that unexpectedly small increments in IUI may cause thyroid effects; and/or that perchlorate may act through additional mechanisms not captured in current models. Although NIS inhibition has been viewed as perchlorate's primary mode of action, other possible mechanisms that could contribute to its toxicity have been suggested. Based on a biologically-based dose response model of the hypothalamus-pituitary-thyroid axis and PBPK modeled perchlorate distribution and inhibition of thyroid iodide uptake, a recent assessment concluded that IUI was insufficient to explain observed changes in rat thyroid hormone levels attributable to perchlorate (McLanahan et al. 2009). These results suggest either that an additional mechanism of action exists, perhaps attributable to perchorate uptake into the thyroid and interference with other targets involved in hormone synthesis and release or that the PBPK modeling is inaccurate.

3) Although the impact of thyroid toxicants on the fetus can be buffered by the thyroid hormone synthesis and reserve capacities of the mother, iodide insufficiency and pregnancy-related stresses on maternal thyroid function increase the potential for perchlorate effects during fetal development (Glinoer 2001; Ginsberg et al. 2007). These are factors that the PBPK modeling does not adequately account for and could lead to a significant underestimate of NIS inhibition.

4) Available data indicate that neonatal exposures to perchlorate in breast milk are significant. The median perchlorate exposure to two week old nursing infants in the U.S. was predicted to be

0.206 µg/kg/day (95th percentile = 0.744 µg/kg/day) (Ginsberg et al. 2007). Other data indicate that nursing infant perchlorate exposures in the U.S. can be even higher. Based on a breast milk intake rate of 0.172 L/kg/day and reported median breast milk perchlorate concentrations (Kirk et al. 2005 and 2007; Pearce et al. 2007a), we estimate that nursing infant perchlorate intakes in three U.S. cohorts ranged from 0.56 to 1.57 µg/kg/day. Dasgupta et al. (2008) estimated breast milk perchlorate intake rates ranging from 0.3–2.1 µg/kg/day, with intakes of 9 of 13 infants exceeding the National Research Council's (NRC) RfD (NRC 2005) (Dasgupta et al. 2008).

Due to the significance of this exposure pathway, PBPK modeled estimates of perchlorate and iodide concentrations in breast milk warrant close scrutiny and additional validation. In response to peer review comments, EPA added section 4.1.1 to the May 2009 report, "Inhibition Of The Sodium-Iodide Symporter By Perchlorate: An Evaluation Of Life Stage Sensitivity Using Physiologically Based Pharmacokinetic (PBPK) Modeling." This section includes several informative comparisons of model predictions with published data but no comparison of predicted human breast milk perchlorate concentrations with published data. A comparison of breast milk data from Pearce et al 2007; Kirk et al 2005 and 2007 etc. combined with estimated US median perchlorate intakes (Blount et al 2006) should be completed, as this would provide important insight into model uncertainty regarding this critical exposure pathway.

Section III(B): Comments on Alternative Approaches for Calculating Health Reference Levels (HRLs)

1) MassDEP recommends that EPA use the approach to setting HRLs as shown in Section III, Subsection B-3.

2) We support EPA's reassessment of exposure assumptions for life stages, including fetuses of gestation week 40, infants and developing children. Application of EPA's Guidance on Selecting Age Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants is appropriate along with application of EPA's Guidance for Risk Characterization to convey the variability in risk levels experienced by different individuals in the population. In doing so, EPA has appropriately taken into account specific and appropriate exposure values for many but not all potentially sensitive life stages. Because of the potential sensitivity of the early neonatal period from birth to several days thereafter, we believe that exposures to the bottle-fed 7-day old should also be considered. In EPA's Interim Drinking Water Health Advisory for Perchlorate, the 7-day old bottle-fed infant was estimated to have the highest perchlorate exposure per body weight.

3) Other sensitive populations should not be forgotten when EPA is addressing levels of health concern and potential numbers of people exposed to perchlorate in drinking water. Other sensitive subgroups not explicitly addressed include individuals with low iodine intake, untreated thyroid conditions, those suffering from cardiovascular and renal diseases (Miller et al. 2009; Iglesias and Diez 2009), individuals exposed to mixtures of other thyroid stressors, the elderly who are often prone to thyroid problems, and people with thyroid cancer. The results of Blount et al 2006 also indicate that women should be considered a sensitive group, certainly at the current RfD.

4) MassDEP supports setting the HRL on the basis of the life stage(s) with highest exposure and risk with a 90% percentile ingestion rate, which is standard practice. Based on Table 2, this would support an HRL of 2 ppb (or perhaps somewhat lower depending on the exposure estimate for the 7-day old). It is worthwhile to note that the alternative HRLs calculated using the 95th percentile exposure values for early life stages are not very different than the HRL values estimated using the 90th percentile ingestion rates, especially considering the rounding involved in the final calculation of the HRLs. Although EPA's concern about sample size and aggregation of life stages is legitimate, the aggregation of life stages in the current document (birth to < 6 months) yield closely similar HRL values derived for life stages birth to < 1 month, 1 to < 3 months, and 3 < 6 months and birth < 6 months and therefore appear to be reasonably stable estimates (Table 2).

5) Although the HRL of 2 ppb recommended above is numerically similar to the maximum contaminant level adopted by MassDEP and protective of the sensitive segment of the population, the RfDs used by the two agencies as the bases to derive the drinking water levels are different. MassDEP concluded that the National Research Council's (NRC) RfD is not protective of public health (Zewdie et al. 2009). Although uncertain, the EPA's modified PBPK analysis presented in Table 1 for a 7-day-old healthy infant supports this position. In this analysis, the infant gets about 3 times the maternal dose through breast milk at the dose equal to the point-of-departure (POD) in the NRC RfD derivation. This translates to a 7-day infant receiving about 20 µg/kg/day (0.02 mg/kg/d) dose of perchlorate through breast milk from a mother ingesting 7 µg/kg/day. This dose level is equivalent to the exposure level that resulted in significant inhibition (17 %) of iodide uptake in healthy adults in the Greer et al. (2002) study, suggesting that the factor of 10 applied to the POD by the NRC to protect sensitive individuals is insufficient. An additional uncertainty factor is required to extrapolate from LOAEL to NOAEL as 0.02 mg/kg/day is an effect level. Efforts to determine populations at risk based on the NRC RfD will yield significant underestimates of those at risk. MassDEP can support EPA's decision to not re-evaluate the NRC RfD at this time, if EPA adopts an HRL of 2 ppb or lower.

6) We believe that EPA has used the best available exposure data for deriving the HRLs. Use of the 90% percentile ingestion rate addresses uncertainties regarding the issue of minimum data set deficiencies for ingestion rates.

Section III C: Occurrence Analysis

4(a)) EPA's proposal to use a Bayesian model to estimate the number of public water systems, and populations served by such systems, with sample detections at various levels appears to be a reasonable approach. Further details regarding the specific model inputs are, however, needed in order to assess the usefulness of the model. MassDEP will provide U.S. EPA with Massachusetts perchlorate monitoring data to assist in this effort. However, we wish to note that the sampling results and data distribution for MA may not reflect the situation in other states. We also wish to note that the population estimates in column 5 of Table three would be likely to underestimate those exposed in MA, and quite likely other states, due to mixing of supplies from multiple entry points.

4(b)) EPA requested comments on using US Census data to estimate the portions of the population that are sensitive at any one time to perchlorate in drinking water. This analysis is used as one factor in EPA's decision-making on the need for a drinking water standard for perchlorate, based on the number of people in the U.S. who would be at risk. MassDEP believes that it is inappropriate to consider sensitive groups one-by-one using census or any other data. EPA should certainly consider perchlorate exposures to fetuses, infants and young children up to 2 years of age. However, EPA should also, for several reasons, consider the entire population's exposure. . First, Blount et al. (2006) and Steinmaus et al. (2007) reported an association between perchlorate exposure and decreased T4 and increased TSH in iodine deficient adult women and increased TSH in all women. As such, we believe that all women should be included in EPA's analysis as a sensitive subgroup. Secondly, as previously noted, there are other sensitive members of the population beyond fetuses, infants and women, and they should also be factored into EPA's framework for considering the extent of the population at risk to perchlorate exposures from drinking water. Lastly, because significant exposures to other thyroid toxicants are known to occur, other members of the population may also be at increased risk. Thus, any estimate derived based on exposures to the fetus, neonate and women as a group will still be an underestimate of those actually at risk.

We appreciate the opportunity to comment. For further information please contact Carol Rowan West at 617-292-5510 (Carol.RowanWest@state.ma.us), C. Mark Smith at 617-292-5509 (C.Mark.Smith@state.ma.us) or Tsedash Zewdie at (617) 292-5842 (Tsedash.Zewdie@state.ma.us).

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Alliance of Nurses for Healthy Environments

Bringing Science and Passion to the Environmental Health Movement

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University of Maryland

Laura Anderko, PhD, RN
Georgetown University

Evelyn I. Bain MEd, RN, COHN-S, FAAOHN
Massachusetts Nurses Association

Chris Bartholomew, RN, DNS

Betty Bekemeier, PhD, MPH, RN
University of Washington

Pat Butterfield, PhD, MPH, RN
Washington State University

Denise Choiniere, RN, MS
Maryland Hospitals for a Healthy Environment

Rebecca Clouse, RN, MS
Student, Johns Hopkins University

Ann Converso, RN
United American Nurses

Kathy Curtis, LPN
The JustGreen Partnership

Karen G. Duderstadt, PhD, RN
National Association of Pediatric Nurse Practitioners

Tom Engle, RN
Association of State and Territorial Directors of Nurses

Robyn Gilden, RN, MS
University of Maryland

Kathryn V. Hall, RN, MS
University of Maryland

Lisa Hartmayer, RN, BSN
University of California San Francisco Hospital

Wade G. Hill PhD, PHCNS-BC
Montana State University College of Nursing

Katie Huffling, RN, CNM
American College of Nurse-Midwives

Beth Lamanna RN, WHNP, MPH
Public Health Nursing Section,
American Public Health Association

Jeanne Leffers, PhD, RN
University of Massachusetts

Sharon Rainer, RN, MS
New Jersey Nurses Association

Norma Rogers, PhD RN, FAAN
National Association of Hispanic Nurses

Barbara Sattler, RN, DrPH, FAAN
University of Maryland

Patti Gates-Smith MSN, RNC
Pennsylvania State Nurses Association

Mary Jane Williams, PhD, RN
University of Hartford College of Education, Nursing and Health Professions

Sandy Worthington, MSN, WHNP-BC, CNM
Planned Parenthood Federation of America, Inc

Affiliations added for identification purposes only

October 7, 2009

Mr. Eric Burneson
Office of Ground Water and Drinking Water
Standards and Risks Management Division
Environmental Protection Agency
1200 Pennsylvania Avenue, NW, Mailcode 2822T
Washington, D.C. 20460
Re: Docket ID No. EPA-HQ-OW-2009-0297

Dear Mr. Burneson,

On behalf of The Alliance of Nurses for Healthy Environments, we are writing to express our belief that the potential health impacts from exposure to perchlorate through drinking water are significant and that they call for prompt regulation to protect the public's health and safety. Setting a drinking water standard will provide the U.S. Environmental Protection Agency (EPA) with a "meaningful opportunity for health risk reduction for persons served by public water systems". EPA should move as quickly as possible to establish a more protective reference dose for perchlorate and then to promulgate a maximum contaminant level (MCL) for perchlorate that is no higher than one part per billion (ppb).

A 1 ppb or lower MCL is supported by the most recent comprehensive studies, and these should be central to EPA's analysis**.** The industry-supported Greer study, which serves as the basis for EPA's current reference dose consisted of a 14-day study of 37 healthy adults. In more recent years, Blount et al analyzed a nationally representative sample of 2299 U.S. residents, and they have documented anti-thyroid effects in a large population of women exposed to perchlorate at concentrations far lower than levels previously shown to have such effects. This study and subsequent data clearly justify promulgation of a more protective MCL.

Perchlorate has been found in more than 400 drinking water sources in 26 states, potentially affecting tens of millions of people. EPA's own data say that nearly 17 million people receive their water from public water systems where perchlorate has been found at levels exceeding 4 ppb.

P.O. Box 1972 ▪ Baltimore ▪ MD ▪ 21203 ▪ 410-706-1778
*▪ e-commons.org/ANHE * anhe.info@gmail.com*

In responding to this threat, EPA must set a drinking water standard for perchlorate that protects the most vulnerable subpopulations, particularly pregnant women, fetuses, infants, and small children. By interfering with the thyroid's ability to take up iodide, perchlorate can suppress the development of thyroid hormones critical to growth, development, and metabolism. This puts children at particular risk for learning and behavioral disabilities; impaired gait, vision, and hearing; and even mental retardation. Exposure calculations must therefore consider the ingestion rates for these populations, and the reference dose should consider the particular vulnerabilities of these age groups. EPA should also include in its calculations low birth weight babies, and underweight infants as these populations may be extremely vulnerable.

EPA must also consider other exposure pathways and additional contaminants in the environment that impact thyroid function when establishing the MCL. Studies of perchlorate levels in food, including breast milk, show that the population is exposed through multiple pathways in addition to contaminated drinking water.

A perchlorate drinking water standard of no higher than 1 ppb would protect a large share of the American population currently at risk. Given the scope of the perchlorate contamination nationally, the multiple exposure pathways and other environmental contaminants impacting thyroid function and development, and the data demonstrating a serious health threat to a significant part of the country's population, we believe EPA is obligated to establish such a drinking water standard. We applaud the agency's consideration of how to move forward to regulate this contaminant and urge you to take steps to establish a protective MCL as soon as possible.

We look forward to following the EPA response on this critical health issue.

Sincerely,

Kathy Curtis and MaryJane Williams, RN, PhD

Co-chairs, Policy Workgroup

For the Alliance of Nurses for Healthy Environments

P.O. Box 1972 ▪ Baltimore ▪ MD ▪ 21203 ▪ 410-706-1778
*▪ e-commons.org/ANHE * anhe.info@gmail.com*

Comment submitted by Kim Soles, American Lung Association

Document ID:
EPA-HQ-OW-2009-0297-0603
This is comment on PROPOSED RULE: Drinking Water: Perchlorate Supplemental Request for Comments
Docket ID:
EPA-HQ-OW-2009-0297

September 26, 2009

Comment

I urge the U.S. Environmental Protection Agency to move forward with a drinking water standard of no higher than 1 part per billion for perchlorate. perchlorate contamination is a nationwide problem and has health impacts at lower levels than previously thought; protecting infants and children is critical. a national primary drinking water regulation would provide a meaningful opportunity to protect public health.

Comment submitted by James C. Malley, Connecticut Partnership for Sustainability Education, Inc.

Document ID:
EPA-HQ-OW-2009-0297-0145
This is comment on PROPOSED RULE: Drinking Water: Perchlorate Supplemental Request for Comments
Docket ID:
EPA-HQ-OW-2009-0297

September 12, 2009

I urge the U.S. Environmental Protection Agency to move forward with a drinking water standard of no higher than 1 part per billion for perchlorate. Perchlorate contamination is a nationwide problem and has health impacts at lower levels than previously thought; protecting infants and children is critical. A national primary drinking water regulation would provide a meaningful opportunity to protect public health. it is bad enough that, in time, water will become less scarce as the planet heats up - worse that available supplies will be contaminated with carcinogens and other poisons. James C. Malley, Ph.D. Connecticut Partnership for Sustainability Education, Inc.

-END-

ENVIRONMENTAL WORKING GROUP

1436 U Street NW, Suite 100
Washington, DC 20009
T: 202.667.6982
F: 202.232.2592

September 18, 2009

Mr. Eric Burneson
Office of Ground Water and Drinking Water
Standards and Risk Management Division
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Docket ID no. EPA-HQ-OW-2009-0297

Dear Mr. Burneson:

The Environmental Working Group (EWG) strongly supports the Environmental Protection Agency (EPA) establishing a drinking water standard for the rocket fuel ingredient perchlorate. This compound contaminates drinking water supplies nationwide at levels of concern for human health, providing the agency with a meaningful opportunity for human health risk reduction through a national primary drinking water rule:

- The EPA has reported finding perchlorate, a potent thyroid toxin, in public water systems in 28 states and territories and estimated that nearly 17 million people may be served by public water systems with at least one perchlorate detection > 4 ppb
- The Centers for Disease Control and Prevention (CDC) have found perchlorate in the urine of nearly 3,000 Americans who were tested as part of a national biomonitoring study, indicating widespread exposure among the U.S. population (Blount et al 2006a)
- In infants and children, drinking perchlorate contaminated tap water can result in cumulative exposures that exceed the EPA's reference dose (RfD), even at tap water concentrations as low as 1 part per billion (ppb).

Recommendations

- EPA's own analyses show that infants under six months of age are exposed to enough perchlorate via food that additional exposure to perchlorate via tap water concentrations as low as 1 ppb can result in combined exposures that exceed the RfD. To protect these highly vulnerable individuals, EPA must set an MCL of less than 1 ppb for perchlorate in drinking water.

- EPA must modify the RfD that is the basis for its standard setting to include a substantial body of peer-reviewed science published since 2002, including two large, high quality epidemiologic studies from the CDC (Blount et al 2006a, Blount et al 2006b). In addition to these new studies, peer reviewed analyses of the study that forms the basis for the current RfD (Greer 2002) have revealed fatal flaws with this work. A study with such fundamental and well-documented

shortcomings cannot be used as the basis to determine national safety standards for exposure to this potent thyroid toxin.

Background: Perchlorate is unique among chemical contaminants for its ubiquity- it has been found as a contaminant in drinking water in at least 26 states, in 74% of nearly 300 types of commonly consumed foods and beverages tested by the Food and Drug Administration (FDA), and in the urine of 100% of Americans tested by the Centers for Disease Control and Prevention (CDC) (GAO 2005, Blount et al 2006a, Murray et al 2008). Its primary clinical effects are on the thyroid gland, where it can disrupt the production of thyroid hormones that are critical for normal brain development and growth in the fetus, infants, and children. Perchlorate inhibits thyroid hormone synthesis by preventing iodine, the building block for thyroid hormones, from being taken up into the thyroid gland from the circulation. Iodine status is especially important in determining vulnerability to perchlorate, as confirmed by a recent large-scale epidemiological study from the CDC that found that women with lower iodine levels had more significant changes in thyroid hormone levels associated with environmental perchlorate exposure when compared with women with higher iodine levels (Blount et al 2006a).

On August 19, the agency published a notice in the Federal Register seeking comments on its additional approaches to analyzing data related to its perchlorate regulatory determination. These new approaches differ from EPA's prior assessment primarily because they focus on the risks of perchlorate exposure to infants and children, as opposed to the prior assessment that focused on risks to the fetus of the hypothyroid or iodide-deficient woman. EWG fully supports these approaches. Although fetal development is a highly vulnerable life stage for perchlorate exposure, research from the last several years has confirmed that infants and children are an equally high-risk population group due to their small size relative to adults and their high level of perchlorate exposure via water and food.

In this notice, the Agency specifically requests comments on certain approaches within their assessment, including the following:

1) Use of PBPK modeling analysis to inform the regulatory determination for perchlorate
2) Appropriateness of alternative health reference levels (HRLs) described in the notice to address and account for risk to all potentially sensitive life stages
3) Occurrence analysis including use of Bayesian model and U.S. Census data

Use of PBPK model: EWG supports the use of the PBPK model to estimate the extent of iodine uptake inhibition in sensitive life stages only if significant limitations of the current model are addressed.

In this notice, one of the approaches that the Agency considers is the following: "... use the PBPK modeling analysis to explore the relative sensitivity of the various life stages of concern to a fixed dose such as the point of departure (POD) or the reference dose (RfD)." In this case, the agency notes that the "POD is the lowest dose administered in the Greer et al clinical study... ".

The Greer study included only 37 study participants who were divided into several study groups and administered different doses of perchlorate for 14 days (Greer et al 2002). The researchers determined that a daily perchlorate dose of 0.007 mg/kg/day was the no observed effect level (NOEL); the results from this study were used by the National Academy of Sciences (NAS) in setting the reference dose (RfD) for perchlorate of 0.7 ug/kg/day.

The Greer study results and assumptions drawn from them have been questioned in a peer-reviewed article that was published in Environmental Health Perspectives in 2005 (Ginsberg and Rice 2005). Two toxicologists, one from the Connecticut Department of Public Health and the other from the Maine Bureau of Health, conducted an analysis of the raw data from the Greer study and concluded the following: "Individual results of Greer et al. point to an effect in four of the seven individuals tested at the lowest dose (0.007 mg/kg/day), indicating that this dose is an effect level." In other words, while Greer et al. and the NAS both concluded that 0.007 mg/kg/day is a no observed effect level (NOEL), closer analysis of the data reveals that four of the seven study subjects in this group experienced effects at this dose, thereby invalidating 0.007 mg/kg/day as a NOEL.

The Massachusetts Department of Environmental Protection (Mass DEP), which has set the most stringent drinking water standard for perchlorate nationally, had the following observations about the Greer study:

> *"MassDEP has concerns about the lowest dose in the Greer study being a no-effect level based on the facts that: due to the small number of subjects in the lowest dose group, there is low power to detect a statistically significant effect; averaging of group responses obscures positive individual inhibition; a non-statistically significant IUI (iodine uptake inhibition) effect was observed at the lowest dose tested; and, good low dose corroborating data is lacking" (MassDEP 2006).*

In light of these valid criticisms of the Greer study, it is clear that any exposure modeling based on the results of this study, including the agency's current proposal to use PBPK modeling with a POD derived from this particular study, would not be accurate. The PBPK model also does not address iodine status, an important factor in determining vulnerability to perchlorate (Blount et al 2006b).

Appropriateness of alternative HRLs: EWG supports the alternative HRLs if they are modified to reflect risks to infants from widespread perchlorate contamination of powdered infant formula and if infants under six months of age are not aggregated in the agency's exposure assessment.

Further in its assessment, the agency also lists a number of new Health Reference Levels (HRLs) as an alternative to its proposed HRL of 15 ppb from December, 2008. The agency derived these new HRLs by evaluating exposure to perchlorate at different life stages. In Table 2 of the notice, the Agency lists HRLs for 14 different life stages at three different drinking water ingestion rates (average, 90th, and 95th percentile).

Ten of the life stages are for children 16 years old or younger, indicating the Agency's recognition that perchlorate exposures vary during each stage of childhood.

For drinking water ingestion rates at the 90th and 95th percentile rates for infants in the three youngest life stages, the Agency notes that the sample sizes for the estimates of ingestion rates do not meet established minimum data requirements. The actual sample sizes for these three groups are 37 (birth to <1 month), 108 (1 to < 3 months), and 269 (3 to <6 months). While they may not meet minimum data requirements, EWG strongly supports their use because these are the best data available (EPA 2008), and because aggregating these age groups masks significant exposure disparities in these critical life stages.

Infants in the youngest two life stages (birth to <1month and 1 to <3 months) have especially high drinking water ingestion rates. HRLs derived from the aggregated life stage of birth to <6 months would place some of the very young infants at high risk of exceeding the current RfD. For example, the HRL for the aggregated life stage at the mean ingestion rate is 4 ug/L. This would leave infants under three months of age at high risk of exceeding the RfD because they require an HRL of 3 or less to limit cumulative exposure below the RfD.

The HRLs are lowest for children ages two and under, consistent with the published data showing that infants and children have high baseline perchlorate exposures from food and relatively high water ingestion rates; therefore, infants and young children can easily exceed the current RfD by drinking tap water contaminated with even very small concentrations of perchlorate (Murray et al 2008, EWG 2008). For infants six months of age and under, the agency estimates HRLs from 1 to 5 parts per billion, depending on the exact age and mean drinking water ingestion rate.

EWG supports the agency's decision to develop HRLs based on life stage and drinking water ingestion rates but we would like to bring attention to some findings from a recent CDC study of infant formula contamination that we believe would change the HRLs for infants six months of age and under. In this study, researchers tested 15 brands of powdered infant formula for perchlorate and found contamination in every brand; the two most contaminated brands, made from cow's milk, accounted for 87 percent of the U.S. powdered formula market in 2000 (Schier et al 2009).

In Table 4 of the CDC study, the researchers estimate the minimum water perchlorate concentration needed to reach the current RfD for infants at one month and six months of age at different body weight percentiles. At the highest perchlorate concentration found in the formula samples (5.05 ug/l), the researchers found the estimated minimum water perchlorate concentration needed to reach the RfD was zero for the following four exposure scenarios:

- One month old infant, 10th percentile body weight
- One month old infant, 50th percentile body weight
- One month old infant, 90th percentile body weight
- Six month old infant, 90th percentile body weight

In fact, in all four of these exposure scenarios, infants would exceed the current RfD from formula consumption even with perchlorate levels at zero in the water used to reconstitute it. A recent GAO report found that by six months of age, less than 30% of infants are exclusively breast-fed (GAO 2006); in addition, powdered infant formulas account for 50 to 60% of the total infant formula market. This means that millions of infants per year may be exposed to powdered infant formula that is so heavily contaminated with perchlorate that formula exposures alone in these infants may exceed the current RfD.

These results suggest that for infants six months of age and younger who are fed powdered formula, there is no safe HRL since any can of powdered formula may be contaminated with perchlorate at high enough concentrations that formula consumption alone results in exposures above the RfD. EWG recommends that the agency incorporate these exposure dosing scenarios from the formula study and modify the HRLs for infants six months and younger to reflect these findings.

Occurrence analysis: EPA's occurrence analysis grossly underestimates the number of people at risk from perchlorate because of an inappropriately high detection and reporting threshold of four ppb.

In table 3 of the notice in the federal register, the Agency lists the occurrence and population estimates for perchlorate above a number of thresholds, starting at 4ppb. This data is derived from the Agency's Unregulated Contaminant Monitoring Rule (UCMR) 1; the Agency estimates that a total of 16.6 million people in the United States are served by public water systems with at least 1 detection of perchlorate at > 4 ppb.

In table 2 of the federal register, the agency finds that HRLs as low as 1 are necessary to prevent children ages two and younger who have higher water ingestion rates and cumulative perchlorate exposures that can easily exceed the RfD. In addition, as mentioned above, the degree of perchlorate contamination of some powdered infant formulas is so high than an HRL as low as 0 is justified for infants six months and younger. Therefore, the finding of perchlorate in drinking water at any level presents risks to vulnerable populations and until the minimum reporting level (MRL) is decreased to reflect this, the agency's numbers are an underestimate.

In 2005, EWG published findings from a national analysis of tap water contamination based on data provided by public water suppliers from seven states, including Texas and California (EWG 2005). In our analysis, perchlorate levels above the level of quantification were considered significant; we found that over 26 million people in these seven states were served by water systems that had at least one perchlorate detection. Since this data was gathered from only seven states, we expect that the actual number of people in all 50 states who are served by public water systems with at least one perchlorate detection would be much higher.

EWG recommends that the agency consider any perchlorate detections above the level of quantification as significant; this would give a more accurate picture of the number of U.S. residents who are actually drinking perchlorate contaminated water.

The most recent studies show widespread exposures:

The notice in the Federal Register concludes with a section that discusses studies published since EPA adopted the NAS RfD for perchlorate. Since EPA adopted the NAS RfD of 0.7 ug/kg/day, several comprehensive studies have been published that shed new light on the degree of perchlorate contamination in the United States and the possible health implications of this contamination. In a fact sheet that accompanied the August 19th notice in the federal register, the agency notes, "The key focus of the re-evaluation has been consideration of exposure of infants and young children." EWG fully supports this renewed focus on the health threats that perchlorate presents for infants and young children. Research from the last few years has established that not only do infants and children have higher exposures to perchlorate when compared with adults, they are also more vulnerable to its toxic effects. A comprehensive epidemiological study from the CDC also calls into question the safety of the current RfD (Blount et al 2006b). Below, we list the evidence from recent research that confirms that infants and children are particularly at risk from perchlorate contamination of drinking water and why EWG believes that a maximum contaminant level (MCL) of no higher than one ppb is a necessary public health measure:

- A major CDC bio-monitoring study found that children ages six to 11 have higher exposure to perchlorate compared with adults (Blount et al 2006a)
- An FDA study that found perchlorate contamination of 74% of nearly 300 types of commonly consumed foods and beverages also confirmed that young children are exposed to more perchlorate, per unit of body weight, from contaminated food when compared with adults (Murray et al 2008)
- A recent study from CDC scientists found that powdered infant formula is widely contaminated with perchlorate (Schier et al 2009)
- Infants and children require more iodine on a body weight basis than adults and could therefore be more vulnerable to a thyroid toxin like perchlorate that inhibits iodine uptake by the thyroid gland (WHO 1998)
- Breast milk testing in the U.S. has revealed wide-spread contamination with perchlorate (Kirk et al 2005, Kirk et al 2007, Pearce et al 2007)
- Adequate levels of thyroid hormones are critical to normal brain development in infants and children and even subtle decreases in these hormones during these critical periods can have irreversible effects on cognition (Haddow et al 1999, Pop et al 1999)
- A major epidemiological study from the CDC finds that perchlorate exposures far below the current RfD are associated with significant changes in thyroid hormone levels in women (Blount et al 200b)

Each of these points is further discussed in detail below:

CDC bio-monitoring study finds that children have higher perchlorate exposure: In 2006, CDC scientists published the results of a major bio-monitoring study in which nearly 3,000 Americans ages six and older who are representative of the U.S. population were tested for perchlorate. Every single participant was found to have been exposed to perchlorate. Furthermore, children ages six to 11 had the highest exposure of any group tested, with urinary perchlorate levels that were 1.6 times higher on average than in adults (Blount et al 2006a).

As far as EWG is aware, there has been no testing of urinary levels of perchlorate in children under the age of six or infants in the United States. While this is a significant data gap, there is reason to believe that infants and young children may be among the most highly exposed groups in this country. Infants are at risk for high exposures to perchlorate due to widespread contamination of breast milk and infant formula, while young children are especially at risk due to widespread food contamination, especially of dairy products such as cow's milk. Widespread contamination of foods that infants and young children consume heavily coupled with the fact that children consume more food and water per unit of body weight than adults and their relatively small size in comparison with adults virtually guarantees that infants and young children have even higher perchlorate exposures than children in the six to 11 age group and adults.

FDA finds widespread perchlorate contamination of commonly consumed foods and beverages: In 2008, scientists from the FDA published the results of a study in which 285 commonly consumed foods and beverages were tested for perchlorate. Their results revealed widespread food contamination in the U.S.; perchlorate contaminated 74% of foods and beverages that were tested. The FDA scientists went on to estimate daily perchlorate exposures from contaminated foods and beverages (excluding tap water) and found that exposures were highest among two year olds. For this age group, perchlorate exposures from contaminated food and beverages ranged from 50 and 56% of the current EPA RfD of 0.7 ug/kg/day (Murray et al 2008).

The FDA findings are especially concerning because they show that children have high baseline exposures to perchlorate from commonly consumed foods and beverages. Overall, the FDA analysis found that children ages 10 and under are most highly exposed to perchlorate from contaminated foods and beverages. This is because children consume items from food groups that are heavily and consistently contaminated with perchlorate, especially dairy foods. In addition, their smaller size in comparison with adults means that, pound for pound, they are exposed to higher amounts of perchlorate than adults.

The FDA study, while concerning in itself, has even more profound implications for the children who live in any one of the 26 states in which perchlorate has been found in drinking water. EWG analysis finds that every proposed or final drinking water standard for perchlorate in the U.S. fails to protect two year olds from routine, daily, unsafe exposure when combined food and water exposures are considered. A two-year-old of average size could exceed EPA's current RfD by drinking water with just four ppb of perchlorate contamination (EWG 2008). A two-year-old of smaller size or with above average daily water consumption could easily exceed the RfD at even lower drinking water concentrations. The widespread food contamination by perchlorate leading to high baseline perchlorate exposures among children underscores the need to set an MCL of <1 ppb to minimize combined food and tap water exposure among children.

CDC scientists find perchlorate in infant formula: Earlier this year, CDC scientists published results of a study in which they tested 15 brands of infant formula; they found perchlorate contamination of all brands tested. The two most contaminated brands, made from cow's milk, accounted for 87% of the U.S. powdered formula market in 2000. The CDC team warned that mixing perchlorate-tainted formula powder with

tap water containing "even minimal amounts" of the chemical could result in exposures that exceed the current RfD. For example, they note that "reconstitution of PIFs (powdered infant formulas) with water containing perchlorate levels of at least 4 ug/l resulted in 26/48 (54%) dosing scenarios exceeding the RfD". In several other dosing scenarios, the formula was so heavily contaminated with perchlorate that formula consumption alone resulted in exposure levels above the RfD (Schier et al 2009). This study again underscores how easily vulnerable populations such as formula fed infants can exceed EPA's perchlorate RfD when cumulative exposures from contaminated food and tap water are considered.

Increased iodine requirements in infants, children suggest particular vulnerability to perchlorate: The World Health Organization (WHO) recommends that the average adult should consume 2 micrograms of iodine per kilogram of body weight per day to meet daily nutritional requirements. In contrast, WHO recommends that young children and infants ingest 3 and 7.5 times more iodine respectively per kilogram of body weight per day than non-pregnant adults (WHO 1998). This is because thyroid hormone production and turnover are greater in infants and children, compared with adults (Ginsberg et al 2007, Meikle 2007). High iodine requirements among infants and children may result in particular vulnerability to perchlorate related changes in thyroid hormone levels among these populations when compared with adults. This is because perchlorate interferes with iodine uptake by the thyroid gland, and since infants and children require more iodine that adults, any contaminant that disrupts this process may impact them more severely. This particular vulnerability is recognized by the National Academy of Sciences, which noted in a 2005 report that in "pregnant women, infants, and children, and people who have low iodide intake or pre-existing thyroid dysfunction, the dose [of perchlorate] required to cause a decrease in thyroid hormone production may be lower [than for non-pregnant adults]" (NAS 2005).

Studies reveal widespread perchlorate contamination of breast milk: In three recent studies from CDC and academic scientists, samples of human breast milk from different parts of the country were tested for perchlorate. Every single sample of breast milk in all three studies was positive for perchlorate (Kirk et al 2005, Kirk et al 2007, Pearce et al 2007). In addition, the average levels of perchlorate in breast milk in these studies would result in exposure above the agency's RfD for a significant numbers of breast-fed infants.

Further, in all three breast milk studies, a significant number of samples contained insufficient levels of iodine to meet the requirement of breast fed infants, meaning that not only would babies drinking this breast milk be exposed to hazardous levels of perchlorate by EPA's standards, but they would also be deficient in the iodine necessary to counteract the thyroid hormone lowering effects of the contaminant, thereby magnifying potential health effects of perchlorate in these infants.

While there is no question that perchlorate in both food and tap water contributes to breast milk contamination, minimizing perchlorate in tap water is an important overall way in which to decrease this contamination. There is presumably a relationship between the amount of perchlorate a woman consumes and the perchlorate concentration in her breast milk; decreasing her exposure by minimizing tap water contamination would most likely result in decreased perchlorate levels in her breast

milk. In addition, those infants who are fed both breast milk and powdered formula have multiple sources of exposure from contaminated breast milk, formula, and tap water used to reconstitute the formula. For all of these reasons, setting an MCL for perchlorate of <1 ppb would present a meaningful opportunity to reduce breast milk contamination and decrease perchlorate exposure among infants.

Infants and children particularly vulnerable to toxic effects of perchlorate: Adequate circulating levels of thyroid hormones are critical to maintaining normal metabolism in adults, but are especially important for infants and children. Infancy and early childhood are times of rapid growth and brain development, and any abnormal decreases in thyroid hormone levels during these critical periods may lead to inhibition of these processes. Infants and children may suffer from stunted growth and delays in intellectual development if they have inadequate levels of thyroid hormones. These impacts on growth and brain development can be long-term and irreversible. These concerns recently prompted Dr. Melanie Marty, Chair of EPA's Children's Health Protection Advisory Committee (CHPAC) to state in a November 3rd, 2008 letter to the agency:

> *"The life-long consequences of impaired brain development are sufficient to merit setting a protective MCL for perchlorate (CHPAC 2008)."*

Perchlorate exposures below RfD affect thyroid hormone levels: Lastly, EWG would like to address the agency's current RfD for perchlorate. On the last page of the notice, the agency states, "EPA agrees that additional important data have become available since the RfD was derived in 2005. However, EPA has evaluated the new data and has decided to make the regulatory determination based on the current RfD." EWG strongly disagrees with this finding and we urge EPA to revise the RfD to reflect the most current science. The current RfD was derived from the Greer study, which has been critiqued in the peer-reviewed literature and by a state regulatory agency, the Massachusetts Department of Environmental Protection.

A recent large-scale epidemiological study from CDC calls into question the actual safety of the agency's RfD (Blount et al 2006b). In September of 2006, CDC scientists published the first major epidemiological study using National Health and Nutrition Examination Survey (NHANES) data on the potential health impacts of chronic perchlorate exposure. Researchers found a statistically significant, dose-dependent association between perchlorate exposure and changes in thyroid hormone levels in all of the women in the study. In women with lower iodine levels (one third of American women), perchlorate exposure far below the EPA RfD was associated with significant changes in thyroid hormone levels. This is the first study to establish iodine insufficiency among women as a risk factor for perchlorate induced thyroid toxicity. This new discovery highlights a major deficiency in the Greer study; the iodine status of the 37 participants in that study is unknown.

In the Blount study, women were classified based on urinary iodine levels; those women with urinary iodine levels <100 ug/L had significant changes in both TSH and T4 associated with perchlorate exposures far below the current RfD. For a subset of women in the study with lower iodine levels [those with higher baseline thyroid stimulating

hormone (TSH) values], exposure to perchlorate as low as five ppb in drinking water was associated with increases in TSH that fall into the range of a medical condition called subclinical hypothyroidism. While there is disagreement about whether this condition should be treated in non-pregnant women, there is consensus in the medical community that pregnant women who develop this condition should be treated with thyroid hormone in order to ensure normal brain development of their fetus.

The results of the Blount study call into question the safety of the RfD and raise the possibility that perchlorate exposures in infants and children may be exerting a far more significant clinical effect that previously believed. As mentioned above, infants and young children are routinely exposed to perchlorate concentrations close to the current RfD from formula, breast milk, and food exposure. Even minimal drinking water contamination can lead to cumulative exposures that exceed the RfD among these vulnerable populations. The results from CDC's study, which did not include children under the age of 12, suggest that perchlorate exposures far below the current RfD may significantly affect thyroid hormone levels in adult women. If the results from the CDC study are extrapolated to vulnerable populations, millions of infants and children may be experiencing perchlorate-induced disruption in thyroid hormone levels during critical stages of brain development and growth at current levels of exposure, far below the current RfD.

EWG urges the agency to take the results from this CDC study into account and revise the current RfD to reflect these findings. In written responses to questions for the record from the House Committee on Energy and Commerce dated from 2007 (attached), Dr. James Pirkle, Deputy Director for Science at the National Center for Environmental Health and coauthor of the study, had the following comments regarding the study results: "We do not think confirmatory analysis is necessary to validate Blount's analysis of the NHANES data. Although we understand that conclusions of causality can rarely be drawn based upon a single study, when viewed within the context of the available clinical literature, the findings of the Blount study are consistent with causality" (Attached). In addition, an independent analysis of the NHANES data by scientists who work for California's Office of Environmental Health Hazard Assessment confirmed CDC's findings (Steinmaus et al 2007). Given the issues with the data in the Greer study and the strengths of the Blount study, the agency should place greater weight on the results from the Blount study in its determination.

Summary: There is a wealth of evidence from government and academic scientists that strongly suggests that infants and children not only have disproportionately high perchlorate exposure compared with adults, they are also more vulnerable to its toxic effects. Baseline perchlorate contamination of breast milk, powdered infant formula, and commonly consumed foods and beverages ensures that almost every infant and child in the U.S. will have multiple, daily sources of perchlorate exposure during critical periods of growth and brain development. However, for those children who live in states with perchlorate contamination of tap water, the additional exposure from the tap water can easily lead to cumulative exposures that exceed the agency's RfD. A decision by the agency to set an enforceable maximum contaminant level (MCL) of less than 1 ppb could benefit the health of millions of infants and children by decreasing cumulative perchlorate exposures.

Sincerely,

Anila Jacob, M.D., M.P.H.
Senior Scientist

Enc. Attachment 1

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Attachment 1:

Centers for Disease Control and Prevention's Responses to Questions for the Record From House Committee on Energy and Commerce

The Honorable Joe Barton and the Honorable John Shimkus

1. From what I know of the CDC/Blount study, your findings were much different than what was found in previous animal studies used by EPA and human data evaluated by NAS. In the conclusion of your study -- as well as in your testimony -- you claim that subsequent, confirmatory analysis is necessary to verify the findings of your study. What things do you believe need to be followed up on? Have you begun this process? How long do you expect this process to take? Can you be absolutely certain that further information gaps will not emerge when you conduct these studies?

Response:
The Blount study is the only study to focus on women with lower iodine levels (women with urine iodine levels less than 100 micrograms per liter). Thus, for this group, there were no previous results with which to compare the Blount results. NAS did not have any data to examine for this group of women, who account for about 36% of women in the U.S. population. Additionally, the Blount study has a very large sample size compared to previous work. The Blount results for men did not show an association between perchlorate levels and thyroid hormone levels. This finding for men was consistent with findings of other studies. For women with iodine levels greater than 100 micrograms per liter, perchlorate levels were associated with thyroid stimulating hormone (TSH) but not total thyroxine.

The Blount publication stated that "Further research is recommended to affirm these findings." We do not think confirmatory analysis is necessary to validate Blount's analysis of the NHANES data. Although we understand that conclusions of causality can rarely be drawn based upon a single study, when viewed within the context of the available clinical literature, the findings of the Blount study are consistent with causality. That is, we think that there is sufficient evidence from clinical studies that perchlorate directly causes decreases in thyroxine at high levels. The remaining scientific question is whether the direct effect extends to the levels of perchlorate found in the U.S. population. For that reason, we do think that another enhanced NHANES analysis of the relationship between perchlorate exposure and thyroid hormone levels in additional women and men should afford additional evidence regarding the strength of the association by providing more than twice the number of women and men to analyze, substantially improving statistical power.

This would help in the following analyses:
1) Examination of people who have increased exposure to other environmental factors that could affect thyroid hormone levels. For example, people who have higher thiocyanate exposure (from smoking or dietary sources) are important to examine further for a potential synergistic effect with perchlorate. Smoking, thiocyanate and nitrate were adjusted for in the Blount multiple regression analysis, and increasing the sample size will afford a greater ability to detect potential synergistic effects of these factors with perchlorate. It may also be useful

to examine differences in dietary intake in more detail.
2) Separate analysis for women of childbearing age which is important because of the vulnerability of the fetus.
3) Examination of factors that may account for differences in the observed associations between men and women.

In addition, we plan to examine the relationship of free thyroxine and thyroid autoantibodies to perchlorate levels to supplement and aid in understanding the results of the Blount study on total thyroxine and thyroid stimulating hormone.

A second NHANES study is in the planning stage currently. This study will examine about 50% more men and women than the first study. We hope to be able to combine data from the two studies resulting in about 2.5 times the study sample size we currently have. We cannot with confidence provide a firm finish date for the second study, but a reasonable estimate would be December 2008 to February 2009. We are confident that this additional study will provide more information about relationships between perchlorate exposure and thyroid effects at low population levels.

2. Some witnesses claim that your study is definitive and that further study of this issue is
not required. Yet, your study was unique in that the results that you observed were unexpected and different from everything else that previous studies have found. Do you believe it is a good scientific principle to do more study if the results from an existing study are new?

Response:
The Blount study is the only study to focus on women with lower iodine levels (women with urine iodine levels less than 100 micrograms per liter). Thus, for this group, there were no previous results with which to compare these results. In addition, a notable strength of the Blount study was its very large sample size (1,111 women) compared to previous work, affording more statistical power to detect potential effects than other studies.
The decision to conduct additional research is a case-by-case decision that is based on a number of factors including the significance of the original findings, the strength and statistical power of previous studies, study design methods and their limitations, and the likelihood that new research will advance scientific understanding. In the current case, we believe there is value in additional study, and we have itemized that value in answer to question 1.

3. You said in your testimony that the CDC/Blount study showed an "association" between urinary perchlorate and increased TSH and decreased total T4 in women 12 and older, who had urine iodine levels < 100 µg/L. It is possible people might assume then that perchlorate actually "caused" the thyroid changes. Was the CDC/Blount study designed to evaluate whether there is a causal relationship between low levels of perchlorate exposure and thyroid function? Can you please clarify the difference between "an association" and "causation?"

Response:
We begin by clarifying the difference between “an association” (referring to a pattern

in the data) and "causation" (referring to necessary antecedents to a health outcome). Observational data play an important role in establishing statistically significant associations, evaluating dose response gradients, evaluating the influence of potentially confounding variables, and providing information on coherency and consistency of findings. Causality is difficult to determine and relies on the best scientific assessment of the overall weight of evidence based on multiple important factors. We discuss these factors below. Causality is rarely determined on the basis of a single study, but by the weight of evidence from more than one study.

We find important parallels with the discussion of characterizing causation presented in the recent (2004) Surgeon General's Report on Smoking. That report concludes that inferences, whether about causality or statistical associations, are always uncertain to a degree, thus the goal (of that report) is to explain and communicate scientific judgments.

The design of the Blount study itself, referred to as cross sectional study, allows assessment of association, dose response gradient and some other factors useful in a weight-of-evidence evaluation. The Blount study, by itself, does not establish causation, but its findings are consistent with causation. Below, we discuss our assessment of the body of literature and the role that the Blount study plays.

The Blount study used NHANES data to examine the potential relationship between perchlorate levels and thyroid hormone levels in men and women. Establishing a causal relationship rests on weight of evidence of a 1) statistically significant association that is independent of other known variables that affect thyroid hormone levels, 2) a logical temporal association (i.e., exposure precedes effect), 3) biological plausibility and 4) coherency, specificity, and consistency of findings (including dose response effects). The Blount study provides information on the statistically significant association with variables available for analysis from NHANES data, and coherency and consistency of findings, but does not address a logical temporal association or biologic plausibility. Previous medical use of perchlorate has demonstrated that use of perchlorate as a drug directly causes decreases in levels of thyroxine. This direct causal effect is at a dose much higher than experienced by the general population and the Blount study is aimed at determining whether this effect extends to these lower perchlorate exposure levels.

The Blount study concluded that for women, there were statistically significant associations between perchlorate levels and total thyroxine and TSH that are coherent in direction and independent of other variables known to affect thyroid function. The "statistically significant association" found between perchlorate levels and total thyroxine levels means that, after adjusting for effects of other NHANES variables known to affect thyroid function (but not all variables which may impact thyroid function, e.g. some dietary factors), perchlorate levels independently predicted thyroid hormone levels, and this independent relationship was unlikely to be explained by chance.

After finding a statistically significant association that is independent of available variables known to affect thyroid function, the justification for a causal relationship relies mainly on other established evidence such as temporality, biological plausibility, and coherency and consistency of findings. Temporality requires that exposure takes place prior to the effect, in this case a change in thyroid hormone. The Blount study is cross-sectional, so it measured perchlorate levels and thyroid hormones at the same time and cannot determine if exposure occurred prior to effect. As noted above, concerning biological plausibility, it is known that high doses of

perchlorate inhibit the production of thyroxine, leading to lower total thyroxine levels and higher TSH levels. It is important to note that these exposures were far above those experienced by the NHANES cohort analyzed by Blount et al. Concerning coherency and consistency of findings, after adjustment for other variables known to affect thyroid function, increasing perchlorate levels were found in separate analyses to be associated with both decreasing total thyroxine levels *and* increasing TSH levels. This finding is cited in the paper as coherent in direction. By contrast, if increasing perchlorate had been associated with decreasing thyroxine and *decreasing* TSH, such a finding would not be coherent in terms of an effect on thyroid hormones.

Also relevant to coherency and consistency was the finding that women with lower levels of iodine (urine iodine levels of less than 100 micrograms per liter) had a statistically significant and more pronounced association of perchlorate with thyroid hormone levels. This finding is consistent with the mechanism of perchlorate inhibition of iodine uptake.

4. Did the CDC/Blount study show other known thyroid iodine uptake inhibiting agents as not having any effect or actually in one case showing a reverse effect from the recognized biological normal ranges? How can this be explained?

Response:
In the regression analysis examining TSH levels in women with urinary iodine levels greater than or equal to100 micrograms per liter, urinary levels of thiocyanate were negatively associated with TSH levels in the final regression model. (Note: This is *not* the group of women with lower iodine levels in whom the statistically significant and more pronounced association of perchlorate and thyroid hormone levels was found). As stated in the paper, a physiologic explanation for the sign of this coefficient for this group of women with higher iodine levels is unclear. The expected effect of thiocyanate on TSH would be for TSH to increase as thiocyanate increases because thiocyanate inhibits uptake of iodine into the thyroid. One possibility for the current finding is that smoking sources of thiocyanate may include exposures to other chemicals that have mixed effects on thyroid function.

5. In the CDC/Blount study, were fluctuations in thyroid hormones among women with low iodine outside normal ranges?

Response:
Most of the women in the Blount study were within the normal range. Many women with levels of thyroid hormones outside the normal range were excluded from analysis because these women were taking thyroid medications or had a known history of thyroid disease. Women taking thyroid medications had to be excluded because the thyroxine measurement would have been measuring the thyroxine they were taking for treatment.

Of the 1,111 women in the final regression analysis in the Blount study, 51 or 4.6% had levels outside the normal range. Of the 356 women with lower iodine levels who were in the final regression analysis, 11 or 3.1% had levels outside the normal range.

Thyroid hormone levels were measured at one point in time, so it was not possible to detect fluctuations in levels of an individual.

6. Do you believe that the CDC/Blount's thyroid study is sufficiently definitive for EPA Headquarters to rely on in moving forward with a regulatory determination on perchlorate as well as use by EPA Regions in developing site-specific risk assessments and cleanups?

Response:
As we state in CDC (2004), there are differences between both the process and goals of causal inference and decision making. We believe it is more appropriate for EPA to make this determination, based on its own scientific expertise and experience administering the specific statutes at issue.

7. In commenting on the CDC/Blount study, which you spoke of in your testimony, the American Thyroid Association (ATA) states that "[t]hese findings are intriguing, although several features of the study may limit the immediate application to guidelines for perchlorate exposure standards." The ATA also states that "further laboratory information is necessary before the implications of the findings can be understood." The Blount study itself says "further research is recommended to affirm these findings." Would you agree with the ATA and the Blount study in this regard, specifically that more study is needed and this study alone is not sufficient for setting a
regulatory standard, and could you please explain your answer?

Response:
Concerning regulation, as noted above, we defer to EPA on what is sufficient for setting an EPA regulatory standard.

The Blount publication stated “Further research is recommended to affirm these findings.” Another enhanced NHANES analysis of the relationship between perchlorate exposure and thyroid hormone levels in additional women and men should provide more than twice the number of women and men to analyze, substantially improving statistical power.

This enhanced statistical power would help in the following analyses:
1) Examination of people who have increased exposure to other environmental factors that could affect thyroid hormone levels. For example, people who have higher thiocyanate exposure (from smoking or dietary sources) are important to examine further for a potential synergistic effect with perchlorate. Smoking, thiocyanate and nitrate were adjusted for in the Blount multiple regression analysis, and increasing the sample size will afford a greater ability to detect potential synergistic effects of these factors with perchlorate. It may also be useful to examine differences in dietary intake in more detail.
2) Separate analysis for women of childbearing age which is important because of the vulnerability of the fetus.
3) Examination of factors that may account for differences in the observed associations between men and women.

In addition, we plan to examine the relationship of free thyroxine and thyroid autoantibodies to perchlorate levels to supplement and aid in understanding the

findings of the Blount study on total thyroxine and thyroid stimulating hormone. The ATA also suggested adding free thyroxine to the measurements in the Blount study.

8. Many of your studies look at the health effects of various things on people of differing socio-economic backgrounds. Did your recent perchlorate study extrapolate that information?

Response:
In the Blount study, race/ethnicity was a variable included in the regression models, but it was not a significant predictor of thyroid hormones. We did not examine a variable that tracked income.

9. Do you agree with Dr. Utiger that people with hypothyroidism should compensate for potential perchlorate exposures through greater dietary intake of iodine rich foods and vitamins?

Response:
We believe that people with hypothyroidism should be under the care of a physician for appropriate diagnosis and treatment. Adequate intake of iodine has previously been recognized as important for healthy thyroid function. The Blount study results would reinforce that recommendation for women.

The Honorable Albert Wynn

1. Are calculations for median estimated dose of perchlorate for adults about 1/10 of EPA's reference dose of 24.5 ppb.?

Response:
Yes; for adults, the median estimated dose (0.064 µg/kg day) is about 1/10th of the EPA reference dose (RfD) (0.7 µg/kg day).

2. Is it true that the 2006 NHANES study found measurable amount of perchlorate in all 2,820 survey participants and that the levels of perchlorate found in children were 65 percent higher than those found in adults?

Response:
Yes, all 2820 study participants had measurable perchlorate in urine, with the creatinine-adjusted perchlorate levels in children (6-11 years old) being 65% higher than the creatinine-adjusted perchlorate levels in adults (aged 20 years and older).

3. The CDC 2006 NHANES study was peer reviewed and tested multiple times and CDC testified that it has a high level of confidence in its findings. Does CDC agree that this study is based on the best available, high quality, peer reviewed science and that the data was collected by accepted methods?

Response:
Yes

4. CDC's second study examined the relationship between urine perchlorate levels and thyroid hormone level, 12 years old and up using perchlorate levels common in the US populations that are much lower than those used therapeutically. This study was also peer reviewed. Is CDC planning a second study to affirm these findings and expand on the study?

Response:
Yes. A second study is in the planning stages and will include at least as many men and women as the first study.

5. Is it true that CDC NHANES was peer reviewed and is in compliance with the information Quality Act, Pub. L. NO. 106-544?

Response:
The CDC National Health and Nutrition Examination Survey (NHANES) is in compliance with the Information Quality Act. NHANES is conducted by CDC's National Center for Health Statistics (NCHS). Statistical information is subject to quality
guidelines requiring federal agencies to adopt a basic standard of quality (including objectivity, utility, and integrity) and to incorporate quality criteria into agency information dissemination practices, issued by the Office of Management and Budget (OMB). Information dissemination practices of CDC's NCHS, including information dissemination associated with NHANES, comply with these OMB guidelines. In addition, the NHANES undergoes extensive review both within the Department and by OMB as a way to ensure the integrity of the data. NCHS is committed to integrating the
principle of information quality into every phase of information development, including creation, collection, maintenance, and dissemination. Detailed information about how NCHS assures the quality of information disseminated to the public is available on the NCHS Web site http://www.cdc.gov/nchs/about/quality.htm. The Information Quality Bulletin for Peer Review issued by OMB enhances the practice of peer review of government science documents. As specified in the Federal Register Notice on this policy (Vol. 70, No. 10, Page 2677), the Bulletin provides an exemption to the peer review requirement for, "Routine statistical information released by federal statistical agencies (e.g., periodic demographic and economic statistics) and analyses of these data
to compute standard indicators and trends (e.g., unemployment and poverty rates)." As
recommended by the Interagency Council on Statistical Policy, OMB considers NHANES to be covered by this exemption.

In the case of the 2006 analysis of the perchlorate data that is the subject of this question,
scientists in the National Center for Environmental Health of the CDC analyzed the data and wrote the two publications with the standard disclaimer on the publications that the
findings and conclusions in this report are those of the authors and do not necessarily represent the views of CDC. These publications were peer-reviewed by outside experts before being submitted for publication and also peer-reviewed by reviewers of the

publishing journals.

6. Various studies have shown that nursing and bottled fed infants could receive doses of
perchlorate from breast milk above EPA's RfD of 24 ug/L. Recent studies have determined the existence of perchlorate doses that were above EPA's RfD of 24 ug/L for infants drinking reconstituted formula made with water containing perchlorate (Baier-Anderson et al. 2006)(Kirk et al. 2005) and have also estimated that nursing infants could receive doses above the RfD even without considering the added exposure associated with EPA's preliminary remedial goal of 24 ug/L (Pearce et at. 2007 and Kirk et al. 2007). Please describe whether the Agency is considering the impact of perchlorate on nursing and bottle-fed infants and/or whether the Agency intends to utilize the above referenced studies or conduct its own studies on the impact
of perchlorate on nursing and bottle-fed infants.

Response:
We are actively investigating perchlorate exposure and thyroid function in both breast-fed and bottle-fed infants. We first developed high-quality analytical methods for measuring perchlorate in the following body fluids that are relevant to a baby's exposure: breast milk, amniotic fluid, cord blood, newborn dried blood spots, and newborn urine. Our ongoing collaborative studies of perchlorate exposure in infants are listed below:

• Perchlorate exposure and thyroid function in breast-fed and formula-fed infants. In collaboration with Dr. Water Rogan (National Institute of Environmental Health Sciences), we are assessing perchlorate exposure and thyroid function in infants (ages 1 – 12 months) who are consuming either breast milk or infant formula.
• Perchlorate exposure in lactating women and breast-fed infants in West Texas. In collaboration with Dr. Purnendu Dasgupta (University of Texas, Arlington), we are assessing perchlorate exposure in lactating mothers and their breast-fed infants. Perchlorate exposure may be higher in West Texas compared with the rest of the country because of prevalent consumption of well water with naturally-occurring perchlorate contamination.
• Characterizing perchlorate exposure in the developing fetus. In collaboration with Dr. Mark Robson (Rutgers University), we are measuring perchlorate in maternal urine, maternal serum, amniotic fluid, and cord blood. By measuring perchlorate levels in different fluids from the mother and the infant, we can better understand how a mother's exposure to perchlorate may lead to exposure in the developing fetus.
• Perchlorate exposure assessment in lactating women in San Diego. In collaboration with Dr. Phillip Alexander (University of California, San Diego) we are measuring perchlorate and iodine in breast milk and urine samples collected from women who drink tap water with perchlorate contamination below the California Public Health Goal level of 6 µg/L. Perchlorate levels in their drinking water will also be measured. This study will also examine the impact of a therapeutic dose of iodine on perchlorate clearance from the body.

• Perchlorate exposure assessment in lactating West Coast women. In collaboration with Kim Hooper (California EPA) we are measuring perchlorate in breast milk samples collected from nearly 250 women living in California and Washington. We plan to examine both the magnitude and variability in breast milk perchlorate levels. A dietary questionnaire is being used to identify potential sources of perchlorate from the diet.

September 4, 2009

Mr. Eric Burneson
Office of Ground Water and Drinking Water
Standards and Risks Management Division
Environmental Protection Agency
1200 Pennsylvania Avenue, NW, Mailcode 2822T
Washington, D.C. 20460

Re: Docket ID No. EPA-HQ-OW-2009-0297

Dear Mr. Burneson,

On behalf of our various organizations and our tens of thousands of members throughout the United States, we are writing to express our belief that the potential health impacts from exposure to perchlorate through drinking water are significant and that they warrant prompt regulation to protect public health and safety. Setting a drinking water standard will provide the U.S. Environmental Protection Agency (EPA) with a "meaningful opportunity for health risk reduction for persons served by public water systems." Consequently, EPA should move as quickly as possible to establish a more protective reference dose for perchlorate and then to promulgate a maximum contaminant level (MCL) for perchlorate that is no higher than one part per billion (ppb). We base this view on the scope of the contamination in drinking water supplies, exposure of the American population through other pathways, including food, and the most recent scientific studies that demonstrate serious health threats, even at low levels, to a larger portion of the population than previously recognized. These studies are based upon a much larger exposure data set than the studies upon which the current reference dose, and thus the entire regulatory regime, is based.

Perchlorate has been found in over 400 drinking water sources in 26 states, potentially affecting tens of millions of people. EPA's own data say that nearly 17 million people receive their water from public water systems where perchlorate has been found at levels exceeding 4 ppb. Were sampling routinely conducted with a detection limit of 1 ppb, that number would be much higher—particularly considering the estimated 20 million people in the Southwest who receive drinking water from the Colorado River.

In responding to this threat, **EPA must set a drinking water standard for perchlorate that protects the most vulnerable subpopulations, particularly pregnant women, fetuses, infants, and small children.** By interfering with the thyroid's ability to take up iodide, perchlorate can suppress the development of thyroid hormones critical to growth, development, and metabolism. This puts fetuses and children at particular risk for learning and behavioral disabilities; impaired gait, vision, and hearing; and even mental retardation. Exposure calculations must therefore consider the ingestion rates for these populations, and the reference dose should consider the particular vulnerabilities of these age groups. EPA should also include in its calculations low birth weight babies and underweight infants, as these populations may be extremely vulnerable.

EPA must also consider other exposure pathways and additional contaminants in the environment that impact thyroid function when establishing the MCL. Studies of perchlorate levels in food, including breast milk, show that the population is exposed through multiple pathways in addition to contaminated drinking water. EPA should determine potential aggregate exposures based on a broad range of contamination levels, and not just the mean, which was the basis for current estimates.

While data have also demonstrated a particular threat to the significant number of individuals, especially women of child-bearing age who are iodide deficient, the current modeling does not include this threat.

Given this widespread problem (CDC estimates up to 30% of women do not get sufficient dietary iodide), it is critical to take into consideration the potential for exposure to other thyroid-active agents. Consequently, EPA must consider the cumulative impact of perchlorate, other substances in the environment that inhibit the uptake of iodide by the thyroid, and inadequate supplies of iodide in American diets, all of which makes a stringent drinking water standard necessary to be truly health protective.

Moreover, a 1 ppb or lower MCL is supported by the most recent comprehensive studies, and these should be central to EPA's analysis. The industry-supported Greer study, which serves as the basis for EPA's current reference dose as well as California's current 6 ppb standard, consisted of a 14-day study of 37 healthy adults. In more recent years, Blount *et al* analyzed a nationally representative sample of 2299 U.S. residents, and they have documented anti-thyroid effects in a large population of women exposed to perchlorate at concentrations far lower than levels previously shown to have such effects. This study and subsequent data clearly justify promulgation of an even more protective MCL. It should be noted that California's Office of Environmental Health Hazard Assessment is in the process of reevaluating its Public Health Goal, on which the state MCL is based.

Finally, we wish to discourage EPA from again referring the perchlorate assessment to the National Research Council (of the National Academies of Sciences) for further review. The last time (2005) the NRC reviewed perchlorate, it overstepped its charge and recommended a reference dose. This usurped EPA's authority and made it difficult for the public to comment at a key phase in the regulatory process. Furthermore, NRC committees meet a handful of times over many months. A referral would delay the process without a great deal of additional review.

A perchlorate drinking water standard of no higher than 1 ppb would protect a large share of the American population currently at risk. Given the scope of the perchlorate contamination nationally, the multiple exposure pathways and other environmental contaminants impacting thyroid function and development, and the data demonstrating a serious health threat to a significant part of the country's population, EPA is obligated to establish such a drinking water standard. We applaud the agency's consideration of how to move forward to regulate this contaminant and urge you to take steps to establish a protective MCL as soon as possible.

Sincerely,

Andria Ventura
Program Manager
Clean Water Action
San Francisco, CA

Lenny Siegel
Executive Director
Center for Public Environmental Oversight
Mountain View, CA

Jeanne Rizzo, R.N.
President
Breast Cancer Fund
San Francisco, CA

Debra Hall
Founder
Hopewell Junction Citizens for Clean Water
Hopewell Junction, NY

Peter Strauss
President
PM Strauss & Associates
San Francisco, CA

Pamela King Palitz
Environmental Health Advocate and Staff Attorney
Environment California
San Francisco, CA

Ansje Miller
Policy Director
Center for Environmental Health
Oakland, CA

Jerry Bowling III
Behr VOC Area Leaders
Dayton, Ohio

Brian Moench, MD
President
Utah Physicians for a Healthy Environment

David W. Campbell
Secretary-Treasurer
USW Local 675
Carson, CA

Steven B. Pollack, Attorney
Executive Director
Blue Eco Legal Council
Northbrook, IL

Stephen M. Brittle
Don't Waste Arizona
Phoenix, AZ

Dvija Michael Bertish
Rosemere Neighborhood Association
Vancouver, WA

Luis Olmedo Velez
Executive Director
Comite Civico del Valle, Inc.
Brawley, CA

Kent Slowinski
Environmental Health Group
Washington, D.C.

Laura Olah, Executive Director
Citizens for Safe Water Around Badger
Merrimac, WI

Miriam Torres
Environmental Justice Coalition for Water
Santa Monica, CA

Chris Nidel, M.S., J.D.
Nidel Law, PLLC

Jane Horton
Mountain View, CA

Dave Ness, Jr
Bayport, MN

John Yelenick
SSAB - Rocky Mountain Arsenal
Denver, CO

Stephanie Smolen
Former resident
San Gabriel Valley, CA

Barry Kissin, Esq.
Member
Fort Detrick Restoration Advisory Board
Frederick, MD

Gail Shephard
Norwalk, CA

Bruce Oldfield
Professor, Geology
Broome Community College
Binghamton NY

Bob Spiegel
Executive Director
Edison Wetlands Association
Edison, NJ

Robert Stewart
Rural Community Assistance Project
Washington DC

Attachment 3

SCIENTIFIC SUPPORT DOCUMENTATION

FOR

CYCLE 9

REVISIONS OF NR 140.10

GROUNDWATER ENFORCEMENT STANDARD

&

PREVENTIVE ACTION LIMIT

RECOMMENDATIONS

Prepared by:

Lynda Knobeloch, Ph.D., Toxicologist

Wisconsin Department of Health Services
Division of Public Health

Revised February 2010

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ABBREVIATIONS

AA	= Atomic absorption spectrophotometry
cm	= centimeter
DHS	= Wisconsin Department of Health Services
DNR	= Wisconsin Department of Natural Resources
EPA	= Environmental Protection Agency
ES	= Enforcement Standard
g	= gram
HSDB	= Hazardous Substances Data Bank (a computerized database distributed by the National Library of Medicine)
ICP	= inductively-coupled plasma absorption emission spectrophotometry
IRIS	= Integrated Risk Information System (a computerized database distributed by the USEPA)
kg	= kilogram
L	= Liter
LC_{50}	= Lethal Concentration for 50% of Exposed Animals (inhalation exposure)
LD_{50}	= Lethal Dose for 50% of Exposed Animals (oral exposure)
LOAEL	= Lowest Observed Adverse Effect Level
LOEL	= Lowest Observed Effect Level
MCL	= Maximum Contaminant Level
MCLG	= Maximum Contaminant Level Goal
mg	= milligram
MRID	= Master Record Identification (number)
NOAEL	= No Observed Adverse Effect Level
NOEL	= No Observed Effect Level
PAL	= Preventive Action Level
ppb	= parts per billion
ppm	= parts per million
RfD	= Reference Dose
RSC	= Relative Source Contribution
UF	= Uncertainty Factor
USEPA	= United States Environmental Protection Agency
□g	= microgram (0.000001 gram)

INTRODUCTION

This document contains recommendations for the establishment of groundwater enforcement standards (ES) and preventive action limits (PAL) for five substances (Table 1).

The recommendations found in this document contain background information on the chemistry, uses, possible routes of human exposure and occurrence in Wisconsin groundwater of each chemical proposed for regulation. In addition, DHS has included a brief literature review of the important health effects, acute and chronic toxicity, and environmental fate of each substance. Based upon its review, DHS has calculated proposals for enforcement standards and preventive action limits using the risk assessment methods and assumptions provided by s.s. NR Ch. 160.

This statute directs the Department of Natural Resources (DNR) to identify and rank substances which may contaminate Wisconsin groundwater. The Department of Health Services (DHS) then develops recommendations for ES and PALs for these substances. Since 1986, Public Health Groundwater Quality Standards for 123 substances have been adopted under Chapter NR 140, the Wisconsin Administrative Code for Groundwater Quality.

TABLE 1. Recommended Enforcement Standards and Preventive Action Limits

Revisions (15)

Substance	Current ES ug/L	Proposed ES ug/L	Proposed PAL ug/L
1,3-Dichlorobenzene	1,250	600	120
1,3-Dichloropropene	0.2	0.4	0.04
Acetone	1,000	9,000	1,800
Boron	960	1,000	200
Carbaryl	960	40	4
Chloromethane	3	30	3
Dibutyl Phthalate	100	1,000	100
Ethylene Glycol	7,000	14,000	2,800
Methyl Ethyl ketone	460	4,000	800
Metolachlor	15	100	10
Metribuzin	250	70	14
Phenol	6,000	2,000	400
Prometon	90	100	20
Toluene	1,000	800	160
Xylene	10,000	2,000	400

New Standards (15)

Substance	Proposed standards ES ug/L	Proposed standards PAL ug/L
1,4-Dioxane	3	0.3
Acetochlor	7	0.7
Acetochlor ESA plus OXA	230	46
Aluminum	200	20
Ammonia (as N)	9,700	970
Chlorodifluoromethane	7,000	700
Chlorpyrifos	2	0.4
Dimethenamid	50	5
Dinitrotoluenes, Total Residues	0.05	0.005
Ethyl Ether	1,000	100
Manganese	300	60
Metolachlor ESA plus OXA	1,300	260
Perchlorate	1	0.1
Propazine	10	2
Tertiary Butyl Alcohol	12	1.2

STRUCTURE OF THE STANDARDS DOCUMENTS

Introduction: A brief description of the uses of the chemical, if any.

Chemical Profile: A list of the important properties of the substance, including chemical structure, molecular weight, specific gravity and synonyms.

Occurrence: Description of quantities estimated to enter the environment through industrial production and/or waste generation. Includes results of groundwater testing by state and federal agencies.

Human Exposure Routes: Description of observed and potential routes of human exposure, including the estimated contribution of drinking water to total exposure.

Toxicity

> **Acute.** LD_{50}s or LC_{50}s in rats and mice. The LD_{50} is the oral dose which causes lethality in half the exposed animals, while the LC_{50} is a corresponding air concentration from inhalation studies.
>
> **Subchronic.** Results of animal studies of durations from 90 days to 1 year.
>
> **Chronic.** Results of animal or human studies lasting longer than 1 year.
>
> **Carcinogenicity.** Results of animal or human studies on the ability of the chemical to cause cancer.
>
> **Mutagenicity.** Results of any short-term mutagenicity assays, such as the Ames test or the mouse lymphoma forward mutation assay, on the chemical.
>
> **Reproductive and Developmental Effects.** Reports of any effects of the chemical on reproduction or development.
>
> **Interactive Effects.** Results of experiments in which the chemical was administered in combination with other chemicals, or a discussion of concerns related to simultaneous exposure to other chemicals.

Environmental Fate: Description of the stability of the chemical in air, soil, surface water or groundwater, including the chemical's tendency to move from soil to groundwater.

Analytical Laboratory Methods: A brief description of the methods used to detect the chemical, including the current limit of detection or minimum reporting limit.

USEPA Regulatory Position: Availability of toxicity values published by the US EPA.

> **Maximum Contaminant Level (MCL).** The maximum allowable concentration of a chemical allowed in drinking water under the Safe Drinking Water Act. The MCL takes into account cost of remediation and analytical capabilities in addition to potential health effects.

Maximum Contaminant Level Goal (MCLG). The maximum allowable concentration of a chemical allowed in drinking water if only health effects are considered.

Lifetime Health Advisory (LHA). An EPA standard used for health-based guidance for substances for which MCLs and MCLGs have not been promulgated.

For noncarcinogens, the following parameters may be reported.

No Observed Adverse Effect Level (NOAEL). The highest dose of a chemical which produced no adverse effects in experimental animals or humans.

No Observed Effect Level (NOEL). The highest dose of a chemical at which no exposure-related effects were observed.

Lowest Observed Adverse Effect Level (LOAEL). The lowest dose which produced adverse effects in experimental animals or humans.

Lowest Observed Effect Level (LOEL). The lowest dose of a chemical at which no exposure-related effects were observed.

Uncertainty Factor (UF). Divisor applied to a NOAEL/NOEL or LOAEL/LOEL to obtain an acceptable human dose for daily exposure.

Reference Dose (RfD). The RfD is an estimate of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. RfDs are derived on the basis of a NOAEL, LOAEL or benchmark dose, with uncertainty factors applied to reflect limitations of the data used.

Drinking Water Equivalent Level (DWEL). Drinking water concentration derived on the basis of an RfD. Calculations use assumptions of a 70-kg adult human body weight, consumption of 2 liters of water a day and 100% exposure to the chemical occurring via drinking water.

For carcinogens, the following parameters may be reported.

Cancer Potency Factor. U.S. EPA concludes that a chemical is carcinogenic if animals form tumors in a dose-related manner upon exposure. Data on doses and numbers of tumors are entered into a complex computer program and an estimate of the slope of the line is called the cancer potency factor.
10^{-6} Risk Level. The concentration in water calculated to produce an excess cancer risk of 1 in 1,000,000 assuming lifetime exposure to a 70 kg person drinking 2 L/day of water.

Other Toxicology Information: Any other information pertinent to development of groundwater standards.

Recommendations and Conclusions: The following discussion briefly summarizes the procedure by which DHFS is directed to develop recommendations for enforcement standards and preventive action limits:

- If a single federal number exists for a substance, the federal number shall be the enforcement standard;
- If more than one federal number exists for a substance, the most recently established federal number representing the most current data shall be the enforcement standard.
- If no federal number exists for a substance, but there is a state drinking water standard, the state drinking water standard shall be the enforcement standard.
- If neither a federal number nor a state drinking water standard exists for a substance, [DHFS] shall develop a recommended enforcement standard using the methodology under s. 160.13."

In this process, DHS is directed to use a 'federal number' if one exists. In Ch. 160.01(3), the term "federal number" is defined as "a numerical expression of the concentration of a substance in water, established as:

(a) A drinking water standard or maximum contaminant level, by the federal environmental protection agency;
(b) A suggested no-adverse-response level, by the federal environmental protection agency; or
(c) For oncogenic substances, a concentration based on a risk level determination by the federal environmental protection agency or a concentration based on a probability of risk model determined by the national academy of sciences."

For those substances for which neither a federal number nor a state standard exists, DHS is directed to determine the acceptable daily intake for the substance and to convert that value into a numerical drinking water concentration by applying a daily water consumption rate of 1 L/day and a body weight of 10 kg (s. 160.13(2)(c)).

For non-carcinogens, if DHFS finds no serious flaws in the methodology used to derive the RfD, which constitutes a suggested no-observed-effect level from EPA (based on EPA's NOAEL or LOAEL and UF), DHFS is directed to use this value as a basis for setting the enforcement standard. If no RfD exists, or the RfD is determined by DHFS to be based on data that do not accurately reflect current scientific knowledge on the chemical, DHFS is directed to make an independent determination as to a NOEL or LOEL and a UF. In such cases, DHFS uses the assumptions that 1 L (0.9 qt) of this water is consumed by a 10 kg (22 lb) child, and that all (100%) of the chemical consumed by the child comes from drinking water. From this information, a drinking water concentration is calculated using the following formula:

$$\frac{\text{NOEL or LOEL (mg/kg/day)} \times 10\text{ kg} \times 100\%}{\text{UF} \times 1\text{ L}} = \text{ES}$$

For carcinogens, DHFS determines the concentration of the chemical at which lifetime consumption of the chemical would be assumed to cause one excess cancer case among 10,000 to 1,000,000 exposed persons as compared to unexposed persons. The concentration in water associated with a 1 in 10,000 to 1 in 1,000,000 (the "cancer risk") is determined by assuming a 70-year lifetime exposure, a 70-kg (154 lb.) human, 2 L (1.8 qt) water consumption per day and that 100% of exposure to that chemical comes from drinking water. The calculations are as follows:

$$\frac{70\text{ kg} \times \text{cancer risk}}{(\text{Cancer potency factor}) \times 2\text{ L/day}} = \text{ES}$$

Significant figures: All enforcement standards and preventive action limits have been rounded to contain no more than two significant figures.

USEPA CANCER CLASSIFICATIONS

The USEPA has classified environmental chemicals according to their suspected carcinogenicity. The classifications are as follows:

Group A--Human Carcinogen

Sufficient evidence in epidemiologic studies to support causal association between exposure and cancer.

Group B--Probable Human Carcinogen

Limited evidence in epidemiologic studies (Group B1) and/or sufficient evidence in animal studies (Group B2).

Group C--Possible Human Carcinogen

Limited or equivocal evidence from animal studies and inadequate or no data in humans.

Group D--Not Classified

Inadequate or no human and animal evidence of carcinogenicity.

Group E--No Evidence of Carcinogenicity for Humans

No evidence of carcinogenicity in at least two adequate animal tests in different species or in adequate epidemiologic and animal studies.

UNCERTAINTY FACTORS

As described in Ch. 160 Stats., an uncertainty factor is applied to a NOEL or LOEL to obtain a dose level or concentration assumed safe for long-term exposure to human populations. UFs are applied to account for sources of variability which might otherwise cause the observed concentration to be insufficiently protective. Among the most common sources of variability and uncertainty that are addressed by the use of UFs are biological variability among species, biological variability within a species, the lack of an experimental NOEL for a substance, the lack of a chronic health study for a substance, and the lack of data needed to adequately assess effects that could be anticipated based on knowledge of related chemicals or chemical structure, such as carcinogenicity or developmental toxicity.

Typically, uncertainty factors ranging from 10 to 10,000 are used. Low uncertainty factors are common in cases where there is an experimental NOEL based on a chronic health study, especially when the NOEL is derived from experience with human exposure. Higher uncertainty factors are more common when only limited or incomplete chronic or subchronic toxicity data are available, or when experimental data on endpoints of particular concern are unavailable.

METABOLITES

The Department of Health Services recognizes that many substances degrade in the environment to metabolites which may also contaminate groundwater. In the absence of adequate toxicological information, we believe that these breakdown products should be considered to have biological effects similar to those of the parent compound. Under this assumption, these breakdown products, or metabolites, can be regulated using existing groundwater standards which were developed based on the toxicological profile of the parent compound.

We recommend that when a metabolite is detected in the groundwater, and a groundwater standard exists for the parent compound but not for the metabolite, the existing groundwater standard should be used to regulate the sum of any parent and metabolite detected. If the metabolite weighs significantly more or less than the parent compound, a molecular weight conversion should be conducted since the toxicity assumption is based on molecular equivalency.

DNR HEARINGS PROCESS

DNR staff review the DHS recommended standards and hold public hearings for comment on the appropriateness of the proposed numerical standards. After completing the review process, public comments will be incorporated into the technical support document and any changes made will be written into the final text. The DNR Board, after reviewing the recommended groundwater standards document (including responses to public comments), will vote to accept or reject the original or modified risk assessments. Standards accepted by the DNR Board are sent to the Wisconsin State Legislature for their review and approval. Upon acceptance, these standards become law and are printed in the Wisconsin Administrative Code.

1,3-DICHLOROBENZENE (Revision)

1,3-Dichlorobenzene is one of three isomers of dichlorobenzene. It is a colorless liquid which is practically insoluble in water, but soluble in alcohol and ether. The three dichlorobenzene isomers are 1,2-dichlorobenzene, 1,3-dichlorobenzene, and 1,4-dichlorobenzene (also referred to as ortho-, meta-, and para-dichlorobenzene, respectively). Dichlorobenzenes are produced from the reaction of liquid benzene with chlorine gas in the presence of a catalyst.

CAS No	541-73-1
Molecular formula	C6H4Cl2
Molecular weight	147.1
Water solubility	123 mg/L
Physical state	Colorless liquid
Specific gravity	1.28
Synonyms	m-Dichlorobenzene, m-DCB, 2,6-Dichlorobenzene

Production of 1,3-dichlorobenzene in the United States during 1983 was less than 500 tons (IARC, 1999). 1,3-Dichlorobenzene is used in the production of herbicides, insecticides, pharmaceuticals, and dyes (IARC, 1999; U.S. EPA, 1981). Dichlorobenzenes are readily absorbed from the gastrointestinal tract. Following absorption by the gastrointestinal or respiratory tract, dichlorobenzenes are rapidly metabolized and eliminated in the urine. Excretion via exhaled breath or feces represents minor pathways. Dichlorobenzenes are not likely to bioaccumulate.

Occurrence

1,3 Dichlorobenzene is rarely detected in the environment. Federal surveys of drinking water supplies have failed to identify the meta isomer. Human biomonitoring studies have failed to identify this isomer in blood and breast milk samples, as well, although 1,2 and 1,4 dichlorobenzene were detected in the majority of samples.

Acute Toxicity

Rat LC50 = 500 mg/kg

Inhalation exposure to 1,3-dichlorobenzene can cause symptoms of sore throat, cough, drowsiness, nausea and vomiting. Ingestion causes gastric burning, diarrhea, nausea and vomiting. Concentrated product is irritating to skin, eyes and mucous membranes.

Chronic Toxicity

The oral toxicity database contains only one subchronic rat study (McCauley et al., 1995) and one developmental toxicity study that was reported in abstract form (Ruddick et al., 1983). The developmental toxicity study revealed no maternal or developmental toxicity at doses as high as 200 mg/kg-day. In the subchronic toxicity study, rats were exposed to doses of 9, 37, 147, or 588 mg/kg-day 1,3-dichlorobenzene for 90 days. Effects were seen in the thyroid, pituitary, and liver at all tested dose levels. This study was used by the EPA to derive an oral reference dose (EPA, 2003). The thyroid and pituitary effects seen in rats are assumed to be relevant to humans who may be chronically exposed to 1,3-dichlorobenzene. Little is known about the mechanisms responsible for the long-term oral toxicity of 1,3-

dichlorobenzene, but the available evidence suggests that hepatic metabolism to a reactive intermediate is involved.

Potential points of departure were derived by benchmark dose analysis of the thyroid and pituitary data. Modeled bench mark dose lower confidence limits (BMDLs) for thyroid (1.9 mg/kg-day) and pituitary lesions (3.3 mg/kg-day) were similar and since these effects may be related, the average of these values was chosen as the point of departure. The average BMDL of 2.6 mg/kg-day was divided by an uncertainty factor of 3000 to derive a draft reference dose of 0.9 ug/kg/day (EPA, 2003). However, this draft risk assessment was reviewed and withdrawn by the agency in 2006 at which time the EPA determined that there was too much uncertainty to support the development of a reference dose for this substance.

The federal Agency for Toxic Substances and Disease Regisry (ATSDR) has derived a minimal risk level (MRL) of 0.02 mg/kg/day for intermediate-duration oral exposure to 1,3-Dichlorobenzene. The intermediate oral MRL is based on benchmark dose analysis of incidences of pituitary lesions in male rats administered 1,3-dichlorobenzene by daily oral gavage for 90 days (McCauley et al. 1995). The resulting BMDL10 of 2.1 mg/kg/day was divided by an uncertainty factor of 100 (10 for extrapolating from animals to humans and 10 for human variability).

US EPA Cancer Classification

Class D: Not classifiable.

Both the International Agency for Research on Cancer (IARC) and the EPA have concluded that 1,2- and 1,3- dichlorobenzene are not classifiable as to human carcinogenicity.

Regulatory Summary

Reference Dose	None
MCL	None
MCLG	None
NOAEL	None
LOAEL	9 mg/kg/day
DWEL	3 mg/L
Lifetime Health Advisory	0.6 mg/L*
Cancer Class	D, not classifiable*

*2006 Drinking Water and Health Advisory Tables, US EPA Office of Water.

State Drinking Water or Groundwater Quality Standards and Guidelines

Arizona	620 µg/L
California	130 µg/L
Florida	10 µg/L
Idaho	600 µg/L
New Jersey	600 µg/L
Vermont	600 ug/L
Wisconsin	1,250 µg/L

Recommendations and Conclusions

The Department of Health Services recommends that the existing groundwater enforcement standard be lowered from 1,250 ug/L to 600 ug/L to reflect the EPA's Lifetime Health Advisory. Since 1,3-dichlorobenzene is not known to cause cancer or mutations, a 20% PAL is proposed.

Recommended enforcement standard	600 µg/L
Recommended preventive action limit	120 µg/L

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cis, trans 1,3-DICHLOROPROPENE (Revision)

1,3-Dichloropropene (DCP), or Telone, is used in 95% solutions as a soil fumigant for the control of root nematodes as follows: cotton and potatoes, 48%; vegetables, tobacco and sugar beets, 38%; floral, ornamental, fruit trees and miscellaneous, 14%. The principal US manufacturer is Dow Chemical. Dichloropropene is highly irritating to the skin, eyes and mucous membranes. Inhalation causes severe lung damage. The technical product is a mixture of the *cis* and *trans* isomers.

CAS No.	542-75-6
Molecular weight:	110.98
Physical state:	Liquid with chloroform-like odor
Water solubility:	2,700 mg/l at 25°C
Specific gravity:	1.22
Synonyms:	Dichloropropylene, chloroallyl chloride, Telone.

Occurrence

The cis- isomer has been detected in 35 of 5732 wells tested in Wisconsin. The trans- isomer has been detected in 31 of 5684 Wisconsin wells tested.

DCP has been found in 41 of 1,088 surface water samples analyzed and in 10 of 3,949 ground-water samples. Samples were collected in 800 surface water locations and 2,506 ground-water locations. DCP was identified in water samples from 13 states.

In occupational settings humans can be exposed to 1,3-dichloropropene both via inhalation and dermal exposures. These exposures are most often linked to field application of this chemical as a soil fumigant. The general public can be exposed via inhalation near source areas and from contaminated drinking water.

Toxicity

1,3-Dichloropropene is very toxic with an oral lethal dose of between 1 teaspoon and 1 ounce for an adult.

Stott et al. (1995) fed male and female Fischer 344 rats (50/sex/dose) a microencapsulated formulation of Telone II (96% 1,3-dichloropropene) in the diet at doses of 0, 2.5, 12.5, or 25 mg/kg/day for 24 months. Satellite groups of rats (10/sex/dose) were administered Telone II for 12 months. Standard bioassay data including body weights, food consumption, clinical chemistry, hematology, urine analysis, organ weights, pathology, and histopathology were collected. Body weights were decreased in a dose-dependent manner in treated animals. Decreases were statistically and toxicologically significant in both sexes at 25 mg/kg/day. Average organ weight changes in males and females were associated with decreased body weight. The only histopathology observed was in the forestomach which exhibited a mild basal cell hyperplasia of the mucosal lining. The incidence of forestomach lesions was statistically increased in both sexes at 12.5 mg/kg/day and higher. The forestomach hyperplasia is believed to be a manifestation of chronic irritation, which is consistent with the observation of primary dermal irritation (Nater and Gooskens, 1976) and other portal-of-entry effects from 1,3-dichloropropene exposure (Haut et al. 1996; Lomax et al. 1989; Linnett et al. 1988; Stott et al. 1988). Of the two critical effects, body weight decrease and chronic irritation (as evidenced by the forestomach hyperplasia), data from the most sensitive effect, chronic irritation, were used to develop the RfD.

Carcinogenicity

USEPA classification: B2, probable human carcinogen

In a National Toxicology Program (1985) study, F344 rats of each sex were gavaged with Telone II (92% 1,3-dichloropropene, 1% epichlorohydrin) in corn oil at doses of 0, 25, and 50 mg/kg 3 times/week while B6C3F1 mice of each sex were gavaged with 0, 50, and 100 mg/kg 3 times/ week for 104 weeks. In rats, elevated incidences of forestomach squamous cell papillomas and carcinomas and liver adenomas/carcinomas were observed at 50 mg/kg:. This dose level approximated a maximum tolerated dose level. Elevated incidences of forestomach papillomas and carcinomas; squamous cell carcinomas ; urinary bladder transitional cell carcinomas; and lung adenomas/ carcinomas were observed in mice.

In feeding studies, Fischer 344 rats (50/sex/dose) were administered Telone II (96% 1,3-dichloropropene without epichlorohydrin) in the diet at 0, 2.5, 12.5, or 25 mg/kg/day for 24 months (Stott et al., 1995) while B6C3F1 mice (50/sex/dose) received doses of 0, 2.5, 25, or 50 mg/kg/day for 24 months (Redmond et al., 1995). In rats, a statistically significant increase in the incidence of benign liver cell tumors was observed in males in the 25 mg/kg/day group. No increases in tumor incidence were observed in treated mice of either gender.

Quantitative estimate of carcinogenic risk from oral exposure (US EPA, 2000)

Drinking water unit risk	3E-6 per (μg/L) (NTP, 1985; urinary bladder tumors)
Oral slope factor	1E-1 per (mg/kg)/day (NTP, 1985; urinary bladder tumors)

Risk level vs Drinking Water Concentration

Risk level	Concentration
1 in 10,000	40 μg/l
1 in 100,000	4 μg/l
1 in 1,000,000	0.4 μg/l

Mutagenicity

Telone II was a direct acting mutagen in several Salmonella strains and is structurally related to other short chain halogenated hydrocarbons that are known oncogens. These include ethylene dibromide which produces forestomach squamous cell carcinomas in rats and mice after oral administration and vinyl chloride monomer which produces lung adenomas and adenocarcinoma in rats following inhalation exposure (US EPA, 2000).

Reproductive Effects

1,3-Dichloropropene has been evaluated for potential reproductive effects in rats and rabbits exposed via inhalation 6 hrs/day during gestation days 6-15 (rats) or 6-18 (rabbits). No evidence of a teratogenic or embryotoxic response was observed in either species at any exposure level up to 120 ppm tested (US EPA, 2000).

1,3-Dichloropropene was administered by intraperitoneal injections of 0 to 75 mg/kg/day for 5 days had no effect on sperm count, sperm morphology or testicular weights in mice.

Environmental Fate

Aquatic

If released to water 1,3-dichloropropene will be lost primarily due to volatilization (half-life about 4 hr in model river). Hydrolysis and microbial degradation may occur but these process are slow. Adsorption to sediment will not be an important pathway.

Atmospheric
When released into air, 1,3-dichloropropene will degrade by reaction with photochemically generated hydroxyl radicals.

Terrestrial
1,3-Dichloropropene is hydrolyzed in soil to form 3-chlorallyl alcohol. The half-life for this conversion ranges from 3 to more than 69 days.

Eight months after soil fumigant containing 1,3-dichloropropene was applied to muck and sandy loam soils in August during field studies, residues of 1.8 and 4.8 ppm of the cis and trans isomers were found in the muck soil and 0.03 and 0.39 ppm were found in the sandy loam.

Regulatory Summary

EPA regulatory information was obtained from IRIS. This database was last updated on 5/25/2000.

MCL and MCLG	None proposed
BMDL	3.4 mg/kg/day
Oral reference dose	0.03 mg/kg/day
Carcinogen Classification	B2, probable human carcinogen
Oral slope factor	0.1 per mg/kg/day

State Drinking Water Standards and Advisories

California	0.5 µg/L
Florida	0.4 µg/L
Massachusetts	0.5 µg/L
Maine	2.0 µg/L
Minnesota	2.0 µg/L
Wisconsin	0.2 µg/L

Recommendations and Conclusions

In 2000, the US EPA revised the cancer potency estimate for 1,3-Dichloropropene. The new slope factor equates a one-in-a-million lifetime cancer risk with a drinking water concentration of 0.4 µg/L. The previous slope factor equated the same risk to a water concentration of 0.2 µg/L. The Department of Health Services recommends that the groundwater enforcement standard and preventive action limit be revised to reflect this change in the federal risk assessment for 1,3-Dichloropropene.

Recommended Groundwater Enforcement Standard	0.4 µg/L
Recommended Preventive Action Limit	0.04 µg/L

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ACETONE (Revision)

Acetone is a popular industrial solvent for fats, oils, waxes, resins, rubber, plastics, lacquers, varnishes, rubber cements. It is also used in the manufacture of mesityl oxide, acetic acid, diacetone alcohol, chloroform, iodoform, bromoform, explosives, airplane dopes, rayon, isoprene, photographic films, storing acetylene gas it is useful for extraction of various substances from animal and plant tissues; in paint and varnish removers; purifying paraffin, and hardening and dehydrating tissues. Acetone is often found in the home in the form of nail polish or varnish remover.

Most acetone production in the USA is based on a process in which benzene and propylene are reacted to form cumene. Cumene is then oxidized with air to produce cumene hydroperoxide which is then decomposed or cleaved with an acid to yield phenol and acetone.

CAS No.	67-64-1
Chemical formula	C_3H_6O
Molecular weight	58.08
Physical state	Colorless, flammable liquid
Water solubility	Soluble
Specific gravity	0.7899 at 20°
Synonyms	Dimethylformaldehyde, dimethyl ketone, Propanone

Occurrence

There are currently over 5,000 groundwater samples with acetone detections in the DNR Groundwater Retrieval Network (GRN) monitoring database. Reported acetone detection levels range from 0.4 µg/L to 200,000 µg/L.

Human Exposure Routes

Human exposure often occurs as a result of occupational and home use of acetone as a solvent. Most exposure is likely via inhalation, however dermal absorption and incidental ingestion may also occur.

Toxicity

Acetone is moderately toxic with an oral lethal dose between 1 ounce and 1 pint for a 70-kg person (Gosselin et al, 1984) Toxic effects are similar to ethyl alcohol for equal blood levels, but the anesthetic potency is greater.

Groups of 10 male and 10 female F344/N rats were administered acetone in their drinking water at concentrations of 0, 2,500, 5,000, 10,000, 20,000, or 50,000 ppm for 13 weeks (NTP, 1991; Dietz et al., 1991). Time-weighted average doses for males were 0, 200, 400, 900, 1,700, and 3,400 mg/kg-day, respectively, and for females 0, 300, 600, 1,200, 1,600, and 3,100 mg/kg-day, respectively. Water consumption was decreased in high-dose males and in females given 20,000 and 50,000 ppm acetone. Mean final body weight of the high-dose males was 81% of the controls; body weights of the females were unaffected by treatment. At necropsy, statistically significant ($p <= 0.01$ or 0.05) increases kidney and liver weights were noted. In high-dose males, depressed sperm motility, caudal weight, epididymal weight and an increased incidence of abnormal sperm were seen. Males given the two highest concentrations of acetone had increases in the incidence and severity of nephropathy, indicating early onset and enhanced progression of the disease. The authors of the study identified kidney changes as the

most prominent chemically-related effect. Pigment deposition in the spleen was observed in 10/10 males in the 20,000 and 50,000 ppm groups compared with 0/10 controls. In summary, the testis, kidney, and hematologic system were identified by the study authors as target organs for male rats, with a LOAEL of 1,700 mg/kg-day and a NOAEL of 900 mg/kg-day.

Groups of 10 male and 10 female B6C3F1 mice were administered acetone in the drinking water at concentrations of 0, 1,250 (males only), 2,500, 5,000, 10,000, 20,000, or 50,000 (females only) ppm for 13 weeks (NTP, 1991; Dietz et al., 1991). The liver was identified as the target organ in males and females. The LOAELs for males and females were 4,900 and 11,000 mg/kg-day, respectively, and the NOAELs were 2,300 and 5,900 mg/kg-day, respectively.

A point of departure of 900 mg/kg-day was selected by the US EPA based on an increased incidence of mild nephropathy in male rats.

An overall uncertainty factor of 1,000 was applied to account for intra- and inter-species variation, use of a subchronic feeding study, and to account for a deficient database.

Carcinogenicity

Not classified.

In accordance with the Draft Revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999) *data are inadequate for an assessment of the human carcinogenic potential* of acetone.

Mutagenicity

Acetone did not show mutagenic activity when tested in *Salmonella typhimurium* strains TA98 and TA100 or in *Schizosaccharomyces pombe* strain P1 either in the presence or absence of liver homogenates (McCann et al, 1975; Abbondandolo et al, 1980; Maron et al, 1981; Hallstrom et al, 1981) or in cell transformation systems (Freeman et al, 1973; Rhim et al, 1974; Quarles et al, 1979; Norppa, 1981). Furthermore, acetone gave negative results in assays for chromosomal aberrations and sister chromatid exchange (Norppa et al, 1981; Tates and Kriek, 1981) DNA binding (Kubinski, 1981), point mutation in mouse lymphoma cells (Amacher et al, 1980), and transfection of E. coli CR63 cells (Vasavada and Padayatty, 1981). In one study, however, acetone was reported to produce chromosomal aberrations but not sister chromatid exchanges (Kawachi et al, 1980).

Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to acetone. Reproductive effects were assessed in pregnant mice exposed by gavage to acetone during gestation (EHRT 1987). The reproductive index was significantly reduced ($p=0.05$) (number of females producing viable litters/number of surviving females that were ever pregnant; 24/31 treated compared with 34/36 controls). In addition, acetone treatment significantly ($p<0.01$) increased the duration of gestation from 18.1 days in controls to 18.5 days in treated mice.

No effects were observed on the fertility of male Wistar rats treated with drinking water containing acetone at 1,071 mg/kg/day for 6 weeks (Larsen et al. 1991). The indices of fertility examined were successful matings with untreated females, number of pregnancies, number of fetuses, testicular weight, seminiferous tubule diameter, and testicular lesions. However, male Sprague-Dawley rats treated with 3,400 mg/kg/day acetone in drinking water for 13 weeks had significantly increased ($p<0.01$) relative testis weight, probably because body weight was reduced, and significantly ($p<0.05$) decreased sperm

motility, caudal weight and epididymal weight, and increased incidences of abnormal sperm (Dietz et al. 1991; NTP 1991). No testicular lesions were observed upon histological examination. Vaginal cytology examinations of the female rats revealed no effects. No effects on sperm morphology and vaginal cytology were observed in mice similarly treated with drinking water containing acetone at doses <4,858 mg/kg/day in males and <11,298 mg/kg/day in females.

Interactions:

Inhalation and oral administration of acetone potentiate the liver toxicity of carbon tetrachloride (Charbonneau et al., 1986).

Environmental Fate

Aquatic
If released into water, acetone is expected to biodegrade. It is readily biodegradable in screening tests, although data from natural water are lacking. It will also be lost due to volatilization. It's estimated half-life from a river is 20 hours. Adsorption to sediment should not be significant.

Atmospheric
In the atmosphere, acetone will be lost by photolysis and reaction with photochemically produced hydroxyl radicals. Half-life estimates from these combined processes are 79 and 13 days in January and June, respectively, for an overall annual average of 22 days. Therefore considerable dispersion should occur. Being miscible in water, wash out by rain should be an important removal process. This process has been confirmed around Lake Shinsei-ko in Japan (Kato et al, 1980). There acetone was found in the air and rain as well as the lake and the amount of acetone in the rain is what would be expected from the air concentration and solubility.

Terrestrial
If released on soil, acetone will both volatilize and leach into the ground. Acetone readily biodegrades and there is evidence suggesting that it biodegrades fairly rapidly in soils.

Bioconcentration
The recommended log octanol/water partition coefficient for acetone is -0.24 (Hansch and Leo, 1985) and therefore its potential for bioconcentration in fish is negligible. One experimental study of bioconcentration in adult haddock at 7-9 deg C (static test), resulted in a BCF of 0.69.

Regulatory Summary

USEPA regulatory information was obtained from IRIS. This computerized database was updated 07/31/2003 (oral RfD).

LOAEL	1700 mg/kg/day
NOAEL	900 mg/kg/day
MCL	None
MCLG	None
DWEL	None
Oral reference dose	0.9 mg/kg/day (revised from 0.09 mg/kg/day in 2003)
Uncertainty factor	1000
Cancer classification	Not classifiable

State Drinking Water Standards and Health Advisories

Maryland	3,600 ug/L
Massachusetts	700 ug/L
Minnesota	700 ug/L
New Hampshire	700 ug/L
New Jersey	6,000 ug/L
Wisconsin	1,000 ug/L
Vermont	700 ug/L

Recommendations and Conclusions

The Department of Health Services recommends revision of the groundwater standards for acetone to reflect the current federal reference dose. Since acetone is not known to have carcinogenic, mutagenic or reproductive effects, a 20% preventive action limit is proposed.

$$\frac{0.9 \text{ mg/kg/day} \times 10\text{-kg} \times 100\%}{1 \text{ liter/day}} = 9 \text{ mg/L}$$

Recommended groundwater enforcement standard:	9,000 µg/L
Recommended preventive action limit:	1,800 µg/L

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BORON (Revision)

Boron is an element that is commonly found in soil and rocks. In nature boron is rarely found as a pure element, but rather is found in combination with other substances to form borates, boric oxides or boric acid. Borates are used mostly in the production of glass. They are also used in the manufacture of leather tanners, fire-retardant materials, cosmetics, photographic materials, and in some high-energy fuels. Some pesticides used for cockroach control and wood preservatives also contain borates.

CAS No	7440-42-8
Atomic symbol	B
Atomic weight	10.81
Physical state	Solid
Density	2.35
Water solubility	Insoluble as pure element, soluble as salt or acid
Synonyms	None

Occurrence

Boron is widely distributed in nature. Its concentration in sea water averages about 4.5 mg/L. Fresh surface water samples collected in the United States had boron concentrations ranging from 0.001 to 5 mg/L with an average value of about 0.1 mg/L. Background boron levels in U.S. soils were reported at a geometric mean of 26 mg/kg with a maximum concentration of about 300 mg/kg.(ATSDR, 1992) According to the Wisconsin Groundwater Retrieval Network, 2,403 potable and non-potable wells in Wisconsin have been tested for boron. Of these wells, 113 potable wells and 1,986 non-potable wells had detects of boron with an average concentration of 29.7 µg/L and 7.4 µg/L, respectively (WDRN, 1997).

Human Exposure Routes

Human exposure to borates may occur through ingestion of food and water or contact with insecticides used to control roaches. Inhalation of boron-containing dusts or absorption of boron from cosmetics or medical preparations through mucous membranes or damaged skin. Occupational exposures may be higher. Workers may be exposed by inhalation of dusts or gaseous boron compounds. Dermal absorption may also occur but this is considered to be a minor exposure pathway.

Toxicity

LD_{50}(rat) Boric acid: 898 mg/kg; Borax: 642 mg/kg

Ingestion of large amounts of boron can be fatal. Infants who ingested formula accidentally prepared with 2.5% boric acid died within 3 days. It was estimated that the amount of boric acid consumed ranged from 4.51 to 14 g. Infants became lethargic and developed vomiting and diarrhea. Degenerative changes were seen in the liver, kidney, and brain. Acute exposure to dose levels of 895 mg boron per kg body weight as boric acid was not lethal in an adult.

Groups of 4 male and 4 female dogs were fed borax and boric acid in the diet for two years. The NOAEL was established at 8.8 mg B/kg/day which was the highest dose tested. In an additional study, dogs were fed doses of 29 mg B/kg/day for 38 weeks. At this dose, severe testicular atrophy and spermatogenic arrest occurred (Weir and Fisher, 1972). A recent review of pathological records from this study revealed evidence of similar histological abnormalities in three of four animals fed the control diet. The authors of the review concluded that this observation of testicular pathology in control animals rendered the study inadequate for use in quantitative risk assessment (Moore et al, 1997).

Groups of 35 male and 35 female rats were fed borax and boric acid in the diet for 2 years at boron-equivalent doses of 117, 350, and 1170 ppm (5.9, 17.5 or 58.5 mg B/kg/day). No treatment-related effects were seen at 5.9 or 17.5 mg/kg/day. The LOAEL was 58.5 mg B/kg/day, based on the following: significantly decreased testes weights and testes-to-body weight ratios; atrophied seminiferous epithelium; and decreased tubular size in the testes. Brain and brain-to-body weight ratios were also significantly decreased (Weir and Fisher 1972).

Schroeder and Mitchener (1975) reported a lifetime study in which mice were administered boron in drinking water at 8.1 mg B/kg/day. No effects were observed with regard to body weight, longevity or survival.

Carcinogenicity

Under the *Draft Revised Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 1999), data are inadequate for an assessment of human carcinogenic potential for boron.

Mutagenicity

No studies were located regarding genotoxic effects of boron in humans or animals. Results were negative in bacterial assays and in the *in vitro* mammalian assays.

Reproductive/Developmental Effects

Groups of 26-29 female rats were fed boric acid in gestational days 0-20 to assess the toxicity of boric acid in prenatal development and to determine the persistence of effects in a 21-day postnatal period. In the prenatal phase, decreased fetal body weight on gestational day 20 was observed at doses of 74 and 145 mg boric acid/kg/day (13 and 25 mg B/kg/day). A statistically significant increase in the number of fetuses per litter with shortened rib XIII was also observed at both doses. In the postnatal phase, a statistically significant increase in the number of pups per litter with shortened rib XIII was observed at 145 mg boric acid/kg/day (25 mg B/kg/day). The authors identified the prenatal NOAEL as 55 mg boric acid/kg/day (9.6 mg B/kg/day) and the postnatal NOAEL as 74 mg boric acid/kg/day (13 mg B/kg/day) (Price et al, 1996).

Boron exposure resulted in testicular atrophy and reduced sperm counts in dogs, rats and mice. In addition, reduced sperm counts have been observed among occupationally exposed men. These results suggest that reproductive toxicity may be an area of concern following human exposure to boron.

Environmental Fate

Since boron is an element, it is not subject to decomposition and can remain in the environment indefinitely. Its mobility is dependent on its chemical form. Boron salts and acids are water soluble and have a tendency to leach from soils into ground and surface water. Boron dusts and gases discharged into the atmosphere may be carried great distances before removal by wet or dry deposition.

Regulatory Summary

$BMDL_{05}$	10.3 mg/kg/day
UF	66
Reference dose	0.2 mg/kg/day
DWEL	7 mg/L

Lifetime health advisory	1 mg/L
MCL	None
Cancer class	D - Not classifiable

Confidence in the oral Reference Dose: High

EPA's confidence in the data base is high due to the existence of numerous studies, including several subchronic studies; chronic feeding studies in dogs, rats, and mice; a multigeneration study in rats; a continuous breeding reproductive study in mice; and developmental studies in rats, mice, and rabbits.

Existing Drinking Water Standards

Florida	630 µg/L
Maine	630 µg/L
Minnesota	600 µg/L
New Hampshire	630 µg/L
European Union	1,000 µg/L
Vermont	600 µg/L
Wisconsin	960 µg/L

Recommendations and Conclusions

The Department of Health Services recommends revision of Wisconsin's groundwater enforcement standard for boron from 960 to 1,000 µg/L. This revision will provide consistency with the federal advisory for public water supplies. Since boron has not demonstrated carcinogenic or mutagenic effects, a 20% preventive action limit is appropriate.

Recommended enforcement standard	1,000 µg/L
Recommended preventive action limit	200 µg/L

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CARBARYL (Revision)

Carbaryl is an N-methyl carbamate (NMC) pesticide, which was first registered in 1959 for use on cotton. In 2001, the Agency identified the NMC pesticides as a group which shares a common mechanism of toxicity. Therefore, the Agency was required to consider the cumulative effects on human health resulting from exposure to this group of chemicals when considering whether to establish, modify, or revoke a tolerance for pesticide residues in food, in accordance with the Food Quality Protection Act of 1996 (FQPA).

The insecticide carbaryl is used in agriculture to control pests on terrestrial food crops including fruit and nut trees, many types of fruit and vegetables, and grain crops; cut flowers; nursery and ornamentals; turf, including production facilities; greenhouses; golf courses; and in oyster beds. Carbaryl is also registered for use on residential sites (e.g., annuals, perennials, shrubs) by professional pest control operators and by homeowners on gardens, ornamentals and turfgrass.

Technical carbaryl is a white crystalline solid which melts at about 142°C and has no appreciable odor. Carbaryl is soluble in most polar organic solvents such as acetone and mixed cresols and is only slightly soluble in water (40 ppm at 30°C) and hydrolyses rapidly in alkaline solutions. It is stable to light, heat and acid with a melting point of 142°C, a low vapor pressure (0.005 mm Hg at 26°C) and no fumigant action.

CAS No.	63-25-2
Molecular Weight	201.23
Physical State	Odorless crystalline solid that varies from colorless to white or gray, depending on purity.
Water solubility	40 mg/L @ 30° C
Synonyms	Carbamine, Cekubaryl, Denapon, Devicarb, Dicarbam, Hexavin, Karbaspray, Nac, Rayvon, Septene, Sevin, Tercyl, Tricarnam, and Union Carbide-7744

Occurrence

The Wisconsin Department of Natural Resources reports that from 7/1/83 to 12/31/86 carbaryl was found in five well water samples. The highest detected level was 45 µg/L.

Monitoring of humans for carbaryl exposure is performed by analyzing urine for 1-naphthol. Preliminary results of a monitoring program indicate that 1-naphthol was detected at levels above 10 ppb in 19% of 265 samples from the general population with a maximum concentration of 0.24 ppm.

Toxicity

The acute toxicity of carbaryl varies by species and route of administration. Rats are more sensitive than dogs or monkeys. In humans, carbaryl is very highly toxic following absorption through the skin, highly toxic if ingested but only slightly toxic if inhaled. Depending on the route and degree of exposure, symptoms can include redness of the skin, convulsions, dizziness, labored breathing, nausea. unconsciousness, abdominal pain, vomiting, pupillary constriction, muscle cramps and excessive salivation.

Carbaryl is rapidly metabolized to several compounds which can build up in the liver and kidneys. Hydrolysis of carbaryl to the major urinary metabolites 1-napthyl glucuronide and 1-napthyl sulfate appears to be the primary metabolic pathway of carbaryl in man. Carbaryl has been shown to cross the placenta and accumulate in fetal brain, liver and ocular tissues.

In a subchronic neurotoxicity study (MRID 44122601), 12 Crl:CD(SD)BR rats/sex/group were administered technical carbaryl at doses of 0, 1, 10 or 30 mg/kg/day for 13 weeks. Cholinesterase (RBC, whole blood, plasma and brain) determinations were done on an additional three groups of five rats/sex/group at weeks 4, 8 and 13. Neurobehavioral screening, was performed prior to treatment and during Weeks 4, 8 and 13. There were no deaths during the study. There was an increased incidence of clinical signs of toxicity, including slight and moderate salivation and tremors, in the 30 mg/kg/day males and females. Multiple effects were seen in the 10 and 30 mg/kg/day males and females, including slight tremors, gait alterations, pinpoint pupils, increased salivation, reduced extensor thrust, decreased pinna reflex, reduced number of rearings, decreased vocalizations, decreased body temperature and decreased forelimb grip. Motor activity was significantly decreased in the 30 mg/kg/day males at Week 4 and the 30 mg/kg/day females at Weeks 4 and 8. The LOAEL for neurotoxicity was 10.0 mg/kg/day based on an increased incidence of FOB changes; the NOAEL was 1.0 mg/kg/day. The LOAEL for cholinesterase inhibition was 10.0 mg/kg/day based on statistically significant decreases in RBC, whole blood, plasma and brain cholinesterase; the NOAEL was 1.0 mg/kg/day.

Developmental

In a developmental neurotoxicity study the maternal toxicity LOAEL was 10 mg/kg/day based on decreased body weight gain, alterations in functional observation battery (FOB) measurements and red blood cell (RBC), plasma, whole blood and brain cholinesterase inhibition. The maternal NOAEL was 1.0 mg/kg/day. The developmental neurotoxicity LOAEL was 10 mg/kg/day based on a bilateral decrease in the size of the forebrain (Line A) in adult males (7.7-9.8%); a bilateral decrease in the length of the cerebella (Line F) in female pups (15-22%); and a bilateral increase in the length of the cerebella (Line F) in female adults (7.4-15%). The developmental NOAEL was 1 mg/kg/day (US EPA, 2002).

Carbaryl was found to be teratogenic to pups of pregnant beagle dogs fed 3.125, 6.25, 12.5, 25, and 50 mg/kg bw/day of carbaryl throughout gestation. Teratogenic effects observed at all but the lowest dose ranged from abdominal-thoracic fissures with varying degrees of intestinal agenesis and displacement to superfluous phalanges. Teratogenic effects were dose-related with no abnormalities noted in control pups.

A Union Carbide sponsored study confirmed that carbaryl produces teratogenic malformations in beagle dogs. In this experiment, pregnant beagle dogs were fed 2.0, 5.0 and 12.5 mg/kg/day of carbaryl in the diet from day 1 until weaning at 6 weeks. Birth defects including umbilical hernia, cleft palate, fat-like masses in the heart, intussusception of ileum into colon, extravasation of blood into the myocardium and unilateral microphthalmia were reported at the 5.0 and 12.5 mg/kg feeding levels. No defects were seen in control animals or animals dosed at 2.0 mg/kg.

Mutagenicity

Carbaryl was not mutagenic in *S. typhimurium* strains TA 100, TA 98, TA 1535, and TA 1537 in the presence of an aroclor induced rat liver microsome preparation. Carbaryl was not mutagenic with or without activation to *S. typhimurium* strains 1535, 1536, 1537 and 1538. USEPA cites one study in which carbaryl was claimed to be mutagenic to *S. typhimurium* after activation and that the 1-napthol metabolite is mutagenic without activation.

Carcinogenicity

US EPA Cancer Classification: L, Likely human carcinogen

Carbaryl is classified as "likely to be carcinogenic to humans," based on an increased incidence of vascular tumors in mice. Cancer risks are calculated by multiplying dietary exposure by the Q1*, or unit risk, which is a quantitative dose response factor, by the lifetime average daily dose. The Q* for carbaryl is 8.75×10^{-4} per mg/kg/day (US EPA, 2002).

Environmental Fate

Terrestrial

Carbaryl degradation varies with soil types in the order of clay loam> sandy loam> clay> loam> loamy sand. Carbaryl is moderately mobile in soil with decreased mobility related to increased organic carbon content of soils. The major environmental degradation product is 1-napthol.

Carbaryl's leaching characteristics, degradation rates and pathways make it unlikely to contaminate groundwater. Surface water contamination is possible due to spray drift and forest applications.

Aquatic

Carbaryl degrades in natural and sterilized natural water in 4 weeks and in sterilized distilled water in 12 weeks. This data indicates that chemical processes are most important in carbaryl aquatic metabolism with biological degradation of secondary importance.

In Little Miami River water, carbaryl was 95% degraded in one week and undetectable the second. In pond water (pH 7.5-7.8), carbaryl's half-life was between 14 and 21 days, and in creek water (pH 7.0-7.1) at between 34 and 50 days. Carbaryl movement into sediments appears to reduce its persistence in water. One week after a creek was treated with 1 ppm carbaryl, 47% of applied material was found in the bottom sediment vs. 30.2% in the water. From day 8 onward, measurable levels of carbaryl declined faster in creek water than sediment. A similar residue decline pattern was reported for carbaryl in pond water plus bottom sediment.

Bioaccumulation potential in aquatic food chains has not been assessed. One ecosystem study showed bioaccumulation factors of 140, 260, 300, 3600 and 4000 respectively for catfish, crayfish, snails duckweed, and algae. Carbaryl is extremely toxic to invertebrates and certain marine/estuarine organisms, extremely toxic to bees, moderately toxic to warm and cold water fishes. It has low toxicity to birds.

Regulatory Summary

MCL	None
MCLG	None
NOAEL	1.0 mg/kg/day (OPP RfD Tracking Report, 1997)
LOAEL	10.0 mg/kg/day (OPP RfD Tracking Report, 1997)
DWEL	0.4
Uncertainty Factor	100 (to account for the inter- and intra-species differences)
RfD	0.01 mg/kg/day (US EPA/Office of Water, 2006)
Cancer Classification	Likely
Cancer slope factor	8.75 x 10E-4/mg/kg/day

State drinking water standards and advisories

New York	29 µg/L
Vermont	70 µg/L
Wisconsin	960 µg/L

Recommendations and Conclusions

The Department of Health Services recommends revision of the enforcement standard, which is currently set a 960 ug/L to a level that will limit cancer risk to the 1-in-a-million lifetime risk level. Since carbaryl has carcinogenic effects, a 10% preventive action limit is proposed.

$$\frac{1 \times 10\text{-}6 \text{ lifetime risk} \times 70\text{-kg} \times 100\% \text{ exposure}}{8.75 \times 10\text{-}4/\text{mg/kg/day} \times 2 \text{ liters/day}} = 0.04 \text{ mg/L or } 40\ \mu\text{g/L}$$

Recommended Enforcement Standard:	40 µg/L
Recommended Preventive Action Limit:	4 µg/L

References

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CHLOROMETHANE (Revision)

Chloromethane is a gas which has been used as a refrigerant and propellant. Currently it is used as a chemical intermediate, principally in the production of silicones and tetramethyl lead. It is moderately toxic when inhaled causing central nervous system depression.

CAS No.	74-87-3
Chemical formula	CH_3Cl
Molecular weight	50.48
Physical state	Colorless, odorless gas
Density	0.9159
Water solubility	7,400 mg/L at 25 ° C
Synonyms	Methyl chloride

Occurrence

Chloromethane is produced naturally in seawater by the reaction of methyl iodide with chloride ions. It is also released from brush and forest fires and is a volatile compound released from cedar and cypress trees. These natural sources are believed to be responsible for most of the chloromethane found in the global atmosphere. Agricultural slash burning is believed to be the source of high levels of methyl chloride in the Amazon and this, in addition to coal combustion, is thought to contribute to high levels in parts of China. It is formed in the chlorination of drinking water and sewage effluent and is found in the effluent of some publically owned treatment works.

Chloromethane may be emitted as fugitive emissions and in wastewater during its production and use in the manufacture of silicones, agrichemicals, methyl cellulose, quarternary amines, butyl rubber, and tetraethyl lead. It is released in tobacco smoke which contains up to 1200 ppm chloromethane and turbine exhaust as well as in its use as a solvent, propellant, and in the manufacture of fumigants. Natural sources of methyl chloride include forest fires and the intentional burning of wood and plant material.

Most human exposure probably results from inhalation of chloromethane in the workplace where it is used in the manufacture of various synthetic materials, principally silicone. That National Institute for Occupational Safety and Health (NIOSH) has statistically estimated that 40,545 workers are exposed to methyl chloride in the USA. NIOSH has estimated that 4,534 workers are exposed to methyl chloride in the USA.

Evidence of human exposure has been documented. Mother's milk from 4 urban areas of the US - 2 of 8 samples positive detected not quantified. Methyl chloride was detected in expired air from a sample of 62 nonsmoking individuals.

Toxicity

Chloromethane is a relatively potent narcotic in humans. Inhalation exposures are associated with headaches, nervousness, sleepiness, unconsciousness, and in severe cases death. These symptoms may be delayed in onset and may increase in severity for up to 48 hours after the exposure has ended.

A 3 hour exposure to 200 ppm chloromethane resulted in a slight impairment of hand-eye coordination in male and female college students whose average age was 22 years.

Repko studied the effect of occupational exposure to chloromethane in 122 workers. The control group consisted of 49 unexposed workers in the same industry. The concentration of chloromethane in the ambient air of the exposed workers ranged from 7.4 to 70 ppm, with a mean concentration of 34 ppm (70 mg/m^3). A battery of behavioral, psychological and neurological tests, and an electroencephalogram (EEG) was done on each worker. An increase in ambient air concentration and an increase in urine acidity were correlated with a poorer performance on the behavioral tasks. There was no relationship between exposure and psychological or personality effects. Likewise, there was no effect on neurological tests or EEG records. However, chloromethane exposure was correlated with an adverse effect on the performance of cognitive time-sharing tasks and a significant increase in the magnitude of finger tremors.

Carcinogenicity

US EPA Classification: Not Classified

US EPA has determined that there is inadequate information on which to base a classification for carcinogenic effects. In their IRIS document for Chloromethane, EPA states the following, "The few studies that have examined methyl chloride's potential carcinogenicity in humans have failed to convincingly demonstrate any association, and in one instance even indicated a lower cancer incidence than expected in workers chronically exposed to methyl chloride in a butyl rubber manufacturing plant. In animals, the only evidence of carcinogenicity comes from a single 2-year bioassay, which found a statistically significant increased incidence of renal benign and malignant tumors only in male B6C3F1 mice at the high concentration (1,000 ppm), although two renal adenomas occurring in 225-ppm males may also be treatment-related. Neoplasia were not found at lower concentrations or at any other site in the male mouse, nor at any site or concentration in female mice or F-344 rats of either sex. Renal cortical tubuloepithelial hyperplasia and karyomegaly were also confined to 1,000-ppm male mice (IRIS Document accessed January 29, 2009).

Mutagenicity

Chloromethane was mutagenic to TK6 human lymphoid cells in vitro and caused an increased incidence of sister chromatid exchange and breakage of DNA strands. Chloromethane was mutagenic to *Salmonella typhimurium* with and without metabolic activation (US EPA, IRIS).

Reproductive Effects

Hamm et al reported a decrease in male fertility in F344 rats exposed to chloromethane. There was a significant decrease in the number of fertile matings in the males exposed to 475 ppm. Males exposed to 1,500 ppm were sterile. There was no effect on female reproductive ability.

Environmental Fate

Atmospheric

The dominant loss mechanism for chloromethane in the troposphere is upward diffusion although washout by rain may also be important. From the tropopause to about 30 km, both upward diffusion and reaction with hydroxyl radicals will be of approximately equal importance, and above 30 km in the stratosphere diffusion, reaction with hydroxyl radicals, and photo dissociation will have approximately equal weight. The surface half-life resulting from upward diffusion is 80 days (HSDB, 2000).

Aquatic

If chloromethane is released into water, it will be lost primarily by volatilization (half-life 2.1 hr in a typical river (HSDB, 2000).

Terrestrial

Land disposal will result in rapid volatilization to the atmosphere with small amounts leaching to groundwater. Landfill disposal may result in contamination of the groundwater where it may biodegrade very slowly (HSDS, 2000).

Regulatory Summary

MCL/MCLG	None
Lifetime health advisory	30 µg/l (US EPA, 2006)
Reference dose	0.004 mg/kg/day (US EPA, 2006)
Cancer classification	Not classifiable (US EPA, IRIS, 7/17/2001)

State Drinking Water Standards and Advisories

Connecticut	55 µg/L
Arizona	0.19 µg/L
Florida	2.7 µg/L
Maine	3 µg/L
Washington	1.3 µg/L
Wisconsin	3 µg/L

Recommendations and Conclusions

The Department of Health Services recommends revision of the groundwater enforcement standard from 3 to 30 ug/L. This change reflects modification of the US EPA's cancer risk assessment and lifetime health advisory chloromethane. Since chloromethane appears to have weak carcinogenic and mutagenic effects, we recommend that the preventive action limit continue to be set at the 10% level.

Recommended enforcement standard	30 µg/L
Recommended preventive action limit	3 µg/L

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DIBUTYL PHTHALATE (Revision)

Dibutyl phthalate (DBP) is used primarily as a plasticizer for polyvinyl acetate emulsions. Other uses include use as a plasticizer for other specialized vinyl formulations, varnishes and carpet backing and as an insect repellant for impregnation of clothing. Phthalates are used in a variety of personal care products. DBP was used in some nail polishes; all major producers began eliminating this chemical from nail polishes in the fall of 2006.

CAS No.	84-74-2
Chemical Formula	$C_{16}H_{22}O_4$
Molecular Weight	278.34
Density	1.0459 at 20°C
Solubility in Water	13 mg/L at 25°C
Odor	Slight characteristic ester odor
Odor/Taste Threshold in Water	No data
Synonyms	Di-n-butyl phthalate, phthalate acid dibutyl ester

Occurrence

Dibutyl phthalate has been found in the drinking water of six U.S. cities at concentrations ranging from 0.01-5.0 ppb. Concentrations of 0.1-1 ppb have been detected in surface water samples from 14 industrialized U.S. river basins and in urban runoff from U.S. cities at concentrations of 0.5-11 ppb.

Air concentrations in the U.S. range from 0 to 20 ng/m^3. Dibutyl phthalate is used as a plasticizer in food wrappings and food containers and it can migrate from the plastic packaging into foods. It has been estimated that 150 mg of dibutyl phthalate will migrate into 1 kg cheese with 15% fat content.

Daily air and water intake are estimated at 0-400 ng and 20 ng-10,000 ng, respectively. Data on food intake is insufficient, but exposure via this route may be orders of magnitude greater than air or water intake.

Toxicity

LD_{50} (rat, intramuscular injection): 8 g/kg
LD_{50} (mouse, oral): 9 g/kg

The No Observable Adverse Effect Level (NOAEL) used by the U.S. Environmental Protection Agency to develop a reference dose was derived from a 1953 study in which male Sprague-Dawley rats in groups of 10 were fed diets containing 0, 0.01, 0.05, 0.25, and 1.25% dibutyl phthalate for a period of 1 year. One-half of all rats receiving the highest dibutyl phthalate concentration died during the first week of exposure. The remaining animals survived the study with no apparent ill effects. There was no effect of treatment on gross pathology or hematology. While it was stated that several organs were sectioned and stained, no histopathologic evaluation was reported. In this study, a NOAEL of 0.25% dibutyl phthalate, converted to 125 mg/kg/day, was identified. EPA's IRIS data base indicates that newer studies are available and that the reference dose for dibutyl phthalate, which was developed in 1986, is currently under review.

A number of other studies have been performed since that time in which experimental animals were administered higher doses for shorter periods of time. Effects were noted in animal mortality, liver enzyme activity, red blood cell count, and other nonspecific toxic endpoints.

Carcinogenicity

USEPA Cancer Classification: Group D, Not classifiable

No adequate long-term toxicity or carcinogenicity studies in animals or man are available. Phthalate esters are known to induce peroxisomal proliferation in the liver of mice and rats. In general the longer chain and branched chain dialkylphthalates are more potent for the induction of peroxisomal proliferation than others. Many peroxisome proliferators have been shown to induce hepatocellular tumors when administered at high dose-levels for long periods to mice and rats despite being non-genotoxic. The mechanisms of induction of carcinogenicity by peroxisome proliferators may be complex but are considered to have a threshold. A variety of independent studies have shown that there are marked species differences in the sensitivity to chemicals that cause peroxisome proliferation. Rats and mice are extremely sensitive, hamsters show a less marked response while guinea-pigs, primates and man are less sensitive (EU Report, 2004).

Mutagenicity

Dibutyl phthalate did not induce mutations in a modified reverse mutation plate incorporation assay in *Salmonella* strains TA100 and TA98 at concentrations up to 1000 ug/plate in the presence or the absence of S9 hepatic homogenate. It was a weak direct-acting mutagen in a forward mutation assay in *Salmonella typhimurium*. Dibutyl phthalate was mutagenic in the mouse lymphoma forward mutation assay only in the presence of metabolic activation. In addition, dibutyl phthalate showed some evidence of clastogenic activity in Chinese hamster fibroblasts but was negative in human leukocytes.

Reproductive/Developmental Effects

DBP was added to the California Proposition 65 (1986) List of suspected teratogens in November 2006. It is a suspected endocrine disruptor.

In utero exposure to di(n-butyl) phthalate (DBP) leads to a variety of male reproductive abnormalities similar to those caused by androgen receptor antagonists. DBP demonstrates no affinity for the androgen receptor, but rather leads to diminished testosterone production by the fetal testis. A study by Thompson, et al. examined the onset and reversibility of DBP effects on the fetal testis and identify points in the cholesterol transport and steroidogenesis pathways affected by DBP. These investigators concluded that high-dose DBP exposure leads to rapid and reversible diminution of the expression of several proteins required for cholesterol transport and steroidogenesis in the fetal testis, resulting in decreased testosterone synthesis and abnormal male reproductive development (Thompson et al, 2004).

Interactive Effects

No information on the effects of simultaneous administration of dibutyl phthalate with another chemical were located.

Environmental Fate

Di-n-butyl phthalate is a ubiquitous pollutant due to its widespread use primarily as a plasticizer in plastics which are used throughout our society. It may be released into the environment as emissions and in wastewater during its production and use, incineration of plastics and migration of the plasticizer from materials containing it.

If released into water it will adsorb moderately to sediment and particulates in the water column. The compound will disappear in 3-5 days in moderately polluted waters and generally within 3 weeks in cleaner bodies of water. It will not bioconcentrate in fish since it is readily metabolized.

If spilled on land it will adsorb moderately to soil and slowly biodegrade (66 and 98% degradation in 26 weeks from two soils). Dibutyl phthalate is found in groundwater under rapid infiltration sites and elsewhere. It has been suggested that its tendency to form complexes with water-soluble fulvic acids, a component of soils, may aid its transport into groundwater. Although it degrades under anaerobic conditions, its fate in groundwater is unknown.

Regulatory Summary

NOAEL	125 mg/kg/day
LOAEL	600 mg/kg/day (increased mortality)
Uncertainty Factor	1,000
Reference dose	0.1 mg/kg/day (1986)
MCL	None
MCLG	None
DWEL	4.0 mg/L
Cancer classification	D, not classifiable

State Drinking Water Standards and Advisories

Minnesota	700 µg/L
New Jersey	700 µg/L
New York	50 µg/L
Wisconsin	100 µg/L

Recommendations and Conclusions

The Department of Health Services recommends revision of the groundwater standard from 100 µg/L to 1,000 µg/L. This revision is based on the current EPA reference dose for this substance. Since dibutylphthalate has shown some evidence of mutagenicity in in vitro assays a 10% preventive action limit is proposed.

$$\frac{0.1 \text{ mg/kg/day} \times 10 \text{ kg} \times 100\%}{1 \text{ liter/day}} = 1{,}000 \ \mu\text{g/L}$$

Recommended Enforcement Standard	1,000 µg/L
Recommended Preventive Action Limit	100 µg/L

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ETHYLENE GLYCOL (Revision)

Ethylene glycol is a colorless, viscous liquid widely used as an antifreeze/coolant for automobiles and as a chemical intermediate in the production of synthetic fibers and plastics. The compound is also used in inks and skin moisturizing creams. U.S. production and imports of ethylene glycol was 2.2 x 10^9 kg in 1988 (HSDB, 1991).

CAS No.	107-21-1
Molecular Formula	$C_2H_6O_2$
Molecular Weight	62.07
Physical State	Liquid at room temperature
Water Solubility	Absorbs twice its weight in water
Odor/Taste Threshold	No odor, sweet taste (no data on threshold)
Specific Gravity	1.114
Synonyms	1,2-ethanediol, glycol, glycol alcohol

Occurrence

Ethylene glycol can enter the environment when released in waste water or from disposal on land. It is rapidly degraded in soils and surface waters (see **Environmental Fate** below). No information concerning ethylene glycol concentrations in environmental media was located.

The primary mode of human ethylene glycol exposure is thought to be contact with skin and eyes resulting from industrial handling. The chemical is not volatile at room temperature, however, inhalation may be a problem if material is handled hot or if a mist is generated by violent agitation (Clayton and Clayton, 1981). Exposure to ethylene glycol can occur from dermal contact with antifreeze and coolants containing ethylene glycol.

Elimination of administered ethylene glycol occurs in two phases. The half-life of the first phase is about 3-5 hr and of the second phase is about 12 hr (Marshall, 1982). Administered ethylene glycol is primarily excreted as oxalate, hippurate and unchanged ethylene glycol in the urine (Riley, 1982).

Toxicity

LD_{50} (rat, oral):	8.54 g/kg
LD_{50} (mouse, oral):	13.7 g/kg

A number of incidents have been reported in which humans have accidentally ingested large quantities of ethylene glycol. The lethal dose for an adult is estimated to be about 1.4 g/kg or about 100 ml (Kirk-Othmer, 1980). The underlying basis for the toxicity of ethylene glycol can be divided into two major categories: one is tissue destruction due to deposition of calcium oxalate crystals and the second is the production of severe acidosis due to aldehyde, glycolate, and lactate production (Haddad and Winchester, 1983). At lower doses, ingestion of ethylene glycol can result in intoxication resembling that due to alcohol with ataxia, drowsiness, and slurred speech, possibly stupor, coma, and convulsions (Parry and Wallach, 1974).

In one study (DePass et al, 1986) investigators conducted 2-year studies using groups of approximately 30 rats/sex and 20 mice/sex fed diets providing ethylene glycol dosages of 0, 40, 200, or 1000 mg/kg/day. High-dose rats had increased mortality, neutrophil count, water intake, kidney hemoglobin and hematocrit, and chronic nephritis. Female rats exposed to 1000 mg/kg/day had mild fatty changes in the

liver. No adverse effects occurred at other doses in rats or at any dose in mice. Based upon this study, the USEPA determined a NOAEL of 200 mg/kg/day (US EPA, 1991).

In another study (Blood, 1965), groups of Sprague-Dawley rats (16/sex/group) were fed diets containing 0, 0.1, 0.2, 0.5, 1.0, or 4.0% ethylene glycol for 2 years. Male rats at 1.0 and 4.0% and females at 4.0% had increased mortality, decreased growth, increased water consumption, proteinurea, and renal calculi. There was an increased incidence of cytoplasmic crystal deposition in renal tubular epithelium at 0.5 and 1.0%. There were no effects on organ weights or hematologic parameters. The authors concluded that 0.2% (2000 ppm) was a NOEL for rats; the LOAEL was 0.5% (5000 ppm). Assuming that a rat consumes food equivalent to 5% of its body weight/day, the NOEL and the LOAEL in this study are equivalent to 100 mg/kg/day and 250 mg/kg/day, respectively. The EPA chose the former study to determine the NOAEL because of the greater number of animals and overall quality of the data.

Carcinogenicity

EPA classification: D, Not Classified (inadequate human and animal evidence of carcinogenicity).

Two two-year rat studies did not result in increased incidence of tumors in any treated group of animals.

Mutagenicity

No significant mutagenic activity was observed using in *Salmonella typhimurium* with or without microsomal activation (Clark, 1979).

Reproductive Effects

In a study by Maronpot et al., (1983), investigators found increased preimplantation loss and increased incidence of poorly ossified vertebral centra in offspring of rats treated at 1000 mg/kg in the diet on days 6-15 of gestation. No effects occurred at 40 or 200 mg/kg. In another, investigators reported that exposure of male and female mice to 1.0% ethylene glycol in drinking water for 14 weeks resulted in significantly fewer litters, decreased mean live pup weight, and decreased number of live pups/litter (Lamb et al, 1985).

In a 3-generation study in which rats were treated with 0, 40, 200, or 1000 mg/kg/day in the diet (De Pall et al., 1986), no treatment-related effects were observed. Finally, investigators treated rats with gavage doses of 0, 1250, 2500, or 5000 mg/kg/day and mice with 0, 750, 1500, or 3000 mg/kg/day on days 6-15 of gestation (Price et al., 1985). The percentage of litters with malformed fetuses increased in a dose-related manner in both species at all doses. There was a dose-related increase in post-implantation losses per litter in both species, but it was significant only in high-dose rats. Maternal body weight gain was decreased at all doses in rats and at the two higher doses in mice.

Interactive Effects

Magnesium and ethanol have been found to inhibit ethylene glycol metabolism, thus protecting against the compounds toxic effects (HSDB, 1991).

Environmental Fate

Atmospheric
If ethylene glycol volatilizes, it will react in the atmosphere with hydroxyl radical with a half-life of about 1 day (HSDB, 1991).

Aquatic

Ethylene glycol will readily biodegrade in surface water with a half-life of approximately 3 days. Although no data are available on ethylene glycol persistence in groundwater, should the compound leach into the groundwater, biodegradation may occur (HSDB, 1991).

Terrestrial

No data are available that report the fate of ethylene glycol in soils; however, by analogy to its fate in water, biodegradation is probably fast and the dominate removal mechanism (HSDB, 1991).

Regulatory Summary

NOAEL	200 mg/kg/day
UF	100 (10 for animal/human extrapolation, 10 to account for sensitive humans)
RfD	2 mg/kg/day
DWEL	70,000 µg/L
Lifetime HA	14,000 µg/L
MCL	None
MCLG	None
Cancer Class	D, not classifiable

State Drinking Water Standards and Advisories

Arizona	5,500 µg/L
California	14,000 µg/L
Florida	14,000 µg/L
Massachusetts	14,000 µg/L
Minnesota	10,000 µg/L
New Hampshire	7,000 µg/L
New Jersey	300 µg/L
Vermont	7,000 µg/L
Wisconsin	7,000 µg/L

Recommendations and Conclusions

The Wisconsin Department of Health Services recommends revision of the groundwater enforcement standard from 7,000 µg/L to 14,000 µg/L. This change reflects the most current federal risk assessment for this substance. Because ethylene glycol is not known to have carcinogenic or mutagenic effects, a 20% preventive action limit is proposed.

Recommended Enforcement Standard:	14,000 µg/L
Recommended Preventive Action Limit:	2,800 µg/L

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METHYL ETHYL KETONE (Revision)

Methyl ethyl ketone is a common industrial solvent and fabric coating. It is also used as a flavoring and fragrance agent in candy and perfume. Total U.S. production in 1999 was reported to be 260,000 metric tons.

Large quantities of methyl ethyl ketone are used as a solvent especially in the coating industry. MEK is discharged into the atmosphere from this and other industrial uses. It is also discharged in waste water. High atmospheric levels are associated with photochemical smog episodes although it is generally absent from ambient air. It is formed as a result of the natural photooxidation of olefinic hydrocarbons emitted by automobiles, etc.

CAS no.	78-93-3
Chemical Name	2-Butanone
Molecular Formula	$CH_3COCH_2CH_3$
Molecular Weight	72.1
Physical State	Colorless, flammable liquid with fragrant mint-like odor
Water Solubility	353 g/L at 10°C
Specific Gravity	0.805 at 20°C
Synonyms	2-Butanone, Ethyl Methyl Ketone, MEK, Methyl Acetone

Occurrence

Methyl ethyl ketone is an infrequent contaminant in drinking water supplies. In a federal survey of groundwater supplies, less than 5% contained detectable levels (Dyksen, 1982). In Wisconsin, MEK has been found in 18 of 4,893 wells tested in Wisconsin. The highest level detected (5,100 ug/L) was in a sample collected from a monitoring well at a county landfill (WDNR, 1990).

MEK may be found in soil and water in the vicinity of hazardous waste sites. It has also been detected as a natural component of tobacco smoke and in numerous foods, including: raw chicken breast, milk, nuts (roasted filberts), cheese (Beaufort, Gruyere, and cheddar), bread dough and nectarines at concentrations ranging from 0.3 to 19 ppm (ATSDR, 1992; HSDB, 1999; WHO, 1992). WHO (1992) estimated levels of daily MEK intake from different sources as follows: foodstuffs – 1,590 µg/day; drinking water – 3.2 µg/day; rural outdoor air – 36 µg/day; urban outdoor air - 760 µg/day; and tobacco smoke - 1,620 µg/day. NIOSH has estimated worker exposure at 3,031,000 (NIOSH,). People are primarily exposed to methyl ethyl ketone in occupational atmospheres, especially related to coatings, since it is a common solvent; and in polluted atmospheres, particularly during photochemical smog episodes. It is a component of many foods. Non-alcoholic beverages, ice cream, candy and baked goods can contain as much as 70, 270, 100 and 100 ppm MEK, respectively (Furia, 1975).

Toxicity

MEK is similar to, but more irritating than, acetone. Concentrations above 200 ppm are irritating to mucous membranes and eyes.

Evidence that MEK may induce solvent-like effects such as peripheral or central nervous system changes in humans is restricted to a small number of case reports and occupational studies. Three case studies demonstrated adverse effects among men who had repeated, high level exposures to MEK. In 1992, Seaton et al. reported that a maintenance fitter was exposed to MEK for 2–3 hours/day for 12 years.

Exposure was via both dermal and inhalation routes. The worker developed slurred speech, cerebral ataxia, and sensory loss in his arms and on the left side of his face. Nuclear magnetic resonance imaging showed severe cerebellar and brainstem atrophy; however, nerve conduction studies were normal. A survey of his work area revealed peak MEK concentrations in excess of 5,000 mg/m^3 during some operations and 10-minute average concentrations of approximately 900 mg/m^3.

In 1995, Callender reported that a 31-year-old male engineer developed severe chronic headache, dizziness, loss of balance, memory loss, fatigue, tremors, muscle twitches, visual disturbances, throat irritation, and tachycardia after working for 7 months in a quality assurance laboratory where he was exposed daily to MEK and fumes from burning fiberglass material. Personal protection equipment and formal safety training were not provided. Based on a physical examination, neuropsychological tests (Poet Test Battery and WHO Neurobehavioral Core Test Battery), electroencephalographic tests, evoked brain potential tests, nerve conduction velocity tests, rotational and visual reflex testing, vestibular function testing, and SPECT and MRI scans of the brain, the patient was diagnosed with chronic toxic encephalopathy, peripheral neuropathy, vestibular dysfunction, and sinusitis. Information concerning the exposure levels and subsequent possible progression or regression of these conditions was not provided.

In a third case, a 27-year-old man developed multifocal myoclonus, ataxia, and postural tremor after occupational exposure (through dermal and inhalation pathways) over a 2-year period to solvents containing 100% MEK (Orti-Pareja et al., 1996). The actual exposure levels are unknown. The patient reported symptoms of dizziness, anorexia, and involuntary muscle movement, beginning about one month prior to admission. Neurological examination confirmed multifocal myoclonus, ataxia, and tremor. Symptoms of solvent toxicity disappeared after cessation of exposure and treatment with clonazepam and propranolol. Symptoms did not recur after withdrawal of the drugs.

Prolonged exposure may produce CNS depression, however, no adverse health effects have been related to chronic exposure to low atmospheric concentrations in the workplace. Workers exposed by inhalation (300-600 ppm) and by skin contact developed dermatitis and a numbness in the extremities. Headache, mild vertigo, and diminished vision were noted (Clayton, 1981).

Three cases of polyneuropathy occurred in shoe factory workers exposed to combined methyl ethyl ketone and acetone or toluene vapors concentrations below 200 ppm. Skin absorption also occurred. Although not highly neurotoxic itself, MEK may potentiate substances known to cause neuropathy (Dyro, 1978).

In the 1955 study used by the USEPA for deriving an oral reference dose, LaBelle and Brieger (1955) exposed 25 rats to air containing 235 ppm of methyl ethyl ketone for 7 hours/day, 5 days/week for 12 weeks. No effects were observed, but only a few parameters were measured.

Carcinogenicity

USEPA Classification: D, Not classifiable as to human carcinogenicity

According to EPA's draft revised cancer guidelines (U.S. EPA, 1999), the hazard descriptor "*data are inadequate for an assessment of human carcinogenic potential*" is appropriate for MEK because cancer studies of humans chronically exposed to MEK are inconclusive, MEK has not been tested for carcinogenicity in animals by the oral or inhalation routes, and the majority of short-term genotoxicity testing of MEK has demonstrated no activity (EPA, IRIS, updated 2003).

Mutagenicity

The ability of methyl ethyl ketone to produce mutations has been studied in cultured mouse lymphoma cells (Microbiological Assoc, 1984), *Salmonella* and *Escherichia coli* bacteria, *Saccharomyces cerevisiae* tester strain JD1 and in cultured rat liver cells (Shell Sittingbourne Research Center, 1982). All studies done to date have failed to demonstrate a mutagenic effect.

Reproductive/Developmental Effects

Cox et al. (1975) conducted a multigeneration reproductive and developmental toxicity study of 2-butanol in which weanling FDRL-Wistar stock rats (30/sex/group) were given 2-butanol in drinking water at 0, 0.3, 1, or 3% solutions and a standard laboratory ration *ad libitum*. Weekly food consumption, fluid intakes, and body weights were measured to determine the efficiency of food utilization and to calculate the average daily intake of 2-butanol. The average daily intake of 2-butanol as reported by the authors for the initial 8 weeks of the study (intake was not reported for subsequent weeks) was 0, 538, 1,644, and 5,089 mg/kg-day (males) and 0, 594, 1,771, and 4,571 mg/kg-day (females) for the 0, 0.3, 1, and 3% solutions, respectively. Decreased F0 parental weight gain prior to mating, decreased F1A pup survival, and decreased F1A pup weights among survivors at postnatal days 4 and 21 were observed in the groups exposed to 3% 2-butanol in the drinking water. At the 2% level, decreased maternal body weight gain during the second pregnancy of the F0 dams, decreased F1B fetal weights when pregnancy was terminated at gestation day 20, and decreased F2 pup weights at postnatal days 4 and 21 were observed. At the next lower dose level (1%), reduced F1A pup weight was observed, but the reduction was not seen in subsequent generations at the same exposure level. Developmental endpoints were not affected at the 0.3% exposure levels in any of the generations. 2-Butanol increased the incidence of kidney lesions in F1A generation rats that were exposed from gestation continuing through 12 weeks after birth, mating, and gestation and lactation of the F2 generation. No other treatment-related histopathology was observed.

Environmental Fate

Aquatic
When released into water, methyl ethyl ketone will evaporate into the atmosphere with expected half-lives of 3 and 12 days in rivers and lakes, respectively. It will also biodegrade slowly in both fresh and salt water. No information is available concerning its fate in groundwater but biodegradability studies in anaerobic systems suggest that it may degrade slowly after a long acclimation period. Adsorption to sediment will not be a significant loss process (HSDB, 1988).

Atmospheric
When released into the atmosphere, MEK will degrade principally by reaction with photochemically produced hydroxyl radicals. Under photochemical smog situations, degradation may be slightly faster (HSDB, 1988).

Terrestrial
When spilled on land, methyl ethyl ketone will partially evaporate into the atmosphere and partially leach into the ground. Its degradation in soil is unknown (HSDB, 1988).

Bioconcentration
No information concerning the bioconcentration of methyl ethyl ketone was found in the literature. However, it has a very low octanol water partition function which indicates that bioconcentration will not be a significant transport process.

Regulatory Summary

Reference Dose:	0.6 mg/kg/day
Point of Departure:	639 mg/kg/day(EPA 635/R-03/009 Toxicological Review of Methyl Ethyl
UF	1000 (10 each for intra- and interspecies variability, 10 for use of data subchronic study)
MCL/MCLG	None
LHA	4 mg/L
Cancer classification	D, not classifiable

In 2003, the US EPA selected the reproductive and developmental drinking water study of 2-butanol in rats (Cox et al., 1975) as the principal study for deriving an RfD for MEK. This study also served as the principal study for the RfD of 0.6 mg/kg-day that was previously entered in the IRIS database in 1993. Benchmark dose modeling of F1A pup body weight data at postnatal day 21 was used to develop a point of departure of 657 mg/kg/day for 2-butanol (i.e., the lower 95% confidence limit on a dose producing a mean 5% decrease in body weight compared with control). Adjustment to account for differences in the molecular weights of 2-butanol and MEK yielded a point of departure of 639 mg/kg-day. The agency applied a combined uncertainty factor of 1,000 to derive the chronic RfD. This RfD is the same as the RfD from the previous 1993 IRIS assessment. EPA's confidence in the principal study is listed in the IRIS database as medium to low.

State Drinking Water Standards and Advisories

Arizona	170 µg/L
Florida	4,200 µg/L
Connecticut	1,000 µg/L
Massachusetts	4,000 µg/L
Maine	1,440 µg/L
Minnesota	4,000 µg/L
New Hampshire	170 µg/L
New Jersey	270 µg/L
Vermont	4,200 µg/L
Wisconsin	460 µg/L

Recommendations and Conclusions

Following a review of current toxicological information and federal guidelines, the Department of Health Services recommends adoption of the federal lifetime health advisory for methyl ethyl ketone. This action will raise the groundwater enforcement standard from 460 to 4,000 µg/L. A 20% preventive action limit factor is appropriate because MEK has been not shown to have carcinogenic or mutagenic effects.

Recommended Groundwater Enforcement Standard	4,000 µg/L
Recommended Preventive Action Limit	800 µg/L

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METOLACHLOR (Revision)

Metolachlor is a selective herbicide which can be used as either a pre-plant incorporated or pre-emergence surface-applied treatment to control annual grasses, certain broadleaf weeds in field corn (except fresh and popcorn), soybeans, peanuts and grain sorghum. Metolachlor is marketed in two emulsifiable concentrate products (one contains 68.5 percent a.i. and 31.5 percent inerts vs. 86.4 percent a.i. and 13.6 percent inerts for the second product) and in combination with atrazine or propachlor to provide a broader spectrum of weed control. The active ingredients, metolachlor and s-metolachlor are racemic mixtures of two isomers, S and R. There is no analytical distinction between the two racemic mixtures and detections are reported as metolachlor.

CAS No.	51218-45-2
Molecular Weight	283.8
Physical State	Clear liquid
Water Solubility	530 mg/L
Synonyms	DUAL, BICEP, MILOCEP

Occurrence

In its summary of groundwater pesticide monitoring data from July 1, 1983, through April 30, 1986, the Wisconsin Department of Natural Resources reported 27 detects from 141 private wells sampled for metolachlor and 1 detect from 11 wells tested at public facilities. The highest reported level of metolachlor was 230 µg/L in private facilities and 55 µg/L in public facilities.

Most exposure occur among workers involved in the storage, handling, or shipment of the herbicide. Spray droplets produced during application of the herbicide in the field could result in dermal or inhalation exposures. The general population is not expected to be subject to dermal or inhalation exposure whereas these routes of exposure would be of importance to pesticide production plant workers and agricultural workers.

Toxicity

Technical metolachlor has low mammalian toxicity, but is very toxic to fish.

Acute Oral LD50 Rat: 2,780 mg/kg
Rainbow Trout 96 hour LC50: 2 ppm
Bluegill Sunfish 96 hour LC50: 15 ppm
Channel Catfish 96 hour LC50: 4.9 ppm

Albino CD rats were divided into four groups and fed diets containing 0, 1.5, 15, and 150 mg/kg/day of technical metolachlor for 2 years (Ciba-Geigy, 1983). The NOEL for this study is 15 mg/kg/day, based on decreased body weight gain in rats fed the highest dose tested.

Metolachlor technical was fed diets containing 0, 1.5, 15, and 50 mg/kg/day to Charles River CD strain albino rats (15 males and 30 females/group) beginning at 32 days (Ciba-Geigy, 1981). Animals were mated after either 14 weeks (F0) or 17 weeks (F1) on test. Mating occurred once per generation. The F1 parental animals were randomly selected from the F1a litter after weaning of F1a. F0 males were sacrificed after 135 days on test and F0 females were sacrificed after 164 days on test. No compound related effect on parental body weight was observed. Food consumption was not effected by treatment in

the F0 generation, but was significantly reduced among treated females. Pup body weights of the 50 mg/kg/day dose group were significantly reduced for F1a litters on days 14 and 21 and on days 4, 7, 14, and 21 for the F2a litters. Pup body weights of the 1.5 and 15 mg/kg/day dose groups did not appear to be effected in a compound-related manner. Liver-to-body weight ratios were significantly increased for both F1 parental males and females at 50 mg/kg/day. The thyroid-to-body weight ratio and thyroid-to-brain weight ratio of high dose F1 males were significantly increased. Body weights of the weanling high dose F1a females and F2a males were reduced, though not significantly, and body weights of F2a weanling females were significantly reduced. The NOEL and LOEL for reproductive toxicity were 15 and 50 mg/kg/day, respectively, based on reduced pup weights and reduced parental food consumption (EPA, 1994).

Carcinogenicity

US EPA Classification — C; possible human carcinogen.

Metolachlor has been evaluated for carcinogenic activity in both rats and mice. No treatment-related carcinogenic effects were observed in two acceptable chronic studies in mice.

Both Charles River CD-1 mouse studies were two years in duration. One utilized dietary concentrations of 0, 30, 1000, or 3000 ppm and the other used 0, 300, 1000, or 3000 ppm (450 mg/kg/day) (Guideline 83-1, 83-2; 248722; MRID 000015634, 00042725, and 00084003, 00117597).

Metolachlor was fed to CD-Crl:CD (SD) BR albino rats from Charles River for 2 years at 0, 1.5, 13.5 or 150 mg/kg/day as part of a combined chronic toxicity and carcinogenity study. The NOEL was 15 mg/kg/day for systemic toxicity. The LOEL was 150 mg/kg/day based on decreased body weight gain and increased liver weights in high dose males. A significant increase in liver neoplastic nodules was observed in females at the highest dose level. This study satisfies the requirement for a chronic toxicity study in rats. Increases of neoplastic modules and hepatocellular carcinomas were found in high dose females.

The 1991 HED Peer Review Committee recommended that metolachlor be classified as a Group C carcinogen with a Q* of 9.2 x 10 per mg/kg/day. The classification of Group C was based on increases in liver tumors in the female rat, by both pair-wise and trend analysis and the replication of the finding of tumors in the female rat in a second study.

Mutagenicity

Metolachlor was not found to be mutagenic in several tests (US EPA, 1995). The tests for gene mutation were the *Salmonella* assay and an L5178/TK+/- mouse lymphoma test. The tests for structural chromosome aberration were an *in vivo* micronucleus assay in Chinese hamsters and a dominant lethal assay in mice. Tests for other genotoxic activity included DNA damage/repair assays in rat hepatocytes and in human fibroblasts and an *in vivo/in vitro* unscheduled DNA synthesis assay. However, metolachlor was positive in a test for induction of cell proliferation for hepatocytes from male rats.

Environmental Fate

Atmospheric

Metolachlor's use as an herbicide is expected to result in its direct release to the environment. If released to air, a vapor pressure of 3.14 x 10-5 mm Hg at 25 deg C indicates metolachlor will exist in both the vapor and particulate phases in the ambient atmosphere. Vapor-phase metolachlor will be degraded in the

atmosphere by reaction with photochemically- produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 7 hrs. Particulate-phase metolachlor will be removed from the atmosphere by wet and dry deposition. Metolachlor absorbs light in the environmental UV spectrum and has the potential for direct photolysis in the atmosphere with reported half-lives of 8-22 days.

Aquatic

The aquatic biodegradation half-lives for metolachlor under aerobic and anaerobic conditions are 47 and 78 days, respectively. Photolysis is expected to be important in sunlit surface water. The surface photolysis half-life of metolachlor was 11 and 77 days in lake water under summer and winter illumination conditions, respectively. Volatilization from water surfaces is not expected to be an important fate process. Hydrolysis is expected to occur slowly in water based on an estimated hydrolysis half-life of 210 days. Fish are unlikely to accumulate metolachlor because of rapid elimination and low bioconcentration potential of metolachlor.

Terrestrial

If released to soil, metolachlor is expected to be moderately mobile. Volatilization is not expected to be an important fate process, but has been shown to occur in experiments. Cumulative volatilization loss of 22% and 6% applied using broadcast treatment and banded treatment, respectively, was noted during a 10 day field study. Metolachlor degrades with half-lives of 67 and 81 days in a sandy loam soil under aerobic and anaerobic conditions, respectively. If released into water, metolachlor is expected to adsorb to suspended solids and sediment based upon the measured Kocs.

Regulatory Summary (US EPA, 1995)

NOEL	9.7 mg/kg/day
RfD	0.1 mg/kg/day
MCL	None
MCLG	None
Cancer class	C, possible human carcinogen
Cancer slope	9.2 x 10 per mg/kg/day

The RfD for metolachlor was determined to be 0.10 mg/kg/day based on the one-year toxicity study in dogs. The NOEL was 9.7 mg/kg/day, based on decreased body weight gain at 33 mg/kg/day. An uncertainty factor of 100 was used to derive the RfD for metolachlor (US EPA, 1995).

State Drinking Water Standards and Advisories

Florida	100 µg/L
Massachusetts	100 µg/L
Maine	100 µg/L
Minnesota	100 µg/L
New York	10 µg/L
Vermont	70 µg/L
Wisconsin	15 µg/L

Recommendations and Conclusions

The Department of Health Services recommends revision of the enforcement standard for metolachlor from 15 ug/L to 100 ug/L. The revision is based on EPA's current risk assessment for this substance. Because metolachlor is classified as a possible human carcinogen, an uncertainty factor of 10 was applied to the reference dose and a 10% preventive action limit is proposed.

$$\frac{0.1\ \text{mg/kg/day} \times 10\ \text{kg} \times 100\%}{10 \times 1\ \text{liter/day}} = 100\ \mu\text{g/L}$$

Recommended Enforcement Standard	100 µg/L
Recommended Preventive Action Limit	10 µg/L

References

US EPA. 1995. Reregistration Eligibility Decision for Metolachlor.

Hazardous Substances Data Bank: Metolachlor, accessed January 21, 2009.

US EPA. IRIS Database: Metolachlor, accessed January 21, 2009

METRIBUZIN (Revision)

Metribuzin is a triazine herbicide that selectively controls certain broadleaf and grassy weeds on field and vegetable crops, bermuda grass, and noncrop areas. It is used in Wisconsin as a pre- and post-emergence herbicide on corn, soybeans, potatoes and other crops.

Metribuzin works as a systemic herbicide which is absorbed by the root system and then translocated throughout the plant causing chlorosis, growth inhibition, and necrosis. Metribuzin, a photosynthetic inhibitor, was first registered for use in 1973. US production volume in 1987 was 4.8 million pounds.

CAS no.	21087-64-9
Molecular weight	214.3
Physical state	White crystalline solid
Water solubility	very slightly soluble in water (1200 ppm)
Synonyms	Lexone, Sencor, Sencorex

Occurrence

Metribuzin has been detected in ground water in Connecticut, Iowa, Illinois, Kansas, Maine, Minnesota, Missouri, New Jersey, Ohio, South Dakota, Virginia, and Wisconsin because of probable nonpoint source use (US EPA, 1998). Concentrations in ground water range up to 25.1 ppb. Monitoring for metribuzin in 11 other states did not yield any detections. Recent evidence suggests that metribuzin is likely to be detected in ground waters in areas where it is used.

Metribuzin and two of its degradates were detected in groundwater in a small retrospective study conducted in Portage County, Wisconsin. Concentrations ranged up to 2.3 ug/L parent metribuzin and 7.6 ug/L total residues. Residues were still detected in groundwater more than two years after the final application was made. New monitoring information in Wisconsin indicates that metribuzin can leach to groundwater at concentrations as high as 54 ug/L (US EPA, 1998).

Toxicity

In a chronic feeding/carcinogenicity study, metribuzin was fed to Fischer 344 rats at doses of 0, 30, 300, or 900 ppm (0, 1.3, 13.8, or 42.2 mg/kg/day in males; 0, 1.6, 17.7, or 53.6 mg/kg/day in females) for either 52 or 104 weeks. Toxicity was noted at 300 ppm and above based on decreased body weight gain in females; increased thyroid weight and thyroid/body weight ratio in males, increased liver weight and liver/body weight ratio in males and females. At the lowest dose, there were statistically significant changes in thyroxine (T4) and triiodothyronine (T3) levels, but no other systemic effects were observed. The OPP/HED RfD Committee determined that the 1.3 mg/kg/day dose level (males) should be considered as the NOEL since the effects at the 1.3 mg/kg/day dose were considered to be of marginal biological significance. This conclusion was based primarily on the knowledge that metribuzin is a liver enzyme inducer and that the rat has no other compensatory mechanism to re-establish normal levels of thyroid hormones other than to increase thyroid production of these hormones, the effect observed at the lowest dose was considered a compensatory homeostatic response and not a toxic effect. There was no evidence of carcinogenicity and there was no increase in tumor incidence. For chronic toxicity, the NOEL is 30 ppm (1.3 mg/kg/day in males and 1.6 mg/kg/day in females) and the LOEL is 300 ppm (13.8 mg/kg/day in males and 17.7 mg/kg/day in females) based on decreased body weight gains in females, increased thyroid weights in males, and increased liver weights in males and females (US EPA, 1998).

In a carcinogenicity study, dietary doses of 0, 200, 800, or 3200 ppm (0, 25, 111, or 438 mg/kg/day for males; 0, 35, 139, or 567 mg/kg/day for females) metribuzin (92.9% a.i.) were given to CD1 mice for two years. Systemic toxicity was noted at the high dose as increased liver weights along with decreased hemoglobin and hematocrit values. Under these test conditions metribuzin did not increase the incidence of tumors in mice. For chronic toxicity, the NOEL is 800 ppm (111 mg/kg/day in males, 139 mg/kg/day in females) and the LOEL is 3,200 ppm (438 mg/kg/day for males, 567 mg/kg/day for females) based on increased liver weights and decreased hematological parameters (US EPA, 1998).

Developmental Toxicity

Metribuzin was administered in doses of 0, 25, 70, or 200 mg/kg/day by gavage on gestation days 6-18 to pregnant Charles River Crl:CD BR rats. Maternal toxicity was shown at all dose levels as reduced body weight gain, reduced mean gravid uterine weights, and decreased food consumption. The mid (70 mg/kg/day) and high (200 mg/kg/day) doses showed an effect on the thyroid gland as demonstrated by reduced T4 levels. At the high dose there was also increased thyroid weight. The maternal toxicity NOEL is less than 25 mg/kg/day and the maternal toxicity LOEL is equal to or less than 25 mg/kg/day. For developmental toxicity, the NOEL is 70 mg/kg/day and the LOEL is 200 mg/kg/day based on decreased fetal body weight and reduced ossification or unossified skull bones, ribs, vertebrae, sternebrae, pelvic bones, and appendages (US EPA, 1998).

Mutagenicity

The available data indicate that metribuzin is unlikely to be mutagenic.

Carcinogenicity

US EPA Cancer classification: D, Not classified

Studies conducted in experimental animals provide conflicting results and are inadequate to assess the carcinogenic potential of metribuzin. While studies in mice have been negative, one chronic exposure study in rats revealed an increased incidence of liver bile duct and pituitary gland tumors in females. It is not currently clear whether these tumors were compound-related.

Environmental Fate

Terrestrial
Little leaching occurs from soils with high organic content, but metribuzin is readily leached in sandy soils. Adsorption decreases as soil pH increases. Loss from soil surfaces via volatilization is not an important fate process.

Aquatic
Metribuzin has a half-life of about 4 hours in surface water. It is not expected to evaporate, but is degraded by photodecomposition and possibly also be microbial degradation. The potential for metribuzin to bioconcentrate in aquatic organisms is low.

Atmospheric
Metribuzin will exist in both the vapor and particulate phases in the ambient atmosphere. Vapor-phase is degraded by reaction with hydroxyl radicals. The half-life for this reaction in air is estimated to be 21 hrs(SRC), calculated from its rate constant of 1.8X10-11 cu cm/molecule-sec at 25 deg C determined using a structure estimation method. Particulate-phase metribuzin may be removed from the air by wet and dry deposition(SRC). In freshwater lakes and rivers, metribuzin has a half-life of a few 3 days.

Regulatory Summary

The OPP/HED RfD Committee recommended that an RfD be established on the basis of a two-year feeding study in rats (MRID 42672501). Increased absolute and relative weight of thyroid, decreased lung weight in females, statistically significant increases in blood levels of thyroxine (T4) and statistically significant decreases in blood levels of triiodothyronine (T3) were observed at 30 ppm (1.3 mg/kg/day for males and 1.6 mg/kg/day in females). However, as previously stated, the effects observed at the lowest dose tested were considered to be of marginal biological significance. Therefore, the RfD Committee determined that the dose of 30 ppm (1.3 in males) should be considered as a NOEL. An uncertainty factor (UF) of 100 was applied to account for the inter-species extrapolation and intra-species variability. On this basis, the RfD was calculated to be 0.013 mg/kg/day. It was also recommended to use the reproductive toxicity study with a NOEL of 1.5 mg/kg/day as a co-critical study.

Reference Dose	0.01 mg/kg/day (1998)
MCL	None
MCLG	None
DWEL	350 µg/L
Lifetime HA	70 µg/L
Cancer Classification	D, not classifiable

State Drinking Water Standards and Advisories

Florida	180	µg/L
Minnesota	200	µg/L
New York	50	µg/L
Vermont	32.5	µg/L
Wisconsin	250	µg/L

Recommendations and Conclusions

The Department of Health Services recommends adoption of the US EPA Lifetime Health Advisory as the enforcement standard for metribuzin. The recommendation, which reduces the enforcement standard from 250 to 70 µg/L, is based on our review of the most current toxicity database and federal risk assessment for this chemical. Because metribuzin is not known to have carcinogenic or mutagenic effects a 20% preventive action limit is proposed.

Recommended Enforcement Standard:	70 µg/L
Recommended Preventive Action Limit Factor:	20%
Recommended Preventive Action Limit:	14 µg/L

References

US EPA. 1998. Reregistration Eligibility Decision: Metribuzin.

US EPA Office of Water. Drinking Water Standards and Health Advisories, Summer 2006.

US EPA. IRIS Document for Metribuzin, accessed December 2008.

HSDB. Metribuzin, accessed February 27, 2009.

PHENOL (Revision)

Phenol has a wide variety of industrial uses. The major use is in phenolic resins, which are used as glues and plywood adhesives in the construction, automotive and appliance industries. It is also used as an intermediate of many other materials including textiles, paints, dyes, pharmaceuticals, disinfectants and herbicides (ATSDR, 1989). "Phenol" is not the same as "Total Phenolics," which refers to the entire class of compounds containing one or more hydroxylated aromatic rings. In its pure form, phenol is a waxy white solid. However, for most uses, it is either melted or saturated with water such that it remains liquid. Although it has a somewhat low vapor pressure at room temperature (0.41 mm Hg), it can be readily smelled if present. Phenol is very soluble in water.

CAS no.	108-95-2
Chemical Formula	C_6H_6O
Molecular Weight	94.14
Specific Gravity	1.07
Solubility in Water	87 g/L
Odor/Taste Threshold	7.9 mg/L
Physical State	Waxy, white solid with characteristic odor
Synonyms	Hydroxybenzene, phenyl hydroxide, phenic alcohol

Occurrence

Major environmental sources of phenol are emissions from automobiles and woodburning and in wastewater from industries which use phenol as a solvent (plastics, paper pulp mills and wood treatment facilities, disinfectants and pharmaceuticals). Two natural phenol sources are animal wastes and decomposition of organic wastes.

Since phenol is a petroleum derived product, production decreased somewhat during the 1979 oil crisis but has since increased to pre-crisis levels. Production in 1978 and 1983 exceeded 1 billion kg[2]. There are no manufacturers of phenol in Wisconsin (HSDB, 1989).

Phenol has been found in 630 of 3443 groundwater samples taken across the U.S. at a mean level of 1.5 µg/L and in drinking water from 5 of 14 U.S. treatment plants (ATSDR, 1989). In a recent survey by the Wisconsin Department of Natural Resources phenol was detected in 86 of 137 wells with a maximum concentration of 520 µg/L.

Phenol is absorbed readily upon inhalation, ingestion or skin contact. Human exposure occurs primarily through inhalation of cigarette and other smoke, ingestion of contaminated drinking water, and use of phenol-containing consumer products such as mouthwashes, gargles, throat lozenges and ointments. No data exist on the relative contribution of these routes to total phenol exposure.

Toxicity

Argus Research Laboratories. (1997) Oral (gavage) developmental toxicity study of phenol in rats. Horsham, PA. Protocol number: 916-011.

The US EPA used data from a developmental toxicity study conducted by Argus Research Laboratories (1997) to develop a reference dose for phenol. In this study pregnant Sprague-Dawley rats received phenol by oral gavage on gestation days (GDs) 6 through 15. The maternal NOAEL was 60 mg/kg-day, based on small decreases in maternal body weight gain at 120 mg/kg-day, and the developmental NOAEL was 120 mg/kg-day, based on decreased fetal body weight and delayed ossification at 360 mg/kg-day. Benchmark dose (BMD) modeling was also conducted for the decreased maternal weight. Defining the benchmark response as a one-standard-deviation decrease in maternal body weight gain, the 95% lower confidence limit on the BMD (i.e., the BMDL) was 93 mg/kg-day. This BMDL was calculated using the polynomial model, which gave slightly better fit than the power and Hill models, using BMDS Version 1.3 (US EPA, IRIS).

In addition to the Argus Laboratory study described above, the oral toxicity database for phenol includes a 2-year drinking water studies have been conducted in rats and mice (NCI, 1980), a two-generation drinking water study was conducted in rats (Ryan et al., 2001; available in unpublished form as IIT Research Institute, 1999), and gavage developmental toxicity studies in rats (NTP, 1983a; Narotsky and Kavlock, 1995) and mice (NTP, 1983b).

Carcinogenicity

The EPA has classified phenol as Class D, Not Classified

Chronic rat feeding studies have not demonstrated a carcinogenic effect of orally-administered phenol (US EPA, IRIS).

Mutagenicity

Phenol is clastogenic in some mammalian cell culture assays including human lymphocytes but not mutagenic in *Salmonella* assays (Tennant, et al. 1987).

Reproductive Effects

Growth was stunted in rat pups given over 625 mg/kg/day of phenol in drinking water, and tremors, ataxia, lethargy and irritability were noted in pregnant rats given over 140 mg/kg/day phenol in drinking water on days 6 through 15 of gestation (Heller, et al. 1938).

Phenol administered by gavage to pregnant rats on days 6 through 15 of gestation (30, 60 and 120 mg/kg/day) decreased body weights at doses above 60 mg/kg/day; the EPA used this NOAEL in its determination of the RfD (Jones-Price et al, 1983).

Environmental Fate

Atmospheric
Phenol does not remain in air for long periods of time. Its half life in the presence of sunlight was estimated to be 0.61 days. This degradation is likely due to reaction with hydroxyl radicals (ATSDR, 1989).

Aquatic
In surface water, phenol appears to biodegrade readily; complete removal of phenol in river water has been reported after 2 days at 20deg C and 4 days at 4 deg C. However, levels monitored in surface water and at sewage treatment plants indicate that this process is not as efficient as predicted. The degradation rate of phenol in groundwater has not been reported, although the compound was detected in groundwater for at least 1.5 years after a spill in Wisconsin (Delfino, 1976).

Terrestrial
Phenol biodegrades in soil under both aerobic and anaerobic conditions although it may persist in soil for much longer periods at locations such as waste sites where phenol is repeatedly released (Baker, 1980). In one study, soil degradation was completed in 2-5 days (ATSDR, 1988).

Regulatory Summary

RfD	0.3 mg/kg/day
DWEL	11 mg/L
Lifetime HA	2 mg/L
MCL/MCLG	None
Cancer Classification	D, not classifiable

State Drinking Water Standards and Advisories

California	4,200 µg/L
Florida	10 µg/L
Maine	4,000 µg/L
Minnesota	4,000 µg/L
New Hampshire	4,200 µg/L
New Jersey	2,000 µg/L
Vermont	2,100 µg/L
Wisconsin	6,000 µg/L

Recommendations and Conclusions

The Department of Health Services recommends lowering the groundwater enforcement standard from 6,000 µg/L to 2,000 µg/L, which is the level of the EPA Lifetime Health Advisory for phenol. Because phenol is not known to have carcinogenic or mutagenic effects, a 20% preventive action limit is proposed.

Recommended Ground Water Enforcement Standard: 2,000 µg/L
Recommended Preventive Action Limit: 400 µg/L

References

ATSDR. 1988. VIEW database. Atlanta, GA: Office of External Affairs, Exposure and Disease Registry Branch.

ATSDR. 1989. Toxicological Profile for Phenol. Oak Ridge, TN, Oak Ridge National Laboratory.

Baker, M.D. and C.I. Mayfield. 1980. Microbial and nonbiological decomposition of chlorophenols and phenol in soil. Water Air Soil Pollut 13: 411-424.

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NTP. (1983b). Teratologic evaluation of phenol in CD-1 mice. Prepared by Research Triangle Institute, Research Triangle Park, NC. NTIS PB85104461.

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Seaton, MJ; Schlosser, P; Medinsky, MA. (1995). In vitro conjugation of benzene metabolites by human liver: potential influence of interindividual variability on benzene toxicity. Carcinogenesis 16(7):1519-27.

Tennant, R.W., B.H. Margolin and M.D. Shelby et al. 1987. Prediction of chemical carcinogenicity in rodents from in vitro genetic toxicity assays. Science 236: 933-941.

U.S. EPA. 1989. Draft Drinking Water Health Advisory for Phenol. Office of Water. Washington D.C.

PROMETON (Revision)

Prometon is a nonselective triazine herbicide used for control of most annual and perennial broad-leaved, grass and brush weeds on non-crop areas at 10-20 kg active ingredient per hectare. Prometon is not used on cropland, but is used around buildings, on roadsides, and on areas prior to installation of asphalt. Information on use of prometon in residential settings is not available.

Prometon is a photosynthesis inhibitor, disrupting carbon dioxide fixation and production of the intermediary energy components. Prometon affects photosystem II, competing with plastoquinone and modifying electron transport processes. Prometon is registered for weed control for use as a spot treatment around the home, driveways, patios, buildings, storage areas, fences, pumps, machinery, fuel tanks, recreational areas, roadways, guard rails, airports, military installations, highway medians, pipelines, railroads, lumberyards, rights-of-way, and industrial sites (US EPA, 2008).

CAS No.	1610-18-0
Chemical Formula	$C_{10}H_{19}N_5O$
Molecular Weight	225.34
Density	1.088
Solubility in Water	750 mg/L
Physical state (25°C)	White crystals
Odor/TasteThreshold	No data
Synonyms	Gesafram, Ontrack, Pramitol, Prometone

Occurrence

The Wisconsin Department of Natural Resources had tested 45 private wells for prometon in a nonrandom survey. Detects were noted in 31 wells, with the highest concentration at 93 ppb (WDNR, 1995).

Most exposure to prometon is occupational. Workers can be exposed during the mixing and application of the herbicide. People may also be exposed via dermal contact or inhalation when they enter recently treated fields. In rats, 50% of an orally administered dose of prometon was excreted within 12-26 hr. The primary route of excretion is via the urine.

Toxicity

Prometon technical was fed to Sprague-Dawley rats at doses equivalent to 0, 0.89, 23.3 and 73.3 mg/kg/day for 104 weeks. None of these doses increased the incidence of neoplastic lesions or survival. The U.S. EPA's Office of Pesticides and Toxic Substances determined that the systemic LOEL was 23.3 mg/kg/day and the NOEL was 0.89 mg/kg/day based on body weight depression (US EPA, 1992).

Technical grade prometon was fed to dogs (breed unspecified) at doses of 0, 5, 20 and 50 mg/kg/day for a period of one year. Statistically significant effects on body weight gain were noted at the 20 mg/kg/day level in females and at the 50 mg/kg/day level in both sexes. Based on this effect, the NOEL for this study was 5 mg/kg/day. Preliminary and monthly examinations indicated that the dogs were healthy throughout the study. Therefore, episodes of diarrhea and emesis, and reduced weight gain were judged to be compound-related (US EPA, 1993).

Carcinogenicity

U.S. EPA Cancer Classification for Prometon: Not likely to be Carcinogenic to Humans" based on the absence of significant tumor increases in two adequate rodent carcinogenicity studies (US EPA, 2008).

Carcinogenicity studies have been conducted in rats and mice. None of these studies have shown a statistically significant increase in tumor incidence among treated versus control animals.

Mutagenicity

No information on the mutagenicity of prometon was located.

Reproductive Effects

In a two-generation reproductive toxicity study, Sprague-Dawley rats were fed diets containing prometon technical at 0, 20, 500, or 1500 ppm. Reproductive toxicity observed at 1500 ppm in both generations, and at 500 ppm in the second generation, was evident as decreased pup body weight during the entire lactation period. Therefore, the NOEL and LOEL for reproductive toxicity were 20 and 500 ppm, respectively. These feeding levels correspond with daily doses of 1.45 and 35.08 mg/kg/day in males, and 1.59 and 39.17 mg/kg/day in females (USEPA, 1992).

Environmental Fate

Terrestrial
When prometon is applied to land it will adsorb moderately to the soil. It is moderately persistent in soil with an estimated half-life between 1.5 and 6 months. It is not known whether it degrades by chemical or microbial processes. An important mechanism by which prometon is lost from soil is by volatilization. Prometon rises to the soil surface with evaporating water and as the concentration of the herbicide at the soil-air interface increases, the amount of prometon volatilizing increases (Spencer, 1988).

Aquatic
If released into water, prometon will partially adsorb to sediment and particulate matter in the water column. Degradation should be slow. Bioconcentration in fish should not be significant. Volatilization should not be an important fate process (HSDB, accessed Feb 2, 2009).

Atmospheric
In the atmosphere prometon would be expected to degrade by reaction with photochemically produced hydroxyl radical. Its estimated half-life is approximately two hours (Atkinson, 1987).

Regulatory Summary

No federal drinking water standards for prometon have been proposed or adopted. However, USEPA has published the following guidelines:

NOAEL	5 mg/kg/day (1 yr dog study)
LOAEL	20 mg/kg/day
Uncertainty Factor	100 (10 each for inter- and intraspecies differences)
RfD	0.05 mg/kg/day (US EPA, 2008)
DWEL	500 µg/L
Longer-term adult health advisory	500 µg/L
Longer-term child health advisory	200 µg/L
Lifetime health advisory	100 µg/L

MCL/MCLG	None/none
Cancer classification	Not Likely

State Drinking Water Standards and Advisories

Minnesota	100 µg/L
New York	50 µg/L
Prometon	100 µg/L
Vermont	100 µg/L

Recommendations and Conclusions

The Department of Health Services recommends adoption of EPA's lifetime health advisory as a groundwater enforcement standard for Prometon. This revision increases the enforcement standard from 90 to 100 ug/L. Because Prometon is not known to be carcinogenic or mutagenic, a 20% preventive action limit is proposed.

Recommended Enforcement Standard	100 µg/L
Recommended Preventive Action Limit:	20 µg/L

References

Atkinson R; Int J Chem Kinet 19: 799-828, 1987.

Spencer WF et al; J Environ Qual 17: 504-9, 1988.

US EPA. 2008. Reregistration Decision for Prometon. Washington, DC.

USEPA Memorandum from Sheryl K. Reilly to Kathryn Davis/Thomas Luminello, Apr 28, 1993.

USEPA Memorandum from Vivian A. Williams to Thomas Luminello, Aug 18, 1992.

Wisconsin Department of Natural Resources. Groundwater Retrieval Network, 1995.

TOLUENE (Revision)

Toluene is a clear, colorless liquid with many industrial uses. Approximately 92% of the toluene produced in the US is used as a component of gasoline. The remainder is used in manufacture of paints, lacquers, adhesives, rubber and in some printing and leather tanning processes. US production is estimated at around 6.5 billion pounds per year.

A Wisconsin Groundwater Enforcement Standard of 343 μg/L was adopted in 1985 and was later revised to 1 mg/L.

CAS No.	108-88-3
Molecular Formula	C_7H_8
Molecular Weight	92.15
Physical State	Liquid at room temperature
Water Solubility	515 mg/L at 25° C
Odor/Taste Threshold in Water	0.04 mg/L
Specific Gravity	0.8669
Synonyms	Methylbenzene, Toluol

Occurrence

Toluene is found relatively infrequently in municipal water systems. A 1981 survey found the compound in 11
of 929 groundwater systerms and 20 of 99 surface water systems. In private wells, toluene is often found associated with chemicals waste sites or leaking underground fuel storage tanks. In Wisconsin, toluene was detected in 179 of 4633 wells sampled. Toluene concentrations exceeded the enforcement standard in 27 of these (WDNR, 1991).

Toxicity

In humans and animals, the most profound effect of acute toluene overexposure via inhalation is central nervous system depression and narcosis which may lead to death. No other effects have been noted. No studies of acute oral toluene exposures have been performed.

In a two year subchronic gavage study conducted by the National Toxicology Program (NTP, 1990), prostration, hypoactivity, ataxia, lacrimation, excessive salivation and tremors were noted in rats given doses greater than 2500 mg/kg. The same effects were noted in rats that inhaled 300-1250 ppm for up to two years and in humans who intentionally inhaled toluene-containing solvent vapors. In the NTP study, absolute and relative kidney and liver weights were increased in rats treated with doses greater than or equal to 625 mg/kg/day for 5 days/week but not at 312 mg/kg. Benchmark analysis was performed for absolute kidney weight changes in male rats (NTP, 1990). Male rat kidney data were chosen for BMD modeling as these data exhibited a greater response than that seen in female rats. A BMDL of 238 mg/kg-day was derived and used as the point of departure for EPA's reference dose for toluene (EPA, IRIS).

Carcinogenicity

EPA classification: I, Inadequate human and animal evidence of carcinogenicity).

No studies have shown increased cancer incidence among animals inhaling toluene. No carcinogenic response was noted among animals inhaling up to 300 ppm for 6 h/day, 5 d/week, for two years or in rats

inhaling up to 1200 ppm for two years. No ingestion studies investigating carcinogenicity have been performed.

Mutagenicity

Toluene has been found to be non-mutagenic in most *in vitro* microbial and eukaryotic cell assays. Only one study reported potentially positive result in a mouse lymphoma cell line but these results were considered to be equivocal.

Reproductive/Developmental Effects

Epidemiologic studies of women exposed either occupationally or as a result of substance abuse to a number of solvents including toluene during pregnancy have been performed. The investigators in these studies found an increased incidence of central nervous system anomalies, growth retardation and developmental delays in children of exposed women. Exposure to toluene in all of the developmental studies performed in animals was by inhalation. These studies, performed in rats, rabbits, and mice, have shown increased incidences of skeletal anomalies in exposed whose mothers were exposed during gestation. The LOAEL determined in these studies was approximately 780 mg/kg/day.

Environmental Fate

Atmospheric
Toluene is released into the atmosphere principally from the volatilization of petroleum fuels, solvents and thinners, and from motor vehicle exhaust. Its production and use as an intermediate in the production of benzoic acid, benzaldehyde, benzene, explosives, dyes and many other organic compounds may also result in its release to the environment through various waste streams. Toluene has also been detected in emissions from volcanos, forest fires and crude oil. If released to air, a vapor pressure of 28.4 mm Hg at 25 deg C indicates toluene will exist solely as a vapor in the ambient atmosphere. Vapor-phase toluene will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 3 days. Toluene may also be degraded in the atmosphere by reaction with nitrate radicals and ozone molecules, but these reactions are too slow to be environmentally important (HSDB, 2009).

Terrestrial
If released to soil, toluene is expected to have high to moderate mobility based upon Koc values in the range of 37-178. Volatilization from moist soil surfaces is expected to be an important fate process based upon a Henry's Law constant of 6.64X10-3 atm-cu m/mole. Toluene may volatilize from dry soil surfaces based upon its vapor pressure. Biodegradation is expected to occur rapidly in soil surfaces, with half-lives in the range of several hours to 71 days.

Aquatic
If released into water, toluene is not expected to adsorb to suspended solids and sediment based upon a Koc of 166 measured in lake sediment. Biodegradation is expected to occur rapidly in water, with reported half-lives of 4 and 56 days in aerobic and anaerobic water, respectively. Volatilization from water surfaces is expected to be an important fate process based upon this compound's Henry's Law constant. Estimated volatilization half-lives for a model river and model lake are 1 hour and 4 days, respectively. Measured BCF values of 13 and 90 in fish suggest bioconcentration in aquatic organisms is low to moderate. Hydrolysis is not expected to be an important environmental fate process for toluene due to lack of hydrolyzable functional groups (HSDB, 2009).

Regulatory Summary (EPA, IRIS)

BMDL	238 mg/kg/day
UF	3000
RfD	0.08 mg/kg/day [NOAEL/UF]
DWEL	3 mg/L
Lifetime HA	None
MCL	1 mg/L
MCLG	1 mg/L
Cancer class	I, Inadequate information to classify

*The MCL was determined by multiplying the DWEL by 20%. This procedure assumes 20% of the total toluene intake comes from drinking water.

State Drinking Water Standards and Advisories

Minnesota	1,000 µg/L
New Jersey	600 µg/L
Wisconsin	1,000 µg/L
WHO	700 µg/L

Recommendations and Conclusions

Wisconsin Department of Health Services recommends revision of the groundwater enforcement standard from toluene from 1,000 to 800 µg/L. This revision reflects EPA's most current risk assessment for toluene which resulted in a lower reference dose of 0.08 mg/kg/day. Because toluene is not known to have carcinogenic or mutagenic effects, a 20% preventive action limit is proposed.

$$\frac{0.08 \text{ mg/kg/day} \times 10 \text{ kg} \times 100\%}{1 \text{ liter/day}} = 800 \ \mu\text{g/L}$$

Recommended Enforcement Standard:	800 µg/L
Recommended Prev. Action Limit:	160 µg/L

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XYLENE (Revision)

Xylene is a clear, colorless liquid with many industrial uses. The term "xylene" usually refers to a mixture of three isomers, ortho-, meta- and para-xylene (o-, m- and p-xylene, respectively). The mixture is sometimes referred to as "total xylenes." The term "xylene" when used in this document refers to the mixture of isomers.

Xylene occurs in petroleum and coal tar and is a component of refined fuels and gasoline. Approximately 70% of the xylene produced in the US (not including that found in refined fuels) is used in the production of ethylbenzene, another gasoline component, and the remainder is used in the chemical, plastic, synthetic fiber and paper industries (ATSDR, 1990). In 1987, U.S. petroleum refiners produced over two billion kg of mixed xylenes and over 400 million kg of o-xylene (US ITC, 1988).

CAS no.	1330-20-7
Molecular Formula	C_8H_{10}
Molecular Weight	106.16
Physical State	Liquid at room temperature
Water Solubility	130 mg/L at 25° C
Odor/Taste Threshold	0.5-1.5 mg/L
Specific Gravity	0.86
Synonyms	Dimethylbenzene, xylol

Occurrence

Xylene is a common air contaminant in outdoor, industrial and home settings. The compound is present in automobile emissions, as a chemical intermediate in many manufacturing processes and in many consumer products such as gasoline, aerosols and paints, varnishes, shellac and rust preventatives. Median concentrations of 12 $\mu g/m^3$ have been reported in urban areas[3] and approximately 20 $\mu g/m^3$ indoors (Siefert and Abraham, 1982).

Xylene is found relatively infrequently in municipal water systems utilizing either groundwater or surface water; a 1981 survey found the compound in less than 6% of public water systems (US EPA, 1985). In private wells, however, xylene is often found associated with chemical waste sites or leaking underground storage tanks. In Wisconsin, o and p-xylene was detected in 315 of 5709 wells sampled; of those, 55 were at a concentration above the current Enforcement Standard (WDNR, 1991).

In non-occupationally exposed populations, inhalation of xylene is likely to be the major source of exposure, providing an average of approximately 3 µg/day (ATSDR, 1990). Cigarettes can contain up to 30 µg/cigarette (Higgins, et al, 1983).

In humans, approximately 64% of inhaled xylene is absorbed (Sedivec and Flek, 1976). In animals, oral exposure of a single xylene dose results in 90% absorption. In humans, approximately 5-10% of the absorbed xylene dose accumulates in the fat and is taken up in lipid-rich tissues such as brain and blood . The compound is metabolized in the liver to glucuronides and hippuric acid derivatives which are excreted in the urine. The majority of absorbed xylenes are excreted in a matter of hours (ATSDR, 1990).

The odor threshold for p-xylene is 500 µg/L. P-xylene concentrations above the taste and odor threshold may be objectionable to some individuals.

Toxicity

No pathological examinations have been performed in animals given a single lethal dose of xylenes. Impairment of visual function, as evidenced by significant decreases in flash-evoked potentials, was noted in rats treated one time at doses of 250 mg/kg p-xylene and higher.

In a National Toxicology Program (1986) study, mice and rats were treated with 0-1000 mg/kg/day xylenes for up to two years. In this study, increased mortality was noted at 250 mg/kg/day, but this increase was not statistically significant. Based on this study, the EPA uses a NOAEL of 178 mg/kg/day (rats were exposed for 5 days/wk so the NOAEL=250 x 5/7). Also, in this study, mice were hyperactive 5-30 minutes after administration of 1000 mg/kg/day. Although pathological examination of the liver in the NTP study did not reveal any treatment-related effects, other studies found increased liver weight, increased cytochrome P450 content and increased liver enzyme activities in rats given 1060 mg/kg/day for one week (Pykko, 1980). No renal, respiratory, cardiovascular, gastrointestinal, hematological or musculoskeletal effects were noted in the NTP study.

Carcinogenicity

EPA classification: I (inadequate human and animal evidence of carcinogenicity).

A 1986 NTP study reported "no evidence of carcinogenicity" for orally administered mixed xylene in rats or mice of either sex at any dosage tested. No inhalation carcinogenicity studies have been performed. No epidemiologic studies addressing xylene carcinogenicity have been performed.

Mutagenicity

Technical xylene mixtures or individual isomers are not mutagenic in *Salmonella* or *E. Coli* (US EPA, 1987). Chromosomal aberrations were not increased in bone marrow cells of rats exposed to xylenes by inhalation (Donner et al, 1980).

Reproductive/Developmental Effects

In the NTP study, no effects on reproductive organs resulting from oral xylene exposure were noted. However, oral exposure to 2,060 mg/kg/day mixed xylenes was associated with cleft palate and decreased fetal weight in mice (Marks et al, 1982). No human studies addressing reproductive or developmental effects of xylenes have been performed.

Environmental Fate

Atmospheric
Most xylene entering the environment is released directly to the air (approx. 3 x 10^9 kg), with the bulk of these releases from refinery losses, other solvent losses and automobile exhaust (Merian and Alexander, 1982). Once in the air, the predominant method of degradation is photooxidation. The half-life of xylene in the atmosphere is estimated to be 24.1 hr (Jori, 1986).

Aquatic
The predominant method of xylene transformation in surface water is evaporation. Hydrolysis or biotransformation are not expected to be significant (ATSDR, 1990). In groundwater, xylene is moderately biodegraded with an expected half life of 10 days (Merian and Zander, 1982).

Terrestrial

Xylene does not bind tightly to soil particles. However, precise estimates of leachability from different soil types are not available. Anaerobic biodegradation appears to be the predominant transformation process in soils, with an estimated half life of 24 hr (Merian and Zander, 1982).

Regulatory Summary

NOAEL	179 mg/kg/day (250 mg/kg/day x 5/7)
Uncertainty factor	1000 (revised 2/21/2003)*
Reference dose	0.2 mg/kg/day (revised 2/21/2003)
DWEL	7 mg/L
Lifetime Health advisory	None
MCL	10 mg/L
MCLG	10 mg/L
Cancer Classification	I, inadequate

*In its 2003 reassessment of the reference dose for xylene, EPA added an additional UF of 10 to account for database uncertainty stating:

"The available oral database for xylenes includes chronic and subchronic gavage toxicity studies in mice and rats and a developmental toxicity study. None of these studies indicate that additional data would result in a lower RfD. However, the database lacks adequate studies of the oral neurotoxicity of xylenes as well as multigenerational reproductive toxicity and developmental neurotoxicity studies. Given the identification of neurological impairment as a critical health hazard from inhalation exposure to xylenes, the lack of comprehensive neurotoxicity testing following chronic oral exposure is of particular concern. It should be noted that transient neurotoxic effects (e.g., lethargy, tremors and unsteadiness) were reported in mice following oral exposure to xylenes for 13 weeks (NTP, 1986). There are no toxicokinetic data identifying oral dose levels at which first-pass hepatic metabolism of xylenes becomes saturated in animals or humans; such data could decrease uncertainty regarding whether neurological impairment may occur at dose levels below those causing body weight decreases and mortality in rats. It is uncertain whether the availability of comprehensive oral neurotoxicity data would result in a lower RfD."

State Drinking Water Standards and Advisories

New Jersey	1,000 µg/L
Minnesota	10,000 µg/L
Vermont	10,000 µg/L
Wisconsin	10,000 µg/L

On November 1, 1985, Wisconsin adopted an enforcement standard and preventive action limit for xylenes of 620 and 124 µg/L, respectively. The enforcement standard was later revised to 10,000 mg/L to bring it into line with the federal drinking water standard.

Recommendations and Conclusions

The Department of Health Services recommends revision of the groundwater enforcement standard for xylene from 10,000 ug/L to 2,000 ug/L. This action reflects revision of the EPA reference dose for this substance which was finalized in 2003. Since xylene is not known to have carcinogenic or mutagenic effects, a 20% preventive action limit is proposed.

$$\frac{0.2 \text{ mg/kg/day} \times 10 \text{ kg} \times 100\%}{1 \text{ liter/day}} = 2 \text{ mg/L or } 2{,}000 \text{ µg/L}$$

Recommended Enforcement Standard	2,000 µg/L
Recommended Prev. Action Limit:	400 µg/L

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1,4-DIOXANE

1,4-Dioxane is a colorless, flammable liquid with a mild odor. It is miscible with water, most organic solvents, aromatic hydrocarbons, and oils and is available in reagent, technical, spectrophotometric, and scintillation grades (HSDB 2001). 1,4-Dioxane is used as a stabilizer in chlorinated solvents and as a solvent for lacquers, paints, dyes, resins, oils, fats, waxes, and greases. It may also have been used in adhesives, cosmetics, and pharmaceuticals (HSDB 2001).

CAS no.	123-91-1
Chemical Formula	C4H8O2
Molecular Weight	88.1
Physical State	Colorless liquid
Water Solubility	Miscible
Density at 20 deg C	1032.9 g/liter at 20 °C
Synonyms	*p*-Dioxane

Occurrence

1,4-Dioxane has been commercially produced in the United States for more than 50 years. It is currently listed with the US EPA as a high production volume chemical indicating that annual production or importation exceeds 1 million pounds. In 1982, nearly 15 million lb of 1,4-dioxane were produced in the United States (USITC 1983).

According to the Wisconsin Department of Natural Resources GRIN database, 29 wells that have been tested for 1,4-Dioxane. 1,4-Dioxane concentrations ranged from below detection to 1100 ug/L and exceeded 3 µg/L in 25 of these water supplies.

Exposure of the general population to 1,4-dioxane could occur from contact with products containing residues of the compound. According to the Consumer Product Safety Commission (CPSC), consumers may possibly be exposed to residual levels of 1,4-dioxane formed during the manufacture of detergents, shampoos, surfactants, and certain pharmaceuticals. CPSC reported that the presence of 1,4-dioxane, even as a trace contaminant, is cause for concern and the Commission continues to monitor its use in consumer products. Residues may also be present in food packaging and on food crops treated with 1,4-dioxane-containing pesticides. Occupational exposures can occur during its manufacture and use as a solvent.

1,4-Dioxane has a high potential for entering the environment due to its volatility and solubility in water. Emissions to the atmosphere can occur at the sites of manufacture and use. EPA's Toxic Chemical Release Inventory (TRI) estimated that 977,447 lb of 1,4-dioxane were released to the environment (on- and off-site releases) from 64 facilities that produced, processed, or used the chemical in the United States in 1996.

1,4-dioxane is rapidly absorbed following ingestion or inhalation. It is metabolized in the liver and does not accumulate in the body. The principal metabolite in humans and mammals is beta-hydroxyethoxyacetic acid (HEAA). Other metabolites determined in animal studies include 1,4-dioxan-2-one, β-hydroxyethoxyacetaldehyde, Ethylene glycol, oxalic acids and carbon dioxide. Unchanged 1,4-dioxane is excreted in the urine and expired air (DeRosa et al., 1996).

Two occupational fatalities involving exposure to 1,4-dioxane have been described (DeRosa et al., 1996). Haemorrhagic nephritis, centrilobular liver necrosis, severe epigastric pain, convulsion and coma were found as the major effects. In volunteer short-term exposure studies (720 or 1080 mg/m3 for 15 min; 5760 mg/m3 for 10 min; 19 800 mg/m3 for 1 min), mucous irritation in eyes, nose and throat was noted as a clinical sign (DeRosa et al., 1996). After exposure to 1,4-dioxane at 180 mg/m3 for 6 h, only mild eye irritation was noted, with no other clinical signs, as demonstrated by chest X-ray, electrocardiograms, respiratory function tests, blood determinations and urinalysis (Young et al., 1977).

Toxicity

Oral LD50 values are in the range of 5400–7300 mg/kg of body weight in rats, 5900 mg/kg of body weight in mice, 3300–4000 mg/kg of body weight in guinea-pigs and 2000 mg/kg of body weight in rabbits (DeRosa et al., 1996). LC50 values following inhalation for 2 hours were found to be 46 g/m3 in rats and 37 g/m3 in mice (RTECS, 2000). The dermal LD50 in rabbits was 7600 mg/kg of body weight, although there were no equivalent toxicological effects in Wistar rats treated with 8,300 mg/kg of body weight (DeRosa et al., 1996). The main acute effects at near-lethal doses in experimental animals (rats, mice, guinea-pigs, rabbits or dogs) are central nervous system depression (e.g., narcosis) and severe gastric, pulmonary, hepatic and renal lesions (DeRosa et al., 1996).

Male SD rats administered 0, 10 or 1000 mg of 1,4-dioxane per kg of body weight per day in drinking-water for 11 weeks demonstrated increased relative liver weight and a minimal degree of liver lesion at 1000 mg/kg of body weight per day, but not at 10 mg/kg of body weight per day (Stott et al., 1981).

Sherman rats of both sexes were administered 100, 1,000 or 10,000 mg of 1,4-dioxane per liter in their drinking-water for 2 years. The 10,000 mg/liter group exhibited decreased body weight gain, survival rate and water consumption. Other histopathological findings at the 1,000 or 10,000 mg/liter doses included renal tubular and hepatocellular degeneration and necrosis. The NOAEL was determined to be 9.6 mg/kg/day in males and 19 mg/kg/day in females) (Kociba et al., 1974). In F344/DuCrj rats receiving 200, 1000 or 5000 mg/liter in drinking-water for 2 years liver changes were detected at doses equivalent to 16–21 mg/kg/ day in males (Yamazaki et al., 1994).

Reproductive and Developmental Toxicity

SD rats were given 1,4-dioxane at 258, 516 or 1033 mg/kg/day by gavage on days 5–14 of pregnancy (sperm = day 0). Reduced food consumption, decreased fetal weight and delayed ossification were observed at 1.0 ml/kg of body weight per day. These findings support a NOAEL for developmental toxicity of 516 mg/kg of body weight per day (Giavini et al., 1985).

Mutagenicity

1,4-Dioxane has been tested with and without activation in several *in vivo* and *in vitro* systems. The weight of evidence indicates that 1,4-dioxane is probably not mutagenic or genotoxic.

Carcinogenicity

US EPA Cancer Classification: B2, probable human carcinogen

Although there is inadequate evidence for the carcinogenicity of 1,4-dioxane in humans the US EPA and International Agency for Research on Carcinogens have determined that 1,4-Dioxane is likely to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals (EPA, 2008; IARC 1999). When administered in drinking water, 1,4-dioxane increased the incidences of squamous

cell carcinomas of the nasal turbinates as well as hepatocellular adenomas in rats. Drinking water exposure also induced hepatomas and carcinomas of the gallbladder in male guinea pigs and hepatocellular carcinomas in mice of both sexes. As a promoter in a two-stage skin carcinogenesis study, the compound increased the incidence of skin tumors in mice of both sexes. Intraperitoneal injections increased the incidence of lung tumors in male mice.

A Danish mortality study was conducted with 19,000 cases in the cancer registry (Hansen, 1993). Liver cancer death rates were significantly increased among men who worked with 1,4-dioxane. The authors noted that while alcohol consumption did not explain this increase, co-exposure to chemicals other than 1,4-dioxane, exposure time period, and exposure dose were not controlled for.

Regulatory Summary

MCL	None
MCLG	None
RfD	None
10-Day Health Advisory	0.4 mg/L
Lifetime Health Advisory	None
Cancer Classification	B2, Likely to be carcinogenic to humans
Cancer Slope Factor	1.1E-2 per mg/kg/day
10^{-6} Cancer Risk Level in Water	3 µg/L

State Drinking Water Standards and Advisories

California	3 µg/L
Florida	5 µg/L
Maine	32 µg/L
Massachusetts	50 µg/L
Vermont	20 µg/L

Recommendations and Conclusions

The Department of Health Services recommends use of the US EPA's cancer slope factor to develop an enforcement standard (ES) for 1,4-dioxane that equates with a one-in-a million lifetime cancer risk. Because this substance has carcinogenic effects, a 10% preventive action limit (PAL) is proposed.

$$\frac{1 \times 10^{-6} \text{ lifetime risk} \times 70\text{-kg} \times 100\% \text{ exposure} \times 1000\ \mu\text{g/mg}}{0.011 \text{ per mg/kg/day} \times 2 \text{ liters/day}} = 3\ \mu\text{g/L}$$

Recommended Enforcement Standard	3 µg/L
Recommended Preventive Action Limit	0.3 µg/L

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ACETOCHLOR

Acetochlor is a chloroacetanilide herbicide used for pre-emergence control of weeds in corn. Acetochlor is available as an emulsifiable or soluble concentrate, microencapsulated or granular formulation that can be applied as pre-plant, pre-emergence, or early post-emergence weed control treatment.

CAS no.	34256-82-1
Chemical Formula	$C_{14}H_{20}ClNO_2$
Molecular Weight	269.77
Physical State	Amber, oily liquid
Water Solubility	223 mg/L
Density at 20 deg C	1.123 g/ml
Synonyms	None

Occurrence

Acetochlor was given conditional registration by the U.S. Environmental Protection Agency in March 1994 which provided an opportunity to investigate the occurrence of a pesticide during its first season of use. Water samples collected and analyzed by the U.S. Geological Survey during this time documented widespread contamination with detections of the parent herbicide in 29% of the rain samples from four sites in Iowa, 17% of the stream samples from 51 sites across nine states, and 0% of the groundwater samples from 38 wells across eight states. Acetochlor exhibited concentration increases in rain and streams following its application to corn in the midwestern United States, with 75% of the rainwater and 35% of the stream samples having acetochlor detected during this time period. Concentrations in rain decreased as the growing season progressed.

More than 70 wells, including 27 monitoring wells, 22 private drinking water wells, and 23 municipal wells in Wisconsin have been sampled for alachlor, metolachlor, acetochlor, and their ethane sulfonic acid (ESA) and oxanilic acid (OA) metabolites. Wells were selected based on previous detections of pesticides or proximity to agricultural fields to increase the likelihood of exposure to the compounds of interest. Alachlor, metolachlor, and acetochlor are chloroacetanilide herbicides that are commonly used on corn and other crops in Wisconsin. Sample results showed over 80 percent of the monitoring wells and drinking water wells contained the ESA and OA metabolites of alachlor and metolachlor. The metabolites of acetochlor, which has only been used since 1994, showed a lower frequency of detection. Concentrations of the metabolites in groundwater ranged from near the level of detection to 42 µg/l. The monitoring wells and private drinking water wells showed higher detection frequencies and concentrations than the deeper municipal wells, but the municipal wells did show significant impacts. Fifty-two percent of the municipal wells had a detection of at least one of the compounds of interest. However, none of the municipal wells contained pesticide levels that exceeded an enforcement standard (WDATCP, 2000).

Toxicity

Acetochlor has low acute toxicity by the oral, dermal and inhalation routes and is mildly irritating to the eyes. Acetochlor has shown mild skin irritation in one study, however in another study it was a strong skin irritant. Acetochlor is also a strong dermal sensitizer.

Acetochlor is well absorbed by the oral route, undergoes extensive metabolism to produce reactive species that are responsible for its carcinogenicity in nasal tissue. The major target organs affected in rats, dogs and mice exposed to acetochlor appear to be the liver, thyroid, nervous system, kidney, testes,

and erythrocytes. Species specific target organs include the nasal olfactory epithelium in rats and the lungs in mice. Dogs are more sensitive to chronic exposure than rats. Chronic toxicity in the dog appeared in the form of testicular, hepatic, and renal histopathology, and at high doses, brain histopathology. Evidence of neurotoxicity has been observed in several studies.

Groups of 20-week old purebred beagles (5/sex/dose) were administered acetochlor by gelatin capsule for 52 weeks at dose levels of 0, 2, 10, or 50 mg/kg/day. Control animals received empty capsules. Systemic toxicity was evident at 10 and 50 mg/kg-day in both male and female dogs. Symptoms included excessive salivation and abnormal shaking of the head. Significant neurological effects were observed at 50 mg/kg/day and consisted of abnormal head movements; stiffness and rigidity of the hindlimbs; ataxia; tremor; depressed righting, hopping, and flexor reflexes; and exaggerated tonic neck reflex. Three animals in the high dose group were euthanized between weeks 39-51 due to severe neurological effects. Based upon the findings from this study, the LOEL for systemic toxicity is 10 mg/kg-day based on salivation, increased alanine aminotransferase and ornithine carbamyl transferase accompanied by significant increases in triglyceride levels, and decreased blood glucose levels, and histopathological changes in the kidney and testes of males. The NOEL for systemic toxicity in this study was 2 mg/kg/day (EPA, 2006). The US EPA used this study as the basis for its oral reference dose. The agency applied an uncertainty factor (UF) of 100 to account for intra and inter species variability. EPA noted that principal study is of good quality and is given a high confidence rating. Additional studies are of adequate quality and supportive of the critical study. Therefore, the database is given a high confidence rating. High confidence in the RfD follows.

Carcinogenicity

EPA's IRIS document for acetochlor no longer includes a cancer assessment.

A January 3, 2007 report from EPA HED's Cancer Assessment Review Committee indicates a classification as 'Suggestive Evidence"

Various cancer slope factors and cancer classifications have been developed for acetochlor. In the first Cancer Peer Review Committee (CPRC) evaluation meeting of September 12, 1985, it was classified as a B2 carcinogen based on an increased incidence of liver and thyroid tumors in rats and in mice, increased incidence of liver and lung tumors in both sexes and histiocytic sarcoma, kidney and ovarian tumors in females. The second CPRC meeting of February 8, 1989 re-affirmed the classification of B2 based on increased incidence of tumors of the nasal epithelium, liver and thyroid of the rat; and the increased incidence of liver and lung tumors and in female mice, as well as histiocytic sarcoma and tumors of the ovary and kidney in mice. A cancer potency factor (Q*) of 0.010 was developed based on the incidence of nasal epithelial tumors in male and female rats. On October 16, 1991, using the Agency's 1986 Guidelines for Cancer Assessment, the CPRC again classified acetochlor as a B2 carcinogen based on an increased incidence of tumors of the thyroid, liver and nasal epithelium in both sexes of the rat, along with rare benign chondroma of the femur (male and female) and basal cell tumor of the stomach (female) and in the mouse, increased incidence of liver and lung tumors in both sexes and histiocytic sarcoma and tumors of the ovary and kidney in females. The Q* was revised slightly to 0.0169, but was again based on the incidence of nasal epithelial tumors in male and female rats.

On April 21 and 22, 2004, the OPP/HED Cancer Assessment Review Committee (CARC) conducted the agency's fourth review of carcinogenic potential of acetochlor and once again concluded that acetochlor was "Likely to be Carcinogenic to Humans" and assigned a Q* of 0.0327 citing numerous positive findings in mice and rats. The majority of CARC members concluded that acetochlor was likely to be carcinogenic to humans based on the following weight-of-the-evidence considerations:

(1) A dose-related increase was observed in the incidence of lung tumors in males and female mice in two mouse carcinogenicity studies, sometimes exceeding historical controls. An increased incidence of bronchiolar hyperplasia in males in the 23-month study was also observed;
(2) A dose-related increase in the incidence of histiocytic sarcoma in female mice was observed in two carcinogenicity studies, exceeding historical controls at 1500 ppm;
(3) Dose-related increases in the incidence of rare nasal epithelial cell papillary adenomas and carcinomas were observed in male and female rats in three combined chronic toxicity studies, and in F0 and F1 parental animals in a rat multigeneration reproductive toxicity study;
(4) Treatment-related but marginal increases in thyroid follicular cell adenomas were observed in male and female rats but were not included in the cancer quantification because an antithyroid mode of action was accepted;
(5) The available genotoxicity data on acetochlor do not support a genotoxic mode of action for tumor induction. Gene mutation data are inconclusive. Tests for dominant lethality and unscheduled DNA synthesis in rodents and comet assays using rat nasal olfactory and respiratory epithelial cells are negative. Acetochlor is clastogenic *in vitro* in cultured mammalian cells at cytotoxic levels, but not *in vivo*. Clastogenicity is most likely secondary to cytotoxicity resulting from oxidative damage by a reactive quinoneimine intermediate formed during the metabolism of acetochlor.
(6) The structurally related chloroacetanilides alachlor and propachlor are also associated with an increased incidence of nasal epithelial tumors. The FIFRA SAP determined in 1997 that these compounds, together with acetochlor, could be combined for risk assessment purposes based on a common mode of action for induction of nasal tumors.
(7) The mechanistic data on nasal tumorigenesis of acetochlor in the rat, when considered together with the mutagenicity data on acetochlor and the mechanistic data on the closely related compound alachlor, are considered adequate to demonstrate a nonmutagenic mode of tumor induction involving cytotoxicity from oxidative damage by a reactive quinoneimine intermediate.
(8) The relevance of the tumors to humans cannot be discounted. In the case of the rat nasal tumors, although the rat is considered to be more sensitive than humans, there is still the potential for humans to metabolize acetochlor to reactive intermediates with carcinogenic potential secondary to oxidative damage and induction of cell proliferation.

Based on the majority opinion and in accordance with the EPA Draft Guidelines for Carcinogen Risk Assessment (July, 1999), the CARC classified acetochlor as "Likely to Be Carcinogenic to Humans." The other tumor types identified in the mouse and rat studies were not considered as part of the weight-of-the-evidence for the reasons identified above.

The CARC determined that the carcinogenicity of acetochlor should be quantified by linear low dose extrapolation and that either lung tumors or histiocytic sarcomas of the mouse should be used to calculate the Q1*, depending upon which is more potent. Two members of the CARC considered a non-linear (MOE) approach more appropriate for the quantitation of carcinogenic potential of acetochlor, based on the lack of convincing genotoxicity data on acetochlor and the identification of a mode of action for nasal tumors. A similar mode of action to that of nasal tumorigenesis should therefore be operative in tumorigenesis in other tissues. However, the majority of the committee concluded that in the absence of mechanistic data specifically demonstrating an alternative mechanism of carcinogenicity in these tissues (lung and histiocytic sarcoma of the mouse), the default approach of linear low-dose extrapolation approach should be used to quantitate the carcinogenic potential of acetochlor.

One reviewing toxicologist considered the submitted data to be insufficient to support the proposed non-mutagenic mechanism of action for nasal tumor carcinogenesis of acetochlor and prepared a summary of his concerns which were attached to the committee's report as a minority dissenting opinion.

This Q* was based on the incidence of lung tumors in treated mice and the CARC report was refuted by the registrant triggering a fifth review completed in 2006. In this latest review, the CARC concluded that the nasal tumors seen in rats were the result of cytotoxicity and that the tumors in mice were likely not treatment related. The agency advised a margin of exposure approach to risk assessment stating that the reference dose would be adequately protective against carcinogenic as well as non-carcinogenic effects.

Summary of findings in rats

Statistically significant increases in rare olfactory epithelial papillary adenomas were observed at 1000 ppm and above (with a positive trend also identified), and tumors were observed in three 2-yr dietary studies. Nasal tumors were also observed in a two-generation rat reproductive toxicity study. Nasal tumors were identified as early as 19 weeks of treatment. The rapid development of tumors was determined to be consistent with nasal olfactory cell proliferation observed after 160 days and with nasal tumor formation after 5 months of treatment with the closely related compound alachlor. Tumor incidence did not exceed that of comparable dose levels in the chronic studies (compared on a mg/kg/day basis).

Thyroid follicular cell tumors were also observed, but were not used in the development of a cancer slope factor due to their relatively low incidence and evidence for disruption of thyroid hormonal homeostasis as the mode of action. Statistically significant increases in thyroid adenoma and combined adenoma/carcinoma were observed in female rats. Males showed significant increases, but only at an excessively toxic dose.

Liver tumors were observed at toxic doses, but were not considered as part of the cancer classification.

A rare basal cell tumor of the stomach was reported in one female at the high dose level. A re-evaluation diagnosed this tumor as a well-differentiated squamous cell carcinoma of the non-glandular stomach. A squamous cell papilloma with poorly differentiated squamous cell carcinoma in one male at the high dose was also identified. The CARC did not include this tumor in the weight-of-evidence considerations for cancer classification because it was of low incidence and probably was secondary to local irritation of the rat forestomach and, therefore, not considered relevant to human cancer risk.

Summary of findings in mice

Statistically significant increases in the incidence of lung tumors with a positive trend were observed in female mice in a 23-month study at all dose levels (0, 500, 1500 and 5000 ppm). There were no increases observed in males. Incidence exceeded available historical control range for adenoma (9.6% to 14.5%) at 500 and 1500 ppm and were within the high normal range for combined tumors (13.8 to 26.6%).

In the 78-week study (0, 10, 100 and 1000 ppm), the incidence of adenoma and combined tumors was significantly increased in males at 1000 ppm with a positive trend (adenoma 15%, 8%, 19% and 30%; combined 18%, 13%, 22% and 33%). Females showed only a positive trend for increased incidence of combined tumors only (9%, 8%, 14% and 18%); the incidence of adenomas was increased but showed no trend or pairwise increases (7%, 8%, 10% and 15%).

Incidence exceeded in-laboratory historical control values for adenoma and combined tumors at 1000 ppm in males (adenoma 4.0 to 17.3%, combined 15% to 28.9%) and females (adenoma 0% to 9.6% and combined 0% to 9.6%). An increased incidence of bronchiolar hyperplasia was also observed at 100 and 1000 ppm (13%, 10%, 39% and 38%). Based on these findings, the EPA CARC's 2004 report concluded that lung tumors were related to treatment and considered them as part of the cancer classification for acetochlor.

Statistically significant increases in the incidence of histiocytic sarcoma (using liver and uterus for each animal) were observed in female mice at 500, 1500 and 5000 ppm in study 1 (0%, 7%, 15% and 15%; high dose of 5000 ppm considered excessive due to toxicity). A positive trend only was observed in study 2 due to increases at the high dose of 1000 ppm (3%, 2%, 0% and 8%). The incidence at 1500 ppm exceeded the available historical control data range of 0 to 10%. Combination of tumor data from both studies showed a positive dose response. Based on these findings, the 2004 CARC report concluded that histiocytic sarcomas were related to treatment and considered them as part of the weight-of-evidence for cancer classification.

Statistically significant increases in the incidence of liver tumors were observed in both sexes at 5000 ppm and exceeded historical control values, but toxicity at this dose was considered excessive.

Renal adenomas and sarcomas were not considered as part of the cancer classification because they were only observed at an excessively toxic dose.

Benign ovarian tumors were observed at the mid and high dose levels. However, these were not considered treatment-related.

Structure-Activity Relationships

Acetochlor is structurally related to other chloroacetanilide herbicides, including alachlor, butachlor, propachlor and metolachlor. These chemicals have overlapping, but not identical, tumor profiles as compared below. The FIFRA SAP concluded in 1997 that acetochlor, alachlor and butachlor share common modes of action for induction of nasal epithelial tumors and thyroid follicular cell tumors and the CARC affirmed this conclusion.

Mutagenicity

Acetochlor was weakly positive in the CHO/HGPRT gene mutation assay with and without activation in the mouse lymphoma assay. Acetochlor was negative in a DNA damage repair assay in rat hepatocytes, a *Salmonella* assay, and two *in vivo* chromosomal aberration studies (US EPA, 1994).

In mutagenicity tests conducted by ZENECA, acetochlor induced a reproducible, positive, mutagenic response in a strain of *Salmonella typhimurium* with metabolic activation at 100 ug/plate. Significant increases in number of revertant colonies were not induced in four other strains. Acetochlor was not clastogenic (capable of causing breakage to chromosomes) in a mouse micronucleus test at doses tested (898 and 1,436 mg/kg in males; 1,075 and 1,719 mg/kg in females). Acetochlor was clastogenic in cultured human lymphocytes at both 50 and 100 ug/ml. Acetochlor induced a weak DNA repair (measured by UDS) in rat hepatocytes (liver cells) derived from animals exposed in vivo at 2,000 mg/kg. In a structural chromosome aberration-study, acetochlor at doses 1,000 and 2,000 mg/kg resulted in reduced fertility during weeks 2, 3, and 4 of this study, as shown by reduced pregnancy incidence, decreased implants per pregnancy incidence, increased preimplantion loss, and loss, and decreased time implant per pregnancy. Intrauterine deaths were not affected in this study. There was positive evidence of mutagenicity at the mid- and high-dose levels in this study (US EPA, 1994).

Reproductive and Developmental Effects

There is no evidence that acetochlor is teratogenic or that offspring are more susceptible than adults, but acetochlor does cause developmental toxicity in rats at maternally toxic doses.

Environmental Fate

Soil and Groundwater

Acetochlor is adsorbed by soil colloids and leaches very little. Low soil moisture has little influence on efficiency. Laboratory studies indicate that acetochlor does not degrade by hydrolysis or photolysis. The primary method of degradation is microbial breakdown. Acetochlor's average persistence in surface soils at recommended application rates is 8 to 12 weeks, but this rate will vary depending on soil type, temperature and soil organic and moisture content (EPA, 2006). The principal environmental breakdown products are ethane sulfonic acid (ESA) and oxanilic acid (OA) metabolites which are more mobile in soils and more persistent in the environment compared to the parent herbicide (EPA, 2006). These metabolites leach readily and have been detected in a high percentage of groundwater and surface waters in the Midwestern US (Kolpin et al. 2000).

Surface Water

No information was found on degradation in surface waters.

Vegetation

Acetochlor is absorbed by germinating plant shoots and roots and can be translocated throughout the plant, with higher concentrations in vegetative parts rather than in reproductive parts. Acetochlor inhibits protein synthesis in susceptible plants.

Analytical Methods

Acetochlor can be analyzed in water samples using EPA method 525.2. Method 525.2 is used to determine semi-volatile organics in drinking water and drinking water sources. The analytes are extracted from the water using a 47 mm C18 disk. The disk is extracted with ethyl acetate and methylene chloride, the extract dried with sodium sulfate, and reduced in volume to 1.0 mL. Final analysis is by GC/MS.

Regulatory Summary

MCL	None
MCLG	None
LOAEL	10 mg/kg/day
NOAEL	2 mg/kg/day (1 yr dog study)
Uncertainty Factor	100 (10 each for inter- and intra- species variation)
RfD	0.02 mg/kg/day
Cancer Classification	Suggestive Evidence of Carcinogenic Potential
Cancer slope factor	0.0169 (nasal tumors in rats); 0.0327 (lung tumors in mice)

State Drinking Water/Groundwater Standards

Minnesota	9 µg/L (chronic, non-cancer health risk level)
Montana	140 µg/L (surface and groundwater)

Recommendations and Conclusions

The Department of Health Services recommends use of NOAEL from the 1 yr dog study to calculate a groundwater enforcement standard for acetochlor. Since acetochlor is classified as a 'suggestive human carcinogen' and because the reference dose was based on a subchronic toxicity study in dogs, an uncertainty factor of 3,000 is recommended. This UF include factors of 10 each to account for intra- and inter-species variability, a factor of 10 to protect against possible cancer risks, and a factor of 3 to account for the use of subchronic study.

$$\frac{2\ \text{mg/kg/day} \times 10\text{-kg} \times 100\%}{3{,}000 \times 1\ \text{liter/day}} = 0.067\ \text{mg/L rounded to } 7\ \mu\text{g/L}$$

Recommended enforcement standard	7 µg/L
Recommended preventive action limit	0.7 µg/L

References

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WDATCP. 2000. Chloroacetanilide herbicide metabolites in Wisconsin groundwater: Final Report.

ACETOCHLOR ETHANE SULFONIC PLUS OXANILIC ACID METABOLITES

(Combined Standard)

Acetochlor ethane sulfonic acid (ESA) and acetochlor oxanilic acid (OXA) are environmental degradates of acetochlor which is a chloroacetanilide herbicide used for pre-emergence control of weeds in corn.

	Acetochlor OXA	Acetochlor ESA
CAS no.	184992-44-4	187022-11-3
Molecular Weight	267.77	315.80
Physical State	Liquid	Liquid
Water Solubility	Freely soluble	Freely soluble
Density at 20 deg C	Not available	Not available
Synonyms	Acetochlor OXA, MON 52755	Acetochlor ESA, MON 52754

Occurrence

The herbicide acetochlor was given conditional registration by the U.S. Environmental Protection Agency in March 1994 which provided an opportunity to study the environmental distribution and fate of a pesticide during its first season of use. Water samples collected and analyzed by the U.S. Geological Survey during this time documented the distribution of acetochlor in the hydrologic system. It was detected in 29% of the rain samples from four sites in Iowa, 17% of the stream samples from 51 sites across nine states, and 0% of the groundwater samples from 38 wells across eight states. Acetochlor exhibited concentration increases in rain and streams following its application to corn in the midwestern United States, with 75% of the rainwater and 35% of the stream samples having acetochlor detected during this time period. Concentrations in rain decreased as the growing season progressed.

More than 70 wells, including 27 monitoring wells, 22 private drinking water wells, and 23 municipal wells in Wisconsin have been sampled for alachlor, metolachlor, acetochlor, and their ethane sulfonic acid (ESA) and oxanilic acid (OXA) metabolites. Wells were selected based on previous detections of pesticides or proximity to agricultural fields to increase the likelihood of exposure to the compounds of interest. Alachlor, metolachlor, and acetochlor are chloroacetanilide herbicides that are commonly used on corn and other crops in Wisconsin. Sample results showed over 80 percent of the monitoring wells and drinking water wells contained the ESA and OXA metabolites of alachlor and metolachlor. Acetochlor metabolites were detected less frequently. Analytical results for acetochlor OXA ranged from below the level of detection to 1.9 µg/L with detects in 19% of the monitoring wells and 9% of the private drinking water supplies. Analytical results for acetochlor ESA ranged from below the level of detection to 6.4 µg/L with detects in 33% of the monitoring wells and 14% of the private drinking water supplies. None of the public water supplies had detectable levels of these degradates, however (WDATCP, 2000).

Toxicity

The metabolism of acetochlor and the toxicity of its metabolites are summarized in a March 1, 2006 US EPA document titled Acetochlor: Revised HED Chapter of the Tolerance Reassessment Eligibility Decision Document. The following is a summary of information provided by the EPA document.

Following oral dosing of rats, 34 to 39% of acetochlor OXA was absorbed and approximately 85% was excreted untransformed. In a 4-week range finding study conducted in rats, NOAELs of 372.6/367.2 and 370.3/374.6 mg/kg/day (M/F) were established for acetochlor OXA and acetochlor ESA, respectively, based on changes in thyroid hormone levels. A 90-day feeding study in rats yielded a NOAELs of 230.2

and 225.4 mg/kg/day for the OXA and ESA metabolites, respectively, based on reduced body weights, lower weight gains and decreased food intake in males. In comparison, the 90-day NOAEL for acetochlor was 40 mg/kg/day. These findings indicate that the ESA and OXA metabolites of acetochlor are significantly less toxic than the parent herbicide.

Carcinogenicity

Acetochlor ESA and OXA have not been tested for carcinogenicity.

Mutagenicity

In vitro studies using bacterial assays and mammalian cells indicate that acetochlor ESA and OXA are not mutagenic (EPA, 2006).

Reproductive and Developmental Effects

The maternal and developmental toxicity of acetochlor OXA has been studied in rats. The maternal NOAEL and LOAEL were 500 and 1000 mg/kg/day based on maternal mortality. The developmental NOAEL was greater than 1,000 mg/kg/day (EPA, 2006).

Environmental Fate

Soil and Groundwater: The principal environmental breakdown products of acetochlor include the ethane sulfonic acid (ESA) and oxanilic acid (OA) metabolites which are more mobile in soils and more persistent in the environment than to the parent herbicide (EPA, 2006). These metabolites leach readily and have been detected in a high percentage of groundwater and surface waters in the Midwestern US (Kolpin et al. 2000).

Surface Water: Acetochlor ESA and OXA have been detected in surface waters in areas of use. No information was found on its degradation in surface waters, however.

Regulatory Summary

	Acetochlor OXA	Acetochlor ESA
LOAEL	955.2 mg/kg/day	919.4 mg/kg/day
NOAEL	230.2 mg/kg/day	225.4 mg/kg/day
RfD	None	None
MCL	None	None
MCLG	None	None
DWEL	None	None
LHA	None	None
Cancer Classification	Not classified	Not classified

State Drinking Water/Groundwater Standards

None found

Recommendations and Conclusions

The Department of Health Services recommends that NOAELs from 90-day rat feeding studies for acetochlor ESA and OXA be averaged and used as the point of departure for a combined enforcement standard (GWES). A combined standard is justified because these metabolites frequently occur in aquifers together and are similar in molecular structure. Their toxicity profiles are virtually identical with both chemicals having effects on thyroid hormone levels and on body weight gain in rats. Because these substances are not known to have carcinogenic or mutagenic effects, a 20% preventive action limit (PAL) is appropriate. An uncertainty factor of 10,000 is recommended. This includes 4 factors of 10 each to account for the use of a subchronic study, for intra- and inter-species variability, and for gaps in the toxicological database. Data gaps for these substances include the lack of studies in a second species, as well as the lack of chronic toxicity studies and carcinogenicity evaluations.

$$\frac{228 \text{ mg/kg/day} \times 10\text{-kg} \times 100\% \text{ exposure}}{10{,}000 \times 1 \text{ liter/day}} = 228\ \mu\text{g/L (rounded to 230)}$$

Recommended Enforcement Standard	230 µg/L
Recommended Preventive Action Limit	46 µg/L

References

Kolpin DW, Nations BK, Goolsby DA; Thurman EM. (1996) Acetochlor in the hydrologic system in the midwestern united states, 1994. ES&T 30(5):1459-1464.

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ALUMINUM

Aluminum is the third most prevalent element and the most abundant metal in the earth's crust. In nature, aluminum is bound to other elements such as oxygen, silicon, and fluorine. Metallic aluminum, which is used for a variety of industrial and household products, is obtained from these aluminum-containing minerals. Small amounts of aluminum can be found naturally in surface water. Aluminum metal is light in weight and silvery-white in appearance. It is used for beverage cans, cookware, airplanes, siding and roofing, and as aluminum foil. Aluminum is often mixed with other metals to form alloys, which are stronger and harder than pure aluminum.

Aluminum compounds are used as alums in water-treatment and alumina in abrasives and furnace linings. They are also found in consumer products such as antacids, astringents, buffered aspirin, food additives, and antiperspirants.

CAS no.	7429-90-5
Atomic Weight	26.9
Physical State	Shiny, soft metal
Water solubility	Insoluble in metallic form, salts are soluble
Density at 20 deg C	2.7
Synonyms	Aluminium, Bauxite

Occurrence

WDNR's GRIN database provides aluminum data for 399 water supply wells. Levels ranged from <0.0005 to 39,200 uGu/L and exceeded the current health advisory level of 180 µg/L in 31 wells. Levels were highest in Brown and Wood counties where aluminum levels averaged 4,752 and 1,698 ug/L, respectively. Data from private water supply wells tested through the local health departments suggests that elevated aluminum levels are rare with only 6 of 1,128 wells having an aluminum level above 180 ug/L (LIMS, accessed 12/04/08).

Toxicity

In their 2007 review of the human and animal toxicity studies on aluminum Krewski et al. (2007) determined that the most sensitive endpoints were on reproductive and neurological function and concluded that a level of 0.1 mg/L in water was likely protective against these effects.

In Curaçao, distilled seawater from the water plant was used for hemodialysis for several decades. A new water supply pipe, which was lined with cement mortar to prevent corrosion, was installed in May 1996. Because of the aggressiveness of the distilled water, calcium and aluminum leached from the cement mortar into the water causing hard water syndrome and acute Al intoxication. Of the 27 patients who were dialyzed with this water, 10 died from acute Al encephalopathy. The non-survivors were older (64 $\pm$ 3 years vs. 52 $\pm$ 2 years, P , 0.01) and had a lower body weights and lower serum albumin concentrations (33 $\pm$ 1 vs. 36 $\pm$ 1 g/L, P , 0.01). Anuria also tended to be more common in the non-survivors (8 of 10 vs. 8 out of 17, *p-value* 0.05). Serum Al concentrations, available in seven non-survivors, were significantly higher than in the survivors (808 $\pm$ 127 vs. 255 $\pm$ 25 mg/L, P , 0.01). A test of the water revealed an aluminum concentration of 650 µg/L and a calcium content of 17.2 mg/L.

Nine out of 13 published epidemiological studies of Al in drinking water and AD have shown statistically significant positive associations (Flaten et al., 1996). A case-control study conducted in eight regions of England and Wales and found no difference between current aluminum levels in water consumed by people with AD vs controls diagnosed with other forms of dementia, brain cancer or other diseases (Martyn et al. 1997). Two prospective studies found positive associations between aluminum levels in water and the development of AD. Researchers in Quebec reported that 'after adjustment for education level, presence of family cases, and ApoE ε4 allele, exposure to organic monomeric aluminum estimated at the onset of the disease was associated with AD (Gauthier et al, 2000). Rondeau et al. (2009) examined associations between exposure to aluminum or silica from drinking water and risk of AD among elderly subjects followed for 15 years. These researchers also found that the risk of dementia and AD were higher for subjects with high daily aluminum intake while silica content in water had a protective effect.

Dietary aluminum is ubiquitous, but in such small quantities that it is not a significant source of concern in people with normal renal function. Urban water supplies may contain a greater concentration because alum is often used as a flocculant. No known physiologic need exists for aluminum. However, because of its atomic size and electrical charge (0.051 nm and 3+, respectively), it is sometimes a competitive inhibitor of several essential elements such as magnesium, calcium, and iron. Approximately 95% of an aluminum load becomes bound to serum transferrin and albumin and is then eliminated by the kidneys. If exposure levels exceed the body's excretory capacity, the excess is deposited in various tissues including bone, brain, liver, heart, spleen, and muscle. This accumulation causes morbidity and mortality through various mechanisms.

Most cases of human aluminum toxicity have involved patients with impaired renal function or patients who were exposed to high levels of aluminum from contaminated water used in dialysate solutions or parenteral nutrition fluids. Acute intoxication is extremely rare. However, in persons with impaired kidney function, aluminum can accumulate in the body. In the brain, where aluminum has an estimated half life of 7 years, it induces oxidative stress and interferes with neurofilament axonal transport and neurofilament assembly. Some experts believe that exposure plays a role in the formation of the characteristic neurofibrillary tangles seen in Alzheimer's Disease. Aluminum also has a direct effect on the formation of red blood cells inducing microcytic anemia similar to that seen in patients suffering from lead poisoning.

Flaten et al. (1996) described several reports of aluminum accumulation and toxicity in individuals without chronic renal failure, especially preterm infants (primarily fed intravenously), and stated that preterm infants are at risk for aluminum loading because of their immature kidney function. Term infants with normal renal function may also be at risk because of their rapid growth and immature blood-brain barrier. Until they are 1 to 2 years old, infants have lower glomerular filtration rates than adults which affect their ability to excrete aluminum. The US Food and Drug Administration is concerned that young children are at a higher risk resulting from exposure to aluminum. Accordingly, the agency requires warnings on all aluminum-containing antiperspirants to inform parents to keep these products away from children, and to seek professional assistance if accidental ingestion occurs.

Aluminum (Al) impairment of bone matrix formation and mineralization may be mediated by its direct effect on bone cells or indirectly by its effect on parathyroid hormone and calcium metabolism. The risk for Al toxicity is greatest in infants with chronic renal insufficiency, recipients of long term parenteral nutrition, and preterm infants with low Al binding capacity. The rapid growth during infancy would

theoretically potentiate Al toxicity in all infants, although the critical level of Al loading causing bone disorders is not known. To minimize tissue burden, Al content of infant nutrients should be similar to "background" levels, i.e., similar to whole milk -less than 50 micrograms/L (Koo and Kaplan, 1988).

Aluminum, cadmium and lead concentrations in the sperm and seminal plasma of 27 employees of two industrial companies, a refinery and a polyolefin factory, and 45 consecutive sperm donor candidates at a sperm bank were studied using atomic absorption measurements. The relationship between metal concentration and parameters of semen analysis was studied. A high concentration of aluminum in sperm was correlated with decreased sperm motility. The concentrations of cadmium and lead were low and did not show any correlation with parameters of semen analysis. Hovatta et al. (1998) concluded that aluminum may be one of the environmental pollutants that causes impaired semen quality.

Animal studies

Animal studies in rats and recent case reports have implicated the use of oral aluminum-containing antacids during pregnancy as a possible cause for abnormal fetal neurologic development.

Animal reproductive and gestational studies may provide the most sensitive endpoints for selection of a point of departure for risk assessment. In open field tests of motor activity, significant delays in pivoting, longer latencies and more rearings were observed in the offspring of rats administered gavage doses of 73 mg Al per kg/day as aluminum chloride (Misawa and Shigeta, 1992 as cited by ATSDR).

An intermediate duration oral study in male rats found that sperm counts were decreased following exposure to 2.5 mg Al/kg/day as aluminum chloride for 6-12 months. A dose of 0.25 mg/kg was considered the threshold level for adverse effects while a dose of 0.025 mg/kg had no effect on sperm production, chromosomal changes or blood phosphatase levels (Krasovskii et al. 1979 as cited by ATSDR).

Yousef et al. (2005) described the protective effects of ascorbic acid against the toxicity of aluminum chloride (AlCl3) on reproductive performance, lipid peroxidation and enzyme activities in male New Zealand white rabbits. Six rabbits per group were assigned to one of four treatment groups: 0 mg ascorbic acid and 0 mg AlCl3/kg body weight; 40 mg ascorbic acid/kg 34 mg Al (as AlCl3) per kg, 34 mg Al plus 40 mg ascorbic acid/kg. Rabbits were orally administered their respective doses every other day for 16 weeks. Results obtained showed that AlCl3 significantly ($P<0.05$) decreased libido, ejaculate volume, sperm concentration, total sperm output, sperm motility, total motile sperm per ejaculate, packed sperm volume, total functional sperm fraction, normal and live sperm and semen initial fructose while pH and dead and abnormal sperm were increased ($P<0.05$). Live body weight, feed intake and relative weights of testes and epididymis were significantly ($P<0.05$) decreased. The study suggested that ascorbic acid might be protective against aluminum-induced reproductive toxicity.

Guo et al. (2005) demonstrated the effect of aluminum on testosterone levels in male mice. Intraperotineal injections of 35 mg Al/kg body weight /day, administered for 12 days, significantly increased nitric oxide production and decreased both testicular adenosine 3',5'-cyclic monoposphate and testosterone levels.

Azzaoui et al. (2008) investigated the effects of aluminum nitrate administered in drinking water during 90 days on body weight gain, motor activity, brain aluminum accumulation and recognition memory of young, female Wistar rats. Treated rats received 80 mg/L of aluminum nitrate diluted in drinking water, while control rats received drinking water only. Body weight, motor activity, object recognition memory (NOR) and brain aluminum concentration were evaluated. Body weights were taken weekly, whereas the memory abilities and the motor activity are measured once every fourteen days, by submitting rats to the open field test and to the novel object recognizing memory test. The results revealed a significant decrease in body weight ($p < 0.05$). Though, no significant change in motor activity was seen, a significant effect on recognition memory was observed ($p < 0.01$). Brain tissue aluminum levels were not significantly different between treated and control rats.

Carcinogenicity

US EPA: Not classified

IARC: Group 1, carcinogenic to humans

Although the US EPA has not evaluated the carcinogenicity of aluminum, at least two studies have shown carcinogenic effects in animals. Schroeder and Mitchener (1975a) exposed Long-Evans weanling rats (52/sex) to drinking water containing 5 mg/L aluminum (as aluminum potassium sulfate) for life. Specific tumor types were not specified; the incidence of total tumors was 13/25 in treated males and 4/26 in control males. The incidence of malignant tumors was 6/25 in treated males and 2/26 in control males. In another study, groups of 54 Swiss mice/sex were given 5 mg aluminum/L (as aluminum potassium sulfate) in the drinking water for life (Schroeder and Mitchener, 1975b). The incidence of leukemia in treated females was 10/41, while the incidence in control females was 3/47.

IARC has classified aluminum production as a Group 1 human carcinogen citing excess cancers of the lung and bladder among workers in the Canadian Province of Quebec where five aluminum plants were operating using the Söderberg production process (IARC, 1987).

Regulatory Summary

The US EPA has not developed a health-based drinking water standard for aluminum, nor has it developed a reference dose or cancer classification. Under the Safe Drinking Water Act, aluminum is regulated as an aesthetic parameter. The secondary maximum contaminant level (SMCL) for aluminum set at 0.05–0.2 mg/L is based on color. Acute and chronic surface water quality criteria for aluminum are set at 750 and 87 μg/L, respectively (US EPA, 1998).

NOAEL	None
LOAEL	None
MCL	None
SMCL	0.05-0.2 mg/L
MCLG	None
DWEL	None
LHA	None
Cancer Classification	D, not classified

The Food and Drug Administration (FDA) has set the allowable concentration of aluminum in bottled water at 200 μg/L.

The World Health Organization has also assessed the toxicity of aluminum in drinking water. In its Environmental Health Criteria document for aluminum (WHO, 1997) this global health agency concluded:

> "On the whole, the positive relationship between aluminium in drinking-water and AD, which was demonstrated in several epidemiological studies, cannot be totally dismissed. However, strong reservations about inferring a causal relationship are warranted in view of the failure of these studies to account for demonstrated confounding factors and for total aluminium intake from all sources.
>
> Taken together, the relative risks for AD from exposure to aluminium in drinking-water above 100 μg/litre, as determined in these studies, are low (less than 2.0). But, because the risk estimates are imprecise for a variety of methodological reasons, a population-attributable risk cannot be calculated with precision. Such imprecise predictions may, however, be useful in making decisions about the need to control exposures to aluminium in the general population.
>
> The degree of aluminium absorption depends on a number of parameters, such as the aluminium salt administered, pH (for aluminium speciation and solubility), bioavailability, and dietary factors. These should be taken into consideration during tissue dosimetry and response assessment. Thus, the use of currently available animal studies to develop a guideline value is not appropriate because of these specific toxicokinetic/dynamic considerations.
>
> Owing to the uncertainty surrounding the human data and the limitations of the animal data as a model for humans, a health-based guideline value for aluminium cannot be derived at this time.
>
> The beneficial effects of the use of aluminium as a coagulant in water treatment are recognized. Taking this into account and considering the potential health concerns (i.e. neurotoxicity) of aluminium, a practicable level is derived based on optimization of the coagulation process in drinking-water plants using aluminium-based coagulants, to minimize aluminium levels in finished water.
>
> A number of approaches are available for minimizing residual aluminium concentrations in treated water. These include use of optimum pH in the coagulation process, avoiding excessive aluminium dosage, good mixing at the point of application of the coagulant, optimum paddle speeds for flocculation, and efficient filtration of the aluminium floc (Letterman & Driscoll, 1988; WRc, 1997). Under good operating conditions, concentrations of aluminium of 0.1 mg/litre or less are achievable in large water treatment facilities. Small facilities (e.g. those serving fewer than 10 000 people) might experience some difficulties in attaining this level, because the small size of the plant provides little buffering for fluctuation in operation, and small facilities often have limited resources and access to expertise to solve specific operational problems. For these small facilities, 0.2 mg/litre or less is a practicable level for aluminium in finished water (WRc, 1997)."

ATSDR has derived a chronic-duration oral MRL of 1 mg Al/kg/day for aluminum. This MRL is based on a LOAEL of 100 mg Al/kg/day for neurological effects in mice exposed to aluminum lactate in the diet during gestation, lactation, and post-natally until 2 years of age (Golub et al. 2000). The MRL was derived by dividing the LOAEL by an uncertainty factor of 300 (3 for the use of a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability) and a modifying factor of 0.3 to account

for the higher bioavailability of the aluminum lactate used in the principal study, as compared to the bioavailability of aluminum in the human diet and drinking water.

Other Drinking Water Standards and Advisories

British Columbia	200 μg/L (human)
	5 mg/L (livestock)
	100 μg/L (fresh water aquatic life)
California	1,000 μg/L
New Jersey	200 μg/L
New York	100 μg/L
US EPA	87 μg/L (Chronic freshwater criteria)
US FDA	200 μg/L
WHO	200 μg/L

Recommendations and Conclusions

The Department of Health Services' review of toxicity literature has determined that the 2005 study by Yousef et al. provides the most sensitive endpoint for aluminum toxicity that complies with current laboratory standards. In this study, a dose of 34 mg Al per kg body weight every other day for 16 weeks resulted in male reproductive changes. A modifying factor of 2 is recommended to convert this dosing regimen to a daily dose of 17 mg Al per kg body weight. Three uncertainty factors of 10 each were applied to convert a LOAEL to a NOAEL, and to account for intra- and inter- species variability. Because aluminum has been shown to have carcinogenic properties in animals, a 10% PAL is recommended.

In developing this standard, the agency considered the provisional toxicity values established by Regional EPA offices as well as the ATSDR minimal risk value. However, it was determined that these values are based on LOAELs that were higher than the effect level established by Yousef, did not consider the potential carcinogenicity of aluminum, and provided standards that exceeded levels that have been associated with adverse effects in human populations.

$$\frac{17 \text{ mg/kg/day} \times 10\text{-kg}}{1{,}000 \times 1 \text{ liter/day}} = 170 \ \mu\text{g/L}$$

DHS recommends rounding this number to 200 μg/L to make it consistent with federal standard set by the Food and Drug Administration for aluminum in bottled drinking water as well as with the international standard developed by the World Health Organization.

Recommended Enforcement Standard	200 μg/L
Recommended Preventive Action Limit	20 μg/L

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AMMONIA

Ammonia is a naturally-occurring inorganic chemical that is ubiquitous in nature. In aqueous solution, the ammonium ion (NH_4+) and unionized ammonia (NH_3) exist in a pH-dependent equilibrium. Alkaline conditions favor the unionized form, while the ionized form predominates at physiologic pHs. Ammonia is used in fertilizers, refrigeration systems, household cleaners, and manufacturing processes. It is also used in conjunction with chlorine to form chloramine which is used as a drinking water disinfectant.

CAS no.	7664-41-7
Molecular weight	17.03
Physical state	Colorless gas with a very pungent odor, liquid under pressure
Density	0.6818
Water solubility:	531 grams per liter
Taste threshold:	34 mg/L
Synonyms:	Ammonium hydroxide

Occurrence

Major natural sources of ammonia include animal excreta, decaying vegetation, human sewage, industrial wastewater, combustion of fossil and non-fossil fuels. The commercial synthesis of ammonia is a minor source thought to contribute no more than 5% of the total global ammonia budget. Due to its volatility and rapid conversion to nitrate, ammonia is not a major contaminant of groundwater or surface water. Background levels in these media range from 0 to ~1 mg/L.

Most human exposure to ammonia occurs as a result of inhalation of household cleaning products and through dermal contact. Occupational exposure usually involves inhalation of ammonia gas. Ammonia is produced in the human digestive tract during bacterial degradation of nitrogenous compounds from ingested food. Ammonia absorbed from the gastrointestinal tract is transported to the liver where it is converted to urea and glutamine. In healthy adults liver detoxification is rapid and very little ammonia reaches the systemic circulation.

Toxicity

An acute LD50 of 350 mg/kg was reported in rats administered ammonia (Smyth et al, 1941).

Most cases of acute ammonia exposure involve inhalation of concentrated forms of ammonia gas. Clinical effects range from a mild irritation to life-threatening cases of pulmonary edema depending on the concentration and length of exposure. Household ammonia solutions typically contain 5 to 10% ammonia in water. These concentrations rarely cause burns, but can irritate the eyes, nose, throat, and upper respiratory tract. Higher concentrations used in agricultural and industrial settings can cause irritation and severe burns of the eyes, lungs, upper airway, and skin. When heated to decomposition, ammonia emits toxic fumes of ammonia and nitrogen oxides.

Suicidal or accidental ingestion of household ammonia can cause esophageal burns with late resulting strictures. Gastric, duodenal, and jejunal lesions have also been reported. One teaspoonful of strong (28%) ammonia has been reported to be fatal but recoveries have followed ingestion of as much as one fluid ounce on several occasions (Gosselin et al. 1984).
Ammonium chloride has been used as a diuretic and urine-acidifying agent. Therapeutic dosage levels for adults range from 4 to 12 grams/day. Based on an average body weight of 70 kg, these are equivalent to 19 to 57 mg/kg/day as ammonium. The usual acidifying dose for children is 25 mg/kg/day as

ammonium (Reynolds and Prasad, 1982). The drug is given in four divided doses for three to four days, followed by a two-day rest period. If given continuously, particularly to patients with renal impairment, it may cause severe metabolic acidosis. Any use is contraindicated in patients with liver or renal disease since accumulation of ammonia in such patients may lead to central nervous system toxicity. Other adverse effects associated with the administration of ammonium chloride include: gastric irritation, anorexia, metabolic acidosis, and electrolyte disturbances (Amer Hosp Form Serv, 1988).

Chronic toxicity

Enlarged adrenal glands and increases in blood pressure were observed in rabbits that received 124 mg ammonium/kg/day as ammonium hydroxide by gavage for 17 months (Fazekas, 1939). Reduced food intake and decreased body weights were observed in rats fed 500 mg ammonium sulfamate per kg 6 days/week for 90 days. This dose is equivalent to 428 mg/kg/day as ammonium sulfamate, or 79 mg ammonium cation per day. The NOAEL for this study was 214 mg/kg/day (40 mg/kg/day as ammonium) (Gupta et al, 1979). Administration of 0.02 % ammonia (200 mg/L) as drinking water for 24 weeks caused glandular atrophy in the gastric mucosa of male Donryu rats. Treatment at this dose for 8 weeks delayed healing of acetic acid-induced gastric ulcers (Hata et al, 1994).

Absorption and metabolism

Ammonia is rapidly absorbed from the gastrointestinal tract. Absorbed ammonia is transported to the liver where it is converted to urea which is excreted by the kidneys and glutamine which is distributed to the tissues where it is used as a source of nitrogen for protein synthesis. Metabolism and excretion of ammonia is inefficient in persons suffering from certain inherited or acquired metabolic disorders, and in patients with liver or renal diseases (Smith, 1990). Ammonia is normally found in human blood at concentrations of 80 to 110 micrograms/deciliter (Braunwald et al, 1987).

Persons who have been suggested as being more sensitive to the toxic effects of ammonia include: 1) persons suffering from advanced liver or kidney disease; 2) persons with genetic defects in the urea cycle enzymes, or in ornithine transcarbamylase; 3) persons suffering from gout; and 4) women in the last trimester of pregnancy who are at risk for toxemia of pregnancy (Reprotext Database, 1996).

Ammonia accumulates in the blood, brain, and cerebral spinal fluid of patients suffering from acute liver failure causing a condition termed hepatic encephalopathy. High-protein diets, gastrointestinal hemorrhage, and constipation can exacerbate this condition by increasing colonic ammonia production (Kirk, 1986).

Reproductive/developmental effects

Decreased egg production has been demonstrated in birds and pullets. An elevated ammonia tissue concentration in cows has been found to decrease conception rates and increase the calving-to-conception intervals. No data were located regarding the teratogenic potential of ammonia.

Carcinogenicity assessment

EPA cancer classification: D, not classified

Animal studies conducted in Japan have found that the administration of 0.01% (100 mg/L) ammonia in drinking water for 24 weeks significantly increased the number of cancers in the glandular stomach of rats pretreated with the experimental carcinogen N-methyl-N'-nitro-N-nitrosoguanidine (MNNG). These

researchers concluded that ammonia appears to be an important promoter of gastric cancer in rats and possibly in *Helicobacter pylori*-associated gastric carcinogenesis in humans (Tsujii, 1995).

Genotoxicity

Mutations and chromosome aberrations have been reported following exposure of bacteria or cultured cells to lethal concentrations of ammonia gas. The relevance of these findings to sublethal exposure levels is controversial (ATSDR, 1990).

Environmental fate

Aquatic
In surface waters ammonium undergoes microbiological nitrification, which yields hydrogen and utilizes oxygen so that, in certain systems, acidification and oxygen depletion may result. In one study, one-third of the acidifying effect of precipitation was attributed to ammonium deposition. Ammonia may be assimilated by aquatic plants as a nitrogen source or transferred to sediments or volatilized. Concentrations of ammonia that are acutely toxic to fish can cause loss of equilibrium; hyperexcitability; increased breathing, cardiac output, oxygen uptake; and in extreme cases convulsions, coma, and death. 48 and 96-hr LC50s for freshwater fish range from 0.56 to 2.48 mg/L (WHO, 1986). Lower levels and caused reductions in fish egg hatching success, a reduction in growth rate and morphological development, and pathological changes in the tissues of the gills, liver and kidney (USEPA/OWRS, 1986).

Atmospheric
Ammonia that volatilizes into the atmosphere may undergo a variety of reactions with sulfur dioxide or ozone to produce aerosols or ammonium sulfate or ammonium nitrate. These products return to the earth's surface in wet or dry deposition.

Terrestrial
The application of certain synthetic fertilizers also contributes to soil ammonia levels. The ammonium cation is relatively immobile in soil; however, most ammonium is oxidized to nitrate which is highly mobile. Nitrate is removed by leaching, plant root uptake, or denitrification.

Regulatory Summary

NOEL/LOEL	None
RfD	None
MCL/DWEL	None
Lifetime Health Advisory	30 mg/L (taste threshold)
Cancer class	D, Not classified

Summary of toxicity information for ammonia

Species	Route	Exposure Duration	Dose* mg/kg/day	Effect	Form	Reference
Guinea Pig	Oral	1 day	303	Death	NH_4Cl	Koenig, 1941
Human	Oral	3-4 days	25	Gastric irritation, CNS toxicity	NH_4Cl	Reynolds, 1982
Dog	Oral	11 weeks	337	Bone deformity and softening	NH_4Cl	Bodansky, 1932
Rabbit	Oral	17 months	124	Increased blood pressure, Enlarged adrenal glands	NH_4OH	Fazekas, 1939
Rat	Oral	90 days	79	Decreased weight, No systemic effects	$NH_4NH_2SO_3$	Gupta, 1979

*All doses are expressed as ammonium cation

State Drinking Water Standards and Advisories

New Jersey 3 mg/L

Recommendations and conclusions

The U.S. Environmental Protection Agency has not established a health-based drinking water standard for ammonia. Our review of current literature indicates that the federal lifetime health advisory may not be adequate to protect sensitive subpopulations, such as persons suffering from kidney or liver disease, against the toxicity of ingested ammonia. Therefore, in accordance with the provisions of ss NR 160.13, the Department of Health Services recommends that a health-based groundwater enforcement standard be established based on the human toxicity of ammonium chloride which has been used as a therapeutic agent. Following ingestion, ammonium chloride dissociates to produce the chloride anion and the ammonium cation. The chloride anion exerts a diuretic effect, but has little overt toxicity. Chloride is currently regulated in public drinking water supplies and in groundwater as a public welfare parameter. The gastric irritation and neurotoxicity that have been associated with the use of ammonium chloride have been attributed to the effect of ammonia on the upper digestive tract and to its systemic toxicity.

To develop a health-based groundwater standard that will be protective against the toxicity of ingested ammonia, application of an uncertainty factor of 20 to the therapeutic dosage level is recommended. This includes a factor of 10 to convert a human LOAEL to a NOAEL, and an additional factor of 2 to account

for the use of information from a discontinuous exposure. Since ammonia has been shown to have mutagenic and carcinogenic effects, a 10% preventive action limit is proposed.

$$\frac{25 \text{ mg/kg/day} \times 10 \text{ kg}}{20 \times 1 \text{ liter/day}} = 12.5 \text{ mg/L as ammonium (9.7 mg/L as ammonia-nitrogen)}$$

Recommended enforcement standard:	9.70 mg/L (as ammonia-nitrogen)
Recommended preventive action limit:	0.97 mg/L

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CHLORODIFLUOROMETHANE (FREON-22)

Chlorodifluoromethane is a hydrochlorofluorocarbon (HCFC) used in refrigeration and air conditioning. It is currently being used in "closed loop" geothermal heating/cooling systems and may pose a risk to groundwater.

CAS no.	75-45-6
Molecular Weight	86.5
Molecular Formula	CHClF2
Physical State	Ether-like, clear liquid under pressure; gas at room temperature
Water Solubility	3 to 4 grams/L
Synonyms	Freon 22, HCFC-22, CFC-22,Genetron 22

Occurrence

Although Freon 22 has never been detected in WI groundwater, very little testing has been conducted and the risk of contamination is considered to be high due to its use as a refrigerant fluid in "closed loop" geothermal heating/cooling systems.

Toxicity

Freon 22 has low acute toxicity. The 4 hr - inhalation LC50 in the rat is 220,000 ppm.

The compound is a skin irritant and a slight eye irritant, but is not a skin sensitizer in animals. Effects from single high exposures include central nervous system depression, anesthesia, rapid breathing, lung congestion and microscopic liver changes (Dupont, 1996).

Inhalation of high concentrations of vapor is harmful and may cause heart irregularities, unconsciousness or death. Higher exposures may lead to temporary alteration of the heart's electrical activity with irregular pulse, palpitations, or inadequate circulation. Fatality may occur from gross overexposure. Individuals with pre-existing diseases of the central nervous or cardiovascular system may have increased susceptibility to the toxicity of excessive exposures (Dupont, 1996).

After exposure to decomposed chlorodifluoromethane (Freon-22), a 65-year-old man developed respiratory symptoms such as cough, blood-stained sputum, and increasing dyspnea. Three weeks later, he was diagnosed with infectious bronchitis. He died 4 weeks after his exposure due to myocardial infarction. The authors hypothesized that his death resulted from an inflammatory process caused by the inhalation of decomposed freon (Sjogren et al. 2002).

The female rats in the 50,000-ppm group exhibited a statistically significant increase in liver, kidney, adrenal gland, and pituitary weights. No non-neoplastic histopathological changes were observed. The liver weight effect was not considered adverse because it did not exceed a 10% weight change and there was no histopathology observed. Based on effects on the kidney, adrenal gland, and pituitary weight, a NOAEL of 10,000 ppm [NOAEL (HEC) = 5,260 mg/cu.m] and a LOAEL of 50,000 ppm [LOAEL (HEC) = 26,300 mg/cu.m] were estimated (US EPA IRIS document for Chlorodifluoromethane).

Carcinogenicity

US EPA: Not classified

There is *limited evidence* for the carcinogenicity of chlorodifluoromethane to experimental animals (IARC, 1986).

Chlorodifluoromethane was tested for carcinogenicity in one experiment in rats by oral administration by gavage and in experiments in rats and mice by inhalation exposure. No increase in tumor incidence was observed in rats after oral administration. The inhalation study in mice was inconclusive for males, and negative results were obtained for females. In the inhalation study in rats, males receiving the high dose had increased incidences of fibrosarcomas and zymbal-gland tumors. No increased cancers were seen in female rats (IARC, 1986).

Reproductive and Developmental Effects

Chlorodifluoromethane causes malformations of the eyes of fetal rats, but has no reproductive effect in male rats and does not cause prenatal toxicity in rabbits following exposure by inhalation.

Palmer et al. (1978a) conducted a large developmental study in an attempt to elucidate the role of CFC-22 exposure in the eye lesion seen in the previous studies. In this study, 34 control pregnant rats were used, and 22/group were exposed to 100, 1000, or 50,000 ppm of CFC-22 (354, 3,540, or 176,800 mg/cu.m, respectively) for 6 hours/day on gestation days 6-15. This protocol was repeated 19 times so that more than 6,000 control fetuses and 4,000 fetuses from each exposed group were thoroughly examined for the eye defect... The eye abnormalities (small or missing eye) were noted in all exposure groups, but statistical significance for these effects was achieved only in the 50,000-ppm group (US EPA IRIS Document for Chlorodifluoromethane).

Regulatory Summary

RfC	50 mg/cu.m
RfD	None
MCL	None
LHA	None
Cancer	Not classified

State Drinking Water Standards and Advisories

None found

Recommendations and Conclusions for Chlorodifluoromethane:

The Department of Health Services recommends use of the US EPA Reference Concentration as a point of departure for development of a groundwater standard. A relative source contribution factor of 50% is applied assuming that, in situations where household water is contaminated with freon, approximately half of the exposure comes from inhalation. This correction is needed because of the volatility of this chemical at room temperature. Conversion of the reference concentration to a reference dose was accomplished using the following formula:

$$RfD = \frac{RfC \times IR \times AR}{BW \times 100}$$

where:

RfC = Reference Concentration in Air (mg/m^3)
IR = Inhalation Rate (20 m^3/day)
AR = Absorption Rate (100% assumed unless otherwise specified)
BW = Adult Body Weight (70 kg)

$$\frac{50 \text{ mg/cu.m} \times 20 \text{ cu.m/day} \times 100\%}{70 \text{ kg}} = 14.3 \text{ mg/kg/day}$$

The department recommends application of an uncertainty factor of 10 to protect against developmental and carcinogenic effects. A 10% preventive action limit factor is proposed for this substance which has carcinogenic and mutagenic properties.

$$\frac{14.3 \text{ mg/kg/day} \times 10\text{-kg} \times 50\% \text{ RSC*}}{10 \times 1 \text{ L/day}} = 7 \text{ mg/L}$$

*50% relative source contribution assumes equal exposure from oral intake and inhalation. This factor is needed due to the volatility of freon at room temperature.

Recommended Enforcement Standard	7 mg/L
Recommended Preventive Action Limit	0.7 mg/L

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CHLORPYRIFOS

Chlorpyrifos is a broad-spectrum organophosphate insecticide. While originally used primarily to kill mosquitoes, it is no longer registered for this use. Chlorpyrifos is effective in controlling cutworms, corn rootworms, cockroaches, grubs, flea beetles, flies, termites, fire ants, and lice. It is used as an insecticide on grain, cotton, field, fruit, nut and vegetable crops, and well as on lawns and ornamental plants. It is also registered for direct use on sheep and turkeys, for horse site treatment, dog kennels, domestic dwellings, farm buildings, storage bins, and commercial establishments. Chlorpyrifos acts on pests primarily as a contact poison, with some action as a stomach poison. It is available as granules, wettable powder, dustable powder and emulsifiable concentrate. Also known as Lorsban, chlorpyrifos is one of the most widely used insecticides in the U.S.

CAS No:	2921-88-2
Molecular weight	350.62
Physical State	Amber to white crystalline solid with a mild sulfur odor
Specific gravity:	1.162
Water solubility:	2 mg/L @ 25 C
Synonyms	Trade names include Brodan, Detmol UA, Dowco 179, Dursban, Empire, Eradex, Lorsban, Paqeant, Piridane, Scout, and Stipend.

Occurrence

Chlorpyrifos was the most frequently detected pesticide in well water samples located in an area of tobacco production in Brazil. The study investigators found that chlorpyrifos was persistent four months after the application is discontinued. This is due to the long period of application and possibly to the concentration of chlorpyrifos in the same area, as well to the continuous runoff process commonly found in the studied drainage basin (Bortoluzzi et al, 2007).

The US EPA examined data for more than 3,000 samples of filtered well monitoring samples from the NAWQA database, and in the agency's Pesticides in Ground Water Data Base (PGWDB). The NAWQA data showed that chlorpyrifos was detected in groundwater in fewer than 1% of the 3000 wells sampled, with the majority of concentrations reported at <0.01 ppb, and occasional detections at a maximum level of 0.026 ug/L. Although the available monitoring data represent a large part of the U.S., it is not clear that they represent the most vulnerable groundwater where chlorpyrifos is used most intensively. The PGWDB reports a maximum detected concentration of 0.65 ug/L. Chlorpyrifos use as a termiticide is significant, with a recent estimate of 7 million pounds applied annually, constituting about 30% of the total annual use. Chlorpyrifos groundwater exposure from termiticidal use occurs only in wells located within 100 feet of the treatment area and when the well casing is cracked. The maximum reported dissolved concentration following termiticide use is 2,090 ppb (US EPA, Jul 31, 2006).

Toxicity

Chlorpyrifos is readily absorbed following ingestion, inhalation or dermal contact and is eliminated rapidly by the kidneys. Chlorpyrifos does not bioaccumulate in tissues. It is an irreversible inhibitor of cholinesterase (ChE) including acetylcholine esterase (AChE), and inhibition of AChE in the central and peripheral nervous systems causes accumulation of acetylcholine, a neurotransmitter, which in turn results in neurotoxicity in animals and humans. Inhibition of ChE is believed to be the most sensitive response in all animal species evaluated and in humans, regardless of route or duration of exposure (U.S. EPA, 2001).

Chlorpyrifos is toxic to the central nervous system, the cardiovascular system, and the respiratory system and is irritating to the skin and eyes. Symptoms of exposure include numbness and tingling, headache, dizziness, tremor, nausea, abdominal cramps, sweating, blurred vision, breathing difficulties, problems with coordination and slow heartbeat. Very high doses may result in unconsciousness, convulsions and death. Delayed neuropathies can onset up to a month after exposure. Recovery may take several months and may be incomplete resulting in permanent disabilities. Workers who are repeatedly exposed can experience problems with memory and concentration, disorientation, depression, irritability, confusion, headache, speech difficulties, delayed reaction times, nightmares, sleepwalking, and drowsiness or insomnia. An influenza-like condition with headache, nausea, weakness, loss of appetite, and malaise has also been reported (Extoxnet, 1996).

EPA Reference Dose

On March 11, 1986, the US EPA has verified a reference dose of 0.003 mg/kg/day for chlorpyrifos (US EPA, IRIS Database, accessed Jan 2009). This guideline is based on a no effect level of 0.03 mg/kg/day from a study in which 16 male volunteers (4/dose) were treated with 0, 0.014, 0.03, or 0.10 mg/kg/day of chlorpyrifos by capsule for a total of 20 days at the low and mid dose, and for 9 days at the high dose. Treatment of the high-dose group (0.1 mg/kg/day) was discontinued after 9 days due to a runny nose and blurred vision in one individual. Mean plasma ChE in this group was inhibited by about 65% compared to the control average. No effect on RBC ChE activity was apparent at any dose. An uncertainty factor of 10 was applied to account for variations in sensitivity.

Carcinogenicity

US EPA Carcinogenicity Classification: Class D, Not classifiable.

A review of the literature found no evidence to support a carcinogenic effect of chlorpyrifos in animals or in humans.

Reproductive/Developmental Effects

Although some epidemiological studies have found associations between chlorpyrifos exposure and decreased fetal weights among women, animal studies have yielded conflicting findings. No effects were seen in a three-generation study with rats fed dietary doses as high as 1 mg/kg/day. In another study in which rats were fed 1.0 mg/kg/day for two generations, the only effect observed was a slight increase in the number of deaths of newborn offspring (Extoxnet, 1996).

Available evidence suggests that chorpyrifos is not teratogenic. No teratogenic effects in offspring were found when pregnant rats were fed doses as high as 15 mg/kg/day for 10 days. When pregnant mice were given doses of 25 mg/kg/day for 10 days, minor skeletal variations and a decrease in fetal length occurred. No birth defects were seen in the offspring of male and female rats fed 1.0 mg/kg/day during a three-generation reproduction and fertility study (Extoxnet, 1996).

Mutagenicity

There is no evidence that chlorpyrifos is mutagenic. No evidence of mutagenicity was found in any of four tests performed [Extoxnet, 1996].

Environmental Fate

Soil and groundwater: Chlorpyrifos is moderately persistent in soils with a half-life of 60 to 120 days. Chlorpyrifos is subject to degradation by UV light, chemical hydrolysis and by soil microbes. When applied to moist soils, the volatility half-life was 45 to 163 hours, with 62 to 89% of the applied chlorpyrifos remaining on the soil after 36 hours. Chlorpyrifos adsorbs strongly to soil particles and it is not readily soluble in water. It is therefore immobile in soils and unlikely to leach or to contaminate groundwater. TCP, the principal metabolite of chlorpyrifos, adsorbs weakly to soil particles and appears to be moderately mobile and persistent in soils (Extoxnet, 1996).

Breakdown in water: Volatilization is probably the primary route of loss of chlorpyrifos from water. Volatility half-lives of 3.5 and 20 days have been estimated for pond water. The photolysis half-life of chlorpyrifos is 3 to 4 weeks during midsummer in the U.S. Its change into other natural forms is slow. Research suggests that this insecticide is unstable in water, and the rate at which it is hydrolyzed increases with temperature, decreasing by 2.5- to 3-fold with each 10 C drop in temperature. The rate of hydrolysis is constant in acidic to neutral waters, but increases in alkaline waters. In water at pH 7.0 and 25 C, it had a half-life of 35 to 78 days (US EPA, 1989).

Regulatory Summary

Reference Dose	0.0003 mg/kg/day
MCL	None
MCLG	None
Lifetime Health Advisory	0.002 mg/L
Cancer Classification	Not classified

State Drinking Water Standards and Advisories

Florida	21 ug/L
New Jersey	20 ug/L
Vermont	20 ug/L

Recommendations and Conclusions

The Wisconsin Department of Health Services recommends adoption of the US EPA Lifetime Health Advisory as the groundwater enforcement standard for chlorpyrifos. Since this substance is not associated with carcinogenic, mutagenic or teratogenic effects, a 20% PAL is proposed. If chlorpyrifos is identified with other organophosphates, the effects should be considered additive and a hazard index approach should be used to assess the potability of the water supply.

Recommended Enforcement Standard	2.0 µg/L
Recommended Preventive Action Limit	0.4 µg/L

References

Bortoluzzi EC; Rheinheimer DS; Gonçalves CS; PellegriniII JBR; Maroneze AM; Kurz MHS; Bacar NM; Zanella R. 2007. Investigation of the occurrence of pesticide residues in rural wells and surface water following application to tobacco Quím. Nova 30:8.

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US EPA. 2001. Chlorpyrifos Interim Risk Management Decision.

DIMETHENAMID/DIMETHENAMID-P

Dimethenamid was originally registered as a mixture of R and S-isomers (50:50, S:R), and tolerances for the 50:50 mixture were established for dry beans, field corn, sweet corn, peanuts, sorghum, and soybean. Manufacture of the 50:50 mixture has ended and has been replaced by a mixture (Dimethenamid-P) that is enriched in the biologically active S-isomer (90:10, S:R). Registration of the original 50:50 mixture will be cancelled when existing stock is depleted. Currently, both Dimethenamid (50:50, S:R) and Dimethenamid-P, sold under the trade name Outlook (90:10, S:R) are used (Fed Reg, 2004).

Sold under the trade name Frontier, dimethenamid is a widely used amide herbicide. In 2001, about 7 million pounds of dimethenamid were used in the United States.

CAS #:	87674-68-8 (50:50 S:R); 163515-14-8 (90:10 S:R)
Molecular weight	275.8
Physical State	Liquid
Specific gravity:	1.105
Water solubility:	1,450 mg/L
Synonyms	Frontier, Outlook

Occurrence

Dimethenamid was detected in 2 of 428 (0.4%) wells tested by the Wisconsin Department of Agriculture, Trade and Consumer Protection. The highest detect level was 2.79 ug/L.

Acute Toxicity

Dimethenamid (50:50 SR) is less acutely toxic than Dimethenamid-P (90:10). In rats, the oral LD50 for the 50:50 mixture is approximately 2 g/kg body weight, while the LD50s for the 90:10 mixture were 429 mg/kg in males and 531 mg/kg in females. Both mixtures are much more toxic by inhalation with LD50s below 5 mg/kg.

Chronic Toxicity

A chronic toxicity/carcinogenicity study conducted in Sprague-Dawley rats fed a 50/50 mixture of the R and S isomers. This study provided NOAELs of 5.1 mg/kg/day and 6.8 mg/kg/day and LOAELs of 36 and 49 mg/kg/day in male and female rats, respectively, based on decreased weight gain and hepatic lesions in both sexes. A dose related increased incidence of liver tumors was observed in males.

A 13-week rat feeding study yielded a no-observed effect level (NOEL) of 33.5 mg/kg/day for males and 40.1 mg/kg/day for females.

Subchronic oral toxicity study of dimethenamid (50:50 S:R) conducted in dogs yielded NOAELs of 4.72 and 4.98 and LOAELs of 33.6 and 39.7 in males and females, respectively. The critical effects noted by investigators included decreased weight gain in females, increased relative liver weight in both sexes, increased periportal vacuolation in the liver in both sexes and dilation of liver sinusoids in females.

Carcinogenicity

US EPA Cancer classification: Class C, possible human carcinogen

A carcinogenicity study in mice with no carcinogenic effects observed at any dose level under the conditions of the study and a systemic NOEL of 40.8 mg/kg/day for males and 40.1 mg/kg/day for females, based on food consumption and a systemic lowest effect level 205 mg/kg/day for males and 200 mg/kg/day for females based on food consumption based on significantly elevated liver weights.

A rat chronic feeding/carcinogenicity study with a systemic NOEL of 5 mg/kg/day and an LEL of 35 mg/kg/day due to decreased food efficiency and histopathology findings. Under the conditions of the study limited evidence of carcinogenicity was observed based on a statistically significant increasing trend for benign liver cell tumors in male rats and a statistically significant increasing trend for ovarian tubular adenomas in female rats. A re-evaluation of the ovarian neoplasia data indicated that there was no statistically significant, dose-related, trend in the incidence of ovarian tumors in female rats.

The US EPA has classified the pesticide as a possible human carcinogen with limited evidence of carcinogenicity in animals. Based on a review by the Health Effects Division Peer Review Committee for carcinogenicity of the Office of Pesticide Programs, the Agency has determined that a quantitative risk assessment is not appropriate for the following reasons:

- The tumor response was primarily due to a significantly increasing trend for benign and/or malignant liver tumors in male rats and due to a significantly increasing trend for ovarian tubular adenomas in female rats. A re-evaluation of the ovarian neoplasia data indicated that there was not a statistically significant, dose-related, trend in the incidence of ovarian tumors in female rats.

- The chemical was not carcinogenic when administered to mice at dose levels ranging from 30 to 3,000 ppm. Based on this evidence, EPA concludes that dimethenamid poses a negligible cancer risk to humans and that for purposes of risk characterization the Reference Dose (RfD) approach should be used for quantification of human risk. Residues of dimethenamid will not concentrate in processed soybean commodities and a food or feed additive regulation is not required for dimethenamid. The standard risk assessment approach of using the RfD based on systemic toxicity was applied to dimethenamid.

Mutagenicity

An Ames mutagenicity assay negative with and without activation, an in vitro chromosomal aberration using CHO cells positive with and without activation, an unscheduled DNA synthesis in rat hepatocytes unequivocally positive in one in vitro assay and negative in another.

Reproductive Studies

A two generation reproduction study in rats with a parental and reproductive NOEL 36 mg/kg/day for males and 40 mg/kg/day for females and a parental and reproductive LEL 150 mg/kg/day for males and 160 mg/kg/day for females based on reduction of body weight and of food consumption, and increases in liver weights (parental toxicity), and significant reductions in pup weight during lactation.

A rabbit developmental study with a maternal NOEL of 37.5 mg/kg/day and a LEL of 75 mg/kg/day based on decreased body weight and food consumption, and with a developmental NOEL of 75 mg/kg/day and a LOEL of 150 mg/kg/day based on a low incidence of abortion/premature delivery and malformation of the upper mandible.

A rat developmental study with a maternal NOEL of 50 mg/kg/day and a LEL of 215 mg/kg/day based on excess salivation, increased liver weight and reduced body weight gain and food consumption, and with a developmental NOEL of 215 mg/kg/day and a LEL of 425 mg/kg/day based on increased resorptions.

Using an uncertainty factor of 100 and the NOEL of 5 mg/kg/day determined by the 2-year rat feeding study, EPA developed an RfD of 0.05 mg/kg/day.

US EPA Regulatory Position

MCL	None
MCLG	None
RfD	0.05 mg/kg/day
LHA	None
Cancer classification	Class C, Possible human carcinogen

State Drinking Water Standards and Advisories

None found

Recommendations and Conclusions for Dimethenamid

The Wisconsin Department of Health Services recommends use of the chronic reference dose to establish a groundwater enforcement standard for dimethenamid. Since dimethenamid is classified as a possible human carcinogen, an additional uncertainty factor of 10 was applied to the reference dose to protect against this effect and a 10% preventive action limit is proposed.

$$\frac{0.05 \text{ mg/kg/day} \times 10 \text{ kg}}{10 \times 1 \text{ liter/day}} = 0.05 \text{ mg/L } (50\ \mu\text{g/L})$$

Recommended Enforcement Standard	50 µg/L
Recommended Preventive Action Limit	5 µg/L

References

Federal Register: September 24, 2004, Vol 69, No 185. Dimethenamid; Pesticide Tolerance, Environmental Protection Agency, Final rule.

Federal Register, May 3, 2006 Vol 71, No 85. Dimethenamid-p; Pesticide Tolerances for Emergency Exemptions.

US EPA. 1992. Office of Pesticide Programs Reference Dose Tracking Report.

DINITROTOLUENES, Total Residues

Technical grade dinitrotoluene (TG DNT) is a mixture of chemicals. Analysis of TG DNT reveals the following composition: 76.49% 2,4-DNT, 18.83% 2,6-DNT, 0.65% 2,5-DNT, 2.43% 3,4-DNT, 1.54% 2,3-DNT, 0.05% trinitrotoluene (TNT), 0.005% cresols, 0.003% mononitrobenzene, and 0.003, 0.005, and 0.006% ortho-, meta-, and para- mononitrotoluenes, respectively. DNT can be released to the environment as a result of accidental releases and disposal. DNTs are used as gelatinizing and waterproofing agents in the manufacture of explosives, and in smokeless gunpowders. About 500 US workers are potentially exposed to DNT during the production of munitions and explosives. The main route of exposure at ammunition facilities is inhalation, but dermal contact and inadvertent ingestion can also be substantial. The primary route of exposure among the general population is likely the result of ingestion of contaminated food or water. Occupational studies indicate that after inhalation or dermal exposure, TG-DNT is absorbed and excreted in the urine. Oral absorption and excretion occur rapidly and are usually complete within 24 hours to 72 hours.

CAS No.	25321-14-6, See Table 1 for individual congeners
Molecular Weights	182.14
Physical State	Yellow-orange crystalline solid or oily liquid
Specific Gravity	1.32
Water Solubility	270 mg/L
Synonyms	DNT, Dinitrophenylmethane, Methyldinitrobenzene

Occurrence

Dinitrotoluenes have been detected in more than 50 private wells near the Badger Army Ammunition Plant. Levels exceeded 0.05 ug/L in 7 wells. DNT was also been found in 17 private wells located near the DuPont Barksdale Dynamite site and exceeded 0.05 ug/L in 11 wells. Currently, municipal drinking water serves all homes around Barksdale. Under EPA's Unregulated Contaminant Monitoring Program, 2,4 and 2,6 DNT were analyzed in large community water systems and non-transient non-community water systems and in a statistically representative sample of qualifying small systems. Data for samples collected from 2001 through October 2004 indicate that only one water supply (0.04% of the systems) tested positive for 2,4 DNT and that 2,6-DNT was not detected in any of the samples.

Toxicity

Most toxicological and environmental studies have been conducted using either the technical grade mixture of these isomers, or purified 2,4- or 2,6-DNT. Only a few short-term oral exposure or *in vitro* studies have been done on the minor isomers (2,3-; 2,5-; and 3,4-DNT). These studies suggest that the minor isomers are toxicologically similar to 2,4- and 2,6-DNT. Effective oral doses or *in vitro* concentrations of the six DNT isomers are generally within an order of magnitude of each other. In their Dec 8, 1978 progress report submitted to the US Army, Ellis et al. concluded that "The acute oral toxicities of all the nitrotoluenes tested are generally similar."

All DNT isomers are capable of inducing cyanosis secondary to methemoglobin formation. At high doses, methemoglobinemia and central nervous system depression can lead to death. Target tissues include the hematopoetic system, the central nervous system and the male reproductive system. TG DNT, as well as 2,4- and 2,6-DNT are known to cause cancer in animals. Minor isomers have not been tested for this effect. All isomers have shown weak mutagenic effects in the Ames assay using *Salmonella typhimurium* (Ellis, et al. 1978).

The effects of dinitrotoluene are exacerbated by alcohol consumption. In an occupational setting, DNT can be absorbed through the skin in toxic amounts. Human exposure has been linked to a variety of symptoms, including cyanosis, dizziness, headache, metallic taste, shortness of breath, weakness, loss of appetite, nausea, and vomiting. Other symptoms including pain or paresthesia in extremities, abdominal discomfort, tremors, paralysis, chest pain, and unconsciousness have also been reported. The primary targets of DNT toxicity are the blood cell formation, the cardiovascular system, the nervous system and the male reproductive system.

3,5-DNT is more toxic to male and female rats and mice than other isomers. Technical-grade DNT fed to rats for 24-months caused liver discoloration at a dose of 3.5 mg/kg/day and liver nodules and malignancies at a dose of 14 mg/kg/day. An NCI bioassay also showed that technical-grade DNT causes subcutaneous tissue fibromas in male rats and mammary gland fibroadenomas in female rate. DNT administered orally to dogs caused neurotoxic effects, with tremors, loss of coordination, and convulsions; neurotoxic effects are not seen in either rats or mice until much higher doses are given. Oral administration of DNT to rats, mice, and dogs caused reproductive effects, including testicular and ovarian atrophy, decreased fertility, and decreased sperm count.

Table 1. Screening Level Toxicity Information for DNT Isomers

	2,3-DNT	2,4-DNT	2,5-DNT	2,6-DNT	3,4-DNT	3,5-DNT
CAS No	602-01-7	121-14-2	619-15-8	606-20-2	610-39-9	618-85-19
% in Tech Grade	1.3%	78%	0.5%	18%%	2.4%	<0.1%
LD50 (female rat)*	911 mg/kg	650 mg/kg	650 mg/kg	795 mg/kg	807 mg/kg	216 mg/kg
Cancer Class	Not classified	B2	Not classified	B2	Not classified	Not classified
Mutagenicity Ames Test	Weakly Positive	Weakly Positive	Weakly Positive	Weakly Positive	Weakly Positive	Weakly Positive
NOAEL Subchronic Chronic	None None	0.2 mg/kg/day None	None None	4 mg/kg/day 7 mg/kg/day	None None	None None
Aquatic toxicity**	1.8 mg/L	32.8 mg/L	1.3 mg/L	18.5 mg/L	1.5 mg/L	22.6 mg/L
USEPA RfD	None	0.002 mg/kg/day	None	0.001 mg/kg/day	None	None
USEPA MCL	None	None	None	None	None	None
WI ES	None	0.05 µg/L	None	0.05 µg/L	None	None
ACGIH – TLV	1.5 mg/cu m	1.5 mg/cu m	1.5 mg/cu m	1.5 mg/cu m	1.5 mg/cu.m	1.5 mg/cu m

* Rickert et al., 1984.
**96-hr static LC50 *Pimephales promelas* Liu, Bailey and Pearson, 1983

Carcinogenicity

U.S. EPA cancer classification for 2,4- and 2,6-DNT: B2, sufficient evidence of carcinogenicity in animals (USEPA, IRIS 1990)

In chronic studies, 98% pure 2,4-DNT produced kidney tumors in male CD-1 mice and was moderately hepatocarcinogenic in Sprague-Dawley rats (Ellis, 1979).

2,6-DNT and technical grade DNT are potent hepatocarcinogens in rats. Increases in tumors were statistically significant and dose-related.

Several studies have investigated the potential for dinitrotoluenes to cause cancer in exposed workers. In the first of these Levine et al. (1986) found no evidence for a carcinogenic effect in workers at two ammunition plants who were exposed to dinitrotoluenes. However the number of deaths for specific tissue sites was small. In a later study, Stayner et al. (1993) examined nearly 5,000 workers at a munitions factory who were exposed to technical-grade DNT and demonstrated an excess of hepatobiliary cancer in exposed workers (SRR 3.88, 95% CI = 1.04 to 14.41). A smaller study (Brüning et al. 1999, Brüning et al. 2002) of 500 underground miners found a 4.5-fold increased incidence of urothelial cancer and 14.3-fold increased incidence of renal-cell cancer. These data suggest the possibility of carcinogenicity of dinitrotoluenes in humans. Harth et al. (2005) reported a cluster of three cases of urothelial cancer among a group of about 60 workers exposed to dinitrotoluenes. The workers were employed in the manufacturing of nitrotoluene explosives in the former German Democratic Republic. The cases occurred within a period of 12 years (1990-2002) leading to a 15.9 fold higher incidence of cancer of the urinary bladder than observed in the state where the chemical factory was located. The observation of the cluster of urothelial cancer in persons highly exposed to nitrotoluenes underlines the potential human carcinogenicity of dinitrotoluenes.

Mutagenicity

All DNT isomers were weakly positive in the Ames assay *S. typhimurium* histidine reversion assay and the TM 677 forward-mutation assay both with and without metabolic activation but negative in numerous mammalian cell assays.

In the discussion section of Progress Report no. 6 prepared for the U.S. Army December 8, 1978, Ellis et al. provides the following summary:

"All of the nitroaromatics studied appeared to be mutagenic to *Salmonella typhimurium*. Many recent studies show that, in general, nitroaromatics exhibit a high degree of mutagenic activity in the *Salmonella* microsome plate test. These nitroaromatics are thought to exhibit a high degree of mutagen activity to microbial test systems because of their activation by nitroreductases(s) and other metabolizing enzymes endogenous to the microbial tester strains. Furthermore, liver homogenates have recently been shown to activate nitroaromatic compounds to mutagens. In the light of these considerations, it appears that TNT and the six DNT isomers should be considered as potentially mutagenic and possibly carcinogenic."

Reproductive Effects

Male reproductive effects resulting from oral administration of 2,4-DNT include decreased spermatogenesis in rats and dogs at 20-25 mg/kg/day and testicular atrophy at 34 mg/kg/day. In a multigenerational rat study, decreased neonatal viability was noted at 40 mg/kg/day of 2,4-DNT.

A study of reproductive effects in DNT-exposed workers showed decreased sperm counts, slight abnormalities in the sperm of workers, and a slight increase in the rate of spontaneous abortions in their wives. A retrospective cohort mortality study of DNT-exposed workers found a significant increase in mortality due to ischemic heart disease. The average DNT exposure of these workers was estimated to be 1 mg/kg/day or less from inhalation, ingestion, and dermal sources.

Interactive Effects

In a 1942 study, workers exposed to 2,4-DNT were found to be more sensitive to alcohol. Exposure of rats to 2,6-DNT both increased and decreased the rate of phenobarbital metabolism, dependent on the time of exposure.

Environmental Fate

Aquatic

The solubilities of 2,4- and 2,6-DNT in water are 270 and 180 mg/L, respectively. Major routes of DNT degradation in surface water are photo-oxidation and biodegradation. The half life of DNT is 3 to 10 hours in sunlit natural waters and 28 days in anaerobic sewage.

Microbial biodegradation of DNT in water can occur under both aerobic and anaerobic conditions. Biotransformation occurs mainly through the reduction of the nitrogroup. In surface waters, photolysis is probably the major route of degradation (ATSDR, 1998). The half-life of 2,6-DNT in river water exposed to sunlight was 12 minutes and the degradation was determined to be from an indirect photoreaction. Once it reaches groundwater, DNT is much more persistent. However a half-life in groundwater was not found.

Atmospheric

The low vapor pressure of the DNTs (2,4-: 0.005 torr at 20°C; 2,6-: 0.018 Torr at 20°C) suggests that volatilization from contaminated surface water or soil are unlikely. In the atmosphere, DNT is degraded by photochemically produced OH radicals. The half-life is calculated to be approximately 84 days.

Terrestrial

DNTs are poorly adsorbed to soils. As a result, DNTs in buried munition wastes could potentially be released to groundwater or transported as contaminated soil and sediment. No studies have been performed on soil DNT biodegradation.

Regulatory Summary

RfD for 2,4-DNT (non-cancer effects):	0.002 mg/kg/day
RfD for 2,6-DNT (non-cancer effects):	0.001 mg/kg/day
MCL	None
Cancer classification for 2,4- and 2,6-DNT	B2, possible human carcinogen
Cancer slope factor for 2,4- and 2,6-DNT	0.68 per mg/kg/day
Drinking water conc at 1-in-a-million cancer risk	0.05 µg/L
Ambient Water Quality Criteria for Water & Fish	0.11 µg/L
Ambient Water Quality Criteria for Fish only	9.1 µg/L
ATSDR Minimal Risk Level	0.002 mg/kg/day

State Drinking Water Standards and Advisories

None found

Recommendations and Conclusions

The Department of Health Services recommends that all isomeric forms of dinitrotoluene be regulated as a group and that the enforcement standard be set at a concentration that equates with a lifetime cancer risk of 1-in-a-million. This recommendation is based on the following findings:

1). A complete toxicological database is available for technical grade DNT, which is a mixture of all isomers, and for the two major isomers (2,4- and 2,6-DNT). Only limited testing has been conducted with the minor isomers making independent risk assessments impossible. In 2000, the Chemical Manufacturer's Association petitioned the US EPA to remove individual isomers of DNT from the High Production Challenge Program arguing that none of the minor isomers is produced separately in commerce. In a letter to Charles M. Auer, Director of the USEPA's Chemical Control Division, CMA stated, "Separately evaluating each isomer under the HPV program will not result in a better understanding of the adverse health or safety implications of dinitrotoluene." EPA's approval of this request alleviated a requirement for the manufacturers to provide screening level toxicity and environmental fate data for individual DNT isomers and allowed submission of data for technical grade DNT instead.

2). Published studies for the minor isomers indicate that their toxic effects are the same as that of technical grade DNT and that the minor isomers are as toxic or more toxic than 2,4- and 2,6-DNT.

3). All isomers of DNT have shown weak mutagenic activity in the Ames assay.

4). Technical grade DNT, as well as the purified 2,4- and 2,6- isomers, are classified as known animal carcinogens. Minor isomers have not been tested for this effect, but are structurally and toxicologically similar suggesting that they may also contribute to cancer risks.

5) The six isomers of DNT are structurally and toxicologically similar, have a common commercial source and are frequently found together in the environment.

Because dinitrotoluenes have carcinogenic effects, a 10% preventive action limit is proposed.

Recommended enforcement standard: 0.05 µg/L
Recommended preventive action limit: 0.005 µg/L

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ETHYL ETHER

Ethyl ether has limited solubility in water and is often used to extract organic substances from aqueous solutions. Ethyl ether is also used in reactions that involve organometallic reagents, in the production of cellulose plastics, and as a starting fluid for diesel and gasoline engines. Although it was popular clinical anesthetic during the late 1800s and early 1900s, this use of ether has been discontinued following the development of safer and more effective alternatives.

CAS No	60-29-7
Molecular Weight	74.12
Molecular Formula	C2H5OC2H5
Physical properties	Colorless liquid
Synonyms	Ethyl ether, ether 1,1'Oxybisethane;ethyl oxide; Ethyl oxide;

Occurrence

Due to its volatility ether is an uncommon contaminant of Wisconsin groundwater. Ethyl ether has been detected in 44 Wisconsin wells. Levels ranged from 0.3 to 450 ug/L. All of the detections were in wells located in Sauk, Waukesha and Wood Counties.

Toxicity

Ethyl ether is a severe irritant of the eyes and mucous membrane. At high concentrations, it causes central nervous system depression. Exposure to a 6.4 percent concentration caused deep anesthesia in mice, and respiratory arrest occurred at 128,000 ppm ethyl ether. Rats exposed chronically over 30 weeks to 2,000 ppm ethyl ether did not experience adverse effects. However, their blood levels of liver enzymes were elevated.

Ether has been used as a surgical anesthetic at concentrations ranging between 50,000 and 150,000 ppm. It is a nasal irritant at concentrations above 200 ppm and causes dizziness at 2,000 ppm or higher [ACGIH 1991; Hathaway et al. 1991].

Symptoms of exposure vary by concentration and duration, but may include irritation of the nose and eyes, dizziness, excitement, drowsiness, vomiting, paleness, decreased pulse rate, decreased body temperature, irregular respiration, muscle relaxation, lung irritation with increased bronchial secretions, laryngospasm, loss of consciousness, and death [Clayton and Clayton 1982].

Four groups of male and female rats (30/sex/group) were gavaged daily with 0, 500, 2000, and 3500 mg/kg/day of ethyl ether for 13 weeks. Six weeks after the initiation of dosing, an interim sacrifice of 10 rats/sex was performed. The remaining animals continued in the experiment until the day of the final sacrifice. Data generated from this study included body weight changes; food consumption; ophthalmological examinations; clinical, biochemical, and gross morphological changes; and histopathology of target organs. An evaluation of data revealed marked toxicity of ethyl ether at the high dose (3500 mg/kg/day), including mortality, decreased food intake, and body weight loss. Body weight loss was observed in both sexes at the two highest doses; only females showed a significant reduction at the high dosage. Histopathological evaluations of tissues revealed no effects related to the administration of ethyl ether. Based on data available from this study, 500 mg/kg/day is considered a NOAEL and 2000 mg/kg/day a LOAEL (US EPA, 1986).

The US EPA applied an uncertainty factor of 3,000 including a factor of 10 to extrapolated from a subchronic study to chronic data, 10 for interspecies extrapolation, 10 to account for intra-species variability, and an additional factor of 3 for lack of toxicity data in a second species and reproductive/developmental studies to develop an oral reference dose of 0.2 mg/kg/day

Carcinogenicity

No information was found regarding the carcinogenic properties of ethyl ether. EPA has not classified the carcinogenicity of ethyl ether.

Mutagenicity

Ethyl ether is mutagenic in bacterial and mammalian test systems [NIOSH 1991].

Environmental Fate

Aquatic

When discharged to surface water, ethyl ether will evaporate with a half-life of less than 1 day. Very little breakdown is expected as a result of hydrolysis or photolysis. Ether is likely stable in groundwater. Because it is less dense than water, ether will tend to float on the top of the aquifer.

Ethyl ether has a log Kow of < 3.0 and is not expected to bioaccumulate. The LC50/96-hour values for fish are over 100 mg/l. This material is not expected to be toxic to aquatic life (Mallickrodt, 2007).

Atmospheric

When released into the air, this ether is expected to be degraded by reaction with photochemically produced hydroxyl radicals. Ether is not degraded by photolysis. Ether has an atmospheric half-life of 1 to 10 days (Mallinckrodt, 2007).

Terrestrial

When released to the surface soils, ether will tend to is expected to evaporate. However, some ether may also leach into groundwater contaminating underground aquifers. Ether is not expected to biodegrade (Mallinckrodt, 2007).

Regulatory Summary

MCL	None
Lifetime Health Advisory	None
RfD	0.2 mg/kg/day
Cancer classification	Not classified

State Drinking Water Standards and Advisories

Florida	750 µg/L
New Hampshire	1,400 µg/L
New Jersey	1,000 µg/L
Minnesota	1,000 µg/L

Recommendations and Conclusions

Following a review of the literature for ethyl ether, the Wisconsin Department of Health Services recommends the use of the EPA Reference Dose for calculation of a groundwater enforcement standard. A relative source contribution of 50% was applied assuming that in situations where household water is contaminated with ethyl ether, approximately half of the exposure comes from inhalation. This adjustment is needed because ether is volatile at room temperature. Since ethyl ether has been found to have mutagenic activity, a 10% preventive action limit factor is appropriate.

$$\frac{0.2 \text{ mg/kg/day} \times 10 \text{ kg} \times 50\%}{1 \text{ liter/day}} = 1 \text{ mg/L or } 1{,}000\ \mu\text{g/L}$$

Recommended Groundwater Enforcement Standard	1,000 µg/L
Recommended Preventive Action Limit	100 µg/L

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MANGANESE

Manganese is a naturally-occurring element that can be found in the air, soil, and water. It is also an essential trace nutrient for humans and animals. Adverse health effects can be caused by inadequate intake or by over exposure. Manganese deficiency in humans is thought to be rare because manganese is present in red meat and in green vegetables.

CAS no.	7439-96-5
Atomic symbol	Mn
Atomic Weight	54.94
Physical state	Hard, brittle, silvery metal
Density	7.4
Water solubility	Metallic form is practically insoluble, however salts dissolve freely in water

The greatest exposure to manganese is usually from food. Adults consume between 0.7 and 10.9 mg/day in the diet, with even higher intakes being associated with vegetarian diets (IOM, 2002). Intake from drinking water is normally a minor source of exposure. At the median drinking-water level of 10 μg/L the intake of manganese from drinking water would be 20 μg/day for an adult, assuming a daily water intake of 2 L. Inhalation is not a significant source of exposure in non-occupational settings. The Institute of Medicine (IOM, 2002) has set a tolerable upper intake level of 11 mg/day for adults.

Chronic exposure to high doses of manganese can be harmful. While the health effects depend on the route of exposure, the chemical form, and individual susceptibility, the nervous system is the target organ. Many of the reports of adverse effects from manganese exposures in humans are from inhalation exposures in occupational settings. Although there are substantial data supporting the neurological effects of inhaled manganese in humans and animals, there are few data for the association between oral exposure to manganese and toxic effects. Several epidemiological studies associate adverse neurological effects with exposure to manganese from drinking water. However, due to a lack of qualitative and quantitative details of the exposure scenario, these studies cannot be used for quantitative assessment.

As an element, manganese cannot undergo metabolic transformation, but it can exist in many oxidative states and can be converted from one oxidative state to another within the body. Manganese is almost entirely excreted in the feces. Fecal manganese is comprised of unabsorbed dietary manganese and manganese excreted in bile. Groups possibly sensitive to manganese would be those who absorb greater amounts of manganese or those who excrete less. These would include infants, the elderly, and patients with liver disease.

Manganese can exist in several oxidative states; the most environmentally and biologically important manganese compounds are those that contain Mn^{2+}, Mn^{4+}, and Mn^{7+}. At concentrations exceeding 0.1 milligrams per liter (mg/L), the manganese ion imparts an undesirable taste to beverages and stains plumbing fixtures and laundry. When manganese (II) compounds in solution undergo oxidation, manganese precipitates, resulting in encrustation problems. At concentrations as low as 0.02 mg/L, manganese can form coatings on water pipes that may later slough off as a black precipitate. The U. S. and a number of other countries have set secondary standards of 0.05 mg/L for manganese for aesthetic properties.

As a metallic element, manganese does not undergo metabolic conversion to other products. However, manganese has the potential to exist in several oxidation states in biological systems. Circumstantial evidence from the study of manganese-containing enzymes and from electron spin trapping experiments

suggests that manganese undergoes conversion from Mn(II) to Mn(III) within the body (ATSDR, 2000). The conversion from Mn(II) to Mn(III) appears to be catalyzed by ceruloplasmin (Andersen et al., 1999). Manganese plays a catalytic or regulatory role in enzymatic reactions involving select hydrolases, dehydrogenases, kinases, decarboxylases and transferases.

Manganese is almost entirely eliminated in the feces, with only a small proportion (0.1-2%) being excreted in the urine. Fecal manganese is comprised of unabsorbed dietary manganese plus manganese excreted in bile. In humans, elimination is biphasic, with half-lives of 13 and 37 days. Sweat, hair and the milk of lactating mothers also contribute to excretion (EPA, 2004).

Toxicity

Symptoms resembling Parkinson's disease were seen in an individual who ingested 1.8 mg/kg-day potassium permanganate for 4 weeks (Bleich et al., 1999; Holzgraefe et al., 1986). The symptoms onset 9 months after the exposure.

The neurological effects of inhaled manganese have been well documented in humans (ATSDR, 2000). The syndrome known as "manganism" is caused by exposure to very high levels of manganese dusts or fumes and is characterized by a "Parkinsonlike syndrome" including weakness, anorexia, muscle pain, apathy, slow speech, monotonous tone of voice, emotionless "mask-like" facial expression, and slow clumsy movement of the limbs. In general, these effects are irreversible.

An epidemiological study was conducted by Kondakis et al (1989) to investigate the possible correlation between long-term manganese exposure from drinking water and neurological effects in elderly people. The levels of manganese in the drinking-water of 3 different geographical areas were 3.6-14.6 μg/L in the control area and 81-253 μg/L and 1800-2300 μg/L in the manganese-containing areas. The total population in the three areas being studied range from 3,200 to 4,350 people. The study included individuals over the age of fifty drawn from a random sample of 10% of the households. The number of subjects sampled were 62, 49, and 77 for control, low-, and high-exposed groups. The authors performed a neurological examination of the subjects (weakness/fatigue, gait disturbances, tremors, dystonia, etc.) and expressed the results as composite scores. They found no differences in the manganese content in the blood, but a statistically-significant difference in both the manganese content in the hair and composite neurological scores between the high exposed area (concentrations 1,800-2,300 μg/L) and the control area, suggesting neurological impairment in the high exposed area.

Reproductive and Developmental Studies

Men afflicted with clinical manganism may also experience loss of libido and impotence from occupational exposure to manganese. Impaired fertility, as measured by fewer children/married couple, has been observed in men who were exposed to manganese dust at levels that did not produce obvious symptoms of manganism (EPA, 2004).

Mutagenicity

The genotoxic potential of high manganese exposure in humans is not known.

Carcinogenicity

No studies are available on the potential carcinogenicity of high exposure to manganese in humans (ATSDR, 2000).

Variation in Human Sensitivity

Individuals with impaired liver function can be at risk from exposure to manganese because the liver is the main organ for excreting manganese. This group may include the elderly who may have declining organ function, the very young who may have immature and developing organs, and those with liver disease. Neurological symptoms and changes in brains MRI scans have been observed in patients with chronic liver disease (EPA, 2004).

Infants are considered a potential sensitive population due to the increased retention of manganese. Increased retention leads to increased manganese levels in the brain. This is a concern because the nervous system is the primary target organ (EPA, 2004).

Manganese is an essential trace nutrient. However, excess exposure, particularly via the inhalation route, is associated with symptoms that resemble Parkinsonism. The US EPA has estimated that an intake of 10 mg Mn/day (0.14 mg Mn/kg-day, assuming a body weight of 70 kg) in the diet is safe for a lifetime of exposure. This level of manganese represents a NOAEL for chronic ingestion of manganese by adults. Application of an uncertainty factor of 1 was used to derive the dietary RfD of 0.14 mg Mn/kg-day (U.S. EPA, 1997).

U.S. EPA (2008) recommends use of a modifying factor of 3 when assessing exposure to manganese from drinking water. Four reasons for this recommendation include:

1. Uptake of manganese from water appears to be greater in fasted individuals.
2. The study by Kondakis et al. (1989) raises concern for possible adverse health effects associated with a lifetime consumption of drinking water containing 2 mg/L of manganese.
3. Infants seem to absorb more manganese from the gastrointestinal tract, and excrete less of the absorbed manganese than adults.
4. Infant formula typically contains a much higher concentration of manganese than human or cows' milk. Powdered formula reconstituted with drinking water represents an additional source of manganese intake for a potentially sensitive population.

In order to enhance consumer acceptance of water resources, this advisory recommends reducing manganese concentrations to or below 0.050 mg/L, the EPA's Secondary Maximum Contaminant Level (SMCL) for Mn. The SMCL is based on staining and taste considerations.

The lifetime health advisory value of 0.3 mg/L will protect against potential neurological effects. In addition, this document provides a 1-day and 10-day health advisory of 1 mg/L for acute exposure. However, it is advised that for infants younger than 6 months of age, the lifetime HA of 0.3 mg/L be used even for an acute exposure of 10 days, because of the concerns for differences in manganese content in human milk and formula and the possibility of a higher absorption and lower excretion in young infants.

Regulatory Summary

MCL	None
MCLG	None
RfD	0.14 mg/kg/day
Drinking Water Equivalent Level (DWEL)	600 μg/L
Lifetime Health Advisory	300 μg/L
Cancer Classification	Group D: Not classifiable

State Drinking Water Standards and Advisories

California	500 μg/L
Connecticut	500 μg/L
Maine	500 μg/L
Minnesota	100 μg/L
New York	300 μg/L
Vermont	840 μg/L

Recommendations and Conclusions

The Wisconsin Department of Health Services recommends adoption of the federal lifetime health advisory for manganese as a groundwater enforcement standard. Because manganese is not known to have mutagenic or carcinogenic effects, a 20% preventive action limit is proposed.

Recommended Enforcement Standard	300 μg/L
Recommended Preventive Action Limit	60 μg/L

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METOLACHLOR ETHANE SULFONIC PLUS OXANILIC ACID METABOLITES

(Combined Standard)

Metolachlor is a selective herbicide that can be incorporated into the soil before planting or applied to surface soils as a pre-emergent to control annual grasses, certain broadleaf weeds in field corn (except fresh and popcorn), soybeans, peanuts, and grain sorghum. Metolachlor is marketed in two emulsifiable concentrate products (68.5 and 86.4 percent active ingredient) and in combination with atrazine or propachlor to provide broad spectrum weed control. In the US, the Novartis Corporation is the sole registrant and manufacturer of metolachlor. Metolachlor ethane sulfonic acid (ESA) and metolachlor oxanilic acid (OXA) are commonly seen environmental degradates.

	Metolachlor oxanilic acid	Metolachlor ethane sulfonic acid
CAS no.	152019-73-3	171118-09-5
Molecular Formula	C15H21NO4	C15H22NO4S
Molecular Weight	279.33	312.40
Physical State	Na salt, colorless crystal	Na salt, beige crystal
Water Solubility	Freely soluble in water	Freely soluble in water
Density at 20 deg C	Not available	Not available
Synonyms	Metolachlor OXA, CGA 51202	Metolachlor ESA, CGA 354743

Occurrence

More than 70 wells, including 27 monitoring wells, 22 private drinking water wells, and 23 municipal wells in Wisconsin have been sampled for alachlor, metolachlor, acetolachlor, and their ethane sulfonic acid (ESA) and oxanilic acid (OXA) metabolites. Wells were selected based on previous detections of pesticides or proximity to agricultural fields to increase the likelihood of exposure to the compounds of interest. Alachlor, metolachlor, and metolachlor are chloroacetanilide herbicides that are commonly used on corn and other crops in Wisconsin. Sample results showed over 80 percent of the monitoring wells and drinking water wells contained the ESA and OXA metabolites of alachlor and metolachlor. Acetolachlor metabolites were detected less frequently. Analytical results for metolachlor OXA ranged from below the level of detection to 32 µg/L with detects in 63% of the monitoring wells, 86% of the private wells and 35% of the public water supplies. Analytical results for metolachlor ESA ranged from below the level of detection to 14 µg/L with detects in 78% of the monitoring wells, 91% of the private wells and 39% of the public water supplies (WDATCP, 2000).

Toxicity

A series of acute, subchronic, developmental and mutagenicity studies have been conducted with the OXA and ESA metabolites of metolachlor and s-metolachlor. The acute toxicity of these metabolites was essentially the same as the parent herbicide with LD50s >5,000 mg/kg.

In a 90-day rat feeding study (MRID 44931710) 10 male and 10 female CD BR rats were given the ESA metabolite at 0, 25.1, 86.2, 427, or 1545 mg/kg/day for males and 0, 28.4, 98.3, 519 and 1,685 in females. No deaths or clinical signs of toxicity were seen. In addition, no statistically significant changes in body weight, body weight gain, food consumption, food efficiency, ophthalmologic examination, urinalysis, or histopathology were reported. Changes in hematological parameters including increased white blood cell counts in females and mean red blood cell volumes (MCVs) in males were seen at the 6,000 ppm dose, however these effects were not dose-dependent and were within historic reference ranges. Reviewers

assigned the study a NOEL of 427 mg/kg/day in males (6,000 ppm) and a NOAEL 1,545 mg/kg/day. A LOAEL was not established. (Oak Ridge National Laboratory, 2000).

In another 90-day feeding study (MRID 44929509), 10 male and 10 female albino rats were fed diets containing 0, 18.7, 62.1 or 1,000 (males) or 0, 20.6, 67.3 or 1020 mg/kg/day metolachlor OXA. The investigators reported that all animals survived to termination and no treatment related signs were observed. Platelet counts were decreased 16% ($p<0.01$) in high dose males and total protein was decreased slightly in both sexes, however, these effects were not considered biologically significant. The NOAEL was determined to be 1,000 mg/kg/day in males and 1,020 mg/kg/day in females (Oak Ridge National Laboratory, 2000).

Purebred beagle dogs (4/sex/dose) were dosed with CGA-354743 at levels of 0, 50, 200, 500 or 1000 mg/kg/day for 13 weeks (MRID 44931709). There were no significant treatment-related effects on mortality, body weights, food intake, ophthalmological findings, hematology and urinalysis parameters. Vomiting was observed in females at 1,000 mg/kg/day. Absolute and relative liver weights were increased in females at 500 and 1,000 mg/kg/day, however these effects were considered mild and not toxicologically relevant. Reviewers concluded that NOAEL was greater than 1,000 mg/kg/day (Oak Ridge National Laboratory, 2000).

Developmental Toxicity

At the limit dose of 1,000 mg/kg/day, the ESA and OXA metabolites of metolachlor did not induce any maternal or developmental effects in rats. Therefore, the NOAELs for both substances were >1000 mg/kg/day and LOAELs were not established. MRIDs 44929510 and 44931711 (Oak Ridge National Laboratory, 2000).

Carcinogenicity

Metolachlor ESA and OXA have not been tested for carcinogenicity.

Mutagenicity

In vitro studies using bacterial assays and mammalian cells indicate that metolachlor ESA and OXA are not mutagenic (EPA, 2001).

Environmental Fate

Soil and Groundwater

The principal environmental breakdown products of metolachlor include the ethane sulfonic acid (ESA) and oxanilic acid (OXA) metabolites which are more mobile in soils and more persistent in the environment than to the parent herbicide (EPA, 2001). These metabolites leach readily and have been detected in a high percentage of groundwater and surface waters in the Midwestern US (Kolpin et al. 2000; WDATCP, 2000).

Surface Water

Metolachlor ESA and OXA have been detected in surface waters in areas of use (Kolpin et al., 2000).

Regulatory Summary

	Metolachlor OXA	Metolachlor ESA
LOAEL	Not established	Not established
NOAEL	1,000 mg/kg/day	1,545 mg/kg/day
RfD	None	None
MCL	None	None
MCLG	None	None
DWEL	None	None
LHA	None	None
Cancer Classification	Not classified	Not classified

State Drinking Water/Groundwater Standards

None found

Recommendations and Conclusions

The Department of Health Services recommends that NOAELs from 90-day rat feeding studies for metolachlor ESA and OXA be averaged and used as the point of departure for a combined enforcement standard (ES). A combined standard is justified because these metabolites frequently occur together in the environment, have a common source and are similar in molecular structure. Their toxicity profiles are very similar with both chemicals having minimal effects on food utilization and weight gain in experimental animals. Because these substances are considered unlikely to have carcinogenic or mutagenic effects, a 20% preventive action limit (PAL) is appropriate. An uncertainty factor of 10,000 is recommended. This UF includes four factors of 10 each to account for the use of a subchronic study, intra- and inter-species variability, and data gaps. Data gaps for these substances include the lack of a subchronic LOAEL, the lack of studies in a second species, and the lack chronic toxicity information. Existing toxicity information indicates that these metabolites have low toxicity and are unlikely to cause cancer.

(1,000 + 1,545 mg/kg/day)/2 = 1270 mg/kg/day (averaged NOAEL for ESA and OXA metabolites)

$$\frac{1270 \text{ mg/kg/day} \times 10\text{-kg} \times 100\% \text{ exposure}}{10{,}000 \times 1 \text{ liter/day}} = 1{,}270\ \mu\text{g/L (rounded to 1,300 } \mu\text{g/L)}$$

Recommended Enforcement Standard	1,300 µg/L
Recommended Preventive Action Limit	260 µg/L

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PERCHLORATE

Perchlorate refers to the dissociated anion of perchlorate salts such as ammonium, potassium, and sodium perchlorate. Perchlorate and its salts are used in solid propellant for rockets, missiles, and fireworks. It is also used in the production of matches, flares, pyrotechnics, munitions, and explosives. The production and use of perchlorate has resulted in releases to the environment and contamination of groundwater. Perchlorate can also form in hypochlorite drinking water disinfection solutions as a result of oxidation. Griener et al. (2008) found perchlorate in 91% of commercial sodium hypochlorite water treatment solutions that, if used at the certified maximum use level, would result in drinking water concentrations ranging from 0.03 to 29 µg/L.

	Sodium Perchlorate	Ammonium Perchlorate	Potassium Perchlorate
CAS no	7601-89-0	7790-98-9	7778-74-7
Molecular formula	$NaHClO_4^-$	NH_4ClO_4	$KClHO_4$
Molecular weight	81.0	117.49	138.55
Physical state	White crystals	White crystals	Colorless crystals
Density g/cu cm	2.52	1.95	2.53
Water solubility at 25 deg C	2096 g/L	20 g/L	15 g/L
Synonyms	IRENAT, perchloric acid	None	Irenal, Astrumal, Peroidin

Occurrence

An American Water Works Association (AWWA, 2005) study of perchlorate occurrence found the rocket-fuel contaminant in 26 states and Puerto Rico, mostly at levels below 12 µg/L. Analysis of breast milk samples suggests that exposure is widespread in the US.

In 2008, scientists from the FDA published the results of a study in which 285 commonly consumed foods and beverages were tested for perchlorate. Their results revealed widespread food contamination in the U.S.; perchlorate contaminated 74% of foods and beverages that were tested. The FDA scientists went on to estimate daily perchlorate exposures from contaminated foods and beverages (excluding tap water) and found that exposures were highest among two year olds. For this age group, perchlorate exposures from contaminated food and beverages ranged from 50 and 56% of the current EPA RfD of 0.7 µg/kg/day (Murray et al 2008). These findings indicate that children have high dietary exposures to perchlorate from commonly consumed foods and beverages.

In three recent studies from CDC and academic scientists, samples of human breast milk from different parts of the country were tested for perchlorate. Every single sample of breast milk in all three studies was positive for perchlorate (Kirk et al 2005, Kirk et al 2007, Pearce et al 2007). In addition, the average levels of perchlorate in breast milk in these studies would result in exposure above the agency's RfD for a significant numbers of breast-fed infants. Further, in all three breast milk studies, a significant number of samples contained insufficient levels of iodine to meet the requirement of breast fed infants, meaning that not only would babies drinking this breast milk be exposed to hazardous levels of perchlorate by EPA's standards, but they would also be deficient in the iodine necessary to counteract the thyroid hormone lowering effects of the contaminant, thereby magnifying potential health effects of perchlorate in these infants.

Toxicity

Perchlorate has been used medicinally to control hyperthyroidism. However, it was determined that the doses needed could cause fatal aplastic anemia and it is no longer used for this purpose except in very unusual circumstances (Hardman et al. 1996).

Springborn Laboratories studied the subchronic toxicity of ammonium perchlorate in Sprague-Dawley rats (Siglin et al. 2000). The study consisted of a control group and five treatment groups that were exposed for 14 or 90 days via the drinking water at dosage levels of 0.01, 0.05, 0.2, 1.0, and 10.0 mg/kg/day. Significantly increased thyroid weights, follicular cell hypertrophy with microfollicle formation and colloid depletion was observed in male and female rats at the 10 mg/kg/day dose level in both treatment groups. These changes were reversible after a recovery period of 30 days. Statistically significant changes in TSH and thyroid hormone levels were observed at all dose levels. However, no thyroid organ weight or histopathological changes were observed at doses below 10 mg/kg/day.

Greer et al. (2002) studied 21 healthy women and 16 healthy men (mean age 38 years, range 18-57 years) who were given potassium perchlorate in doses of 0.007, 0.02, 0.1 and 0.5 mg perchlorate/kg body weight per day for 14 days. The dose was administered in 400 ml of water with instructions that 100 ml be consumed four times each day. Thyroid uptake of radioiodide was measured at 8 and 24 hours after radioiodide administration: at baseline, on days 2 and 14 of perchlorate administration, and 15 days after cessation of dosing. On day 14, the mean 24-hour radioiodide uptake was 98.2% of the baseline value in the seven subjects given 0.007 mg/kg/day; 83.6% of the baseline value in the subjects given 0.02 mg/kg/day, 55.3% of the baseline value in those given 0.1 mg/kg/day, and 32.9% of the baseline value in those given 0.5 mg/kg/day. The effects of perchlorate in these healthy adults did not change over time, as indicated by very similar results for thyroid radioiodide uptake measurements on day 2 of perchlorate administration compared to day 14 in the three higher dose groups. The 8-hour thyroid radioiodide uptake values 15 days after exposure were very similar to the baseline values, indicating rapid recovery after the exposure ended. The no observed effect level (NOEL) for perchlorate-induced inhibition of thyroid iodide uptake was 0.007 mg/kg/day. There were no changes in serum thyroxine (T4), triiodothyronine (T3) and thyroid stimulating hormone (TSH) concentrations, except for a very small decrease in serum TSH concentrations in the subjects given 0.5 mg/kg/day. One woman had a slightly elevated TSH at baseline, and it was slightly lower on day 14 of perchlorate administration at 0.007 mg/kg/day.

The National Academy of Sciences established a panel of experts to assess the health implications of perchlorate ingestion. The committee addressed a number of charge questions covering key scientific issues associated with perchlorate risk, and in January 2005 recommended a reference dose of 0.0007 mg/kg per day (NRC 2005a). The NAS committee was not unanimous in its view of the RfD with one dissenting member recommending an RfD value of 0.00023 mg/kg per day. The NRC findings were summarized in the 2005 "Report in Brief: Health Implications of Perchlorate Ingestion" which is available

online at http://www.nap.edu/books. The U.S. EPA adopted the NRC recommended reference dose in February 2005 and established an official reference dose (RfD) of 0.0007 mg/kg/day for perchlorate.

The US EPA has developed an interim subchronic health advisory for pregnant women (US EPA, 2008). The agency used the RfD, which is based on fetal iodide uptake studies, and applied a relative source contribution of 0.62 to account for dietary exposures to perchlorate. In its support document, EPA indicated that this advisory may not be protective for infants and children stating, "Because infants and children eat and drink more on a per body weight basis than adults, eating a normal diet and drinking water with 15 ug/L of perchlorate may result in exposure that is greater than the reference dose in these subgroups."

Carcinogenicity

US EPA Cancer Classification: Not Likely/Likely depending on dose

Under U.S. EPA's 1999 Draft Revised Guidelines for Carcinogen Risk Assessment, perchlorate is not likely to pose a risk of thyroid cancer in humans at doses below those necessary to alter thyroid hormone homeostasis.

Epidemiological evidence is insufficient to determine whether or not there is a causal association between exposure to perchlorate and thyroid cancer. Sufficient evidence is available from rodent studies to indicate that goitrogenic doses of perchlorate cause follicular cell tumors of the thyroid, both following prolonged ingestion and from a two-generation study where a low incidence of early onset adenomas was reported.

High doses of perchlorate has been shown to increase the development of follicular cell nodules (Fernandez Rodriguez et al. 1991), adenomas (Kessler and Kruskemper 1966), and carcinomas (Pajer and Kalisnik 1991) in rodents. Other studies have demonstrated the ability of perchlorate to promote the growth of thyroid tumors initiated by other chemicals or by irradiation (Hiasa et al. 1987, Fernandez-Santos et al. 2004; Pajer and Kalisnik 1991).

In a two-generation study (Argus 1999), there were follicular cell adenomas in one control male rat in the initial parent (P1) generation and two high-dose (30 mg/kg/day) males in the first offspring (F1) generation at 19 weeks of age. Statistical analysis of the early onset thyroid adenomas concluded that they were increased relative to the entirety of the National Toxicology Program database (Dunson, 2001). The NRC (2005) concluded that the thyroid tumors in the offspring were most likely treatment related, but that they would be expected in high dose male rats in the presence of a markedly goitrogenic dosing regimen, as existed under the conditions of the study.

Mutagenicity

Perchlorate has not demonstrated mutagenic effects in standard *in vitro* and *in vivo* assays.

Reproductive Effects

Recent research conducted in rats has shown that daily ingestion of water with perchlorate levels as low as 0.01 µg/L can induce significant effects on thyroid hormone levels in pregnant rats, as well as in the fetus and offspring. (Crofton 2001).

Environmental Fate

Terrestrial
Perchlorate is persistent and mobile in most soil types (ATSDR 2005).

Aquatic
When released to water, ammonium perchlorate will dissolve and dissociate to the perchlorate ion. The perchlorate ion is very stable and can persist for decades in groundwater and surface water systems (Gullick et al. 2001).

Regulatory Summary

RfD	0.0007 mg/kg/day
NOAEL	0.007 mg/kg/day
MCL/MCLG	None
DWEL	24.5 µg/L
Subchronic HA	15 µg/L (for pregnant women, only)
Lifetime HA	None
Cancer classification	Not likely at doses below those that alter thyroid homeostasis

State Drinking Water Regulations and Advisories

Arizona	14 µg/L
California	6 µg/L
Massachusetts	2 µg/L
New Jersey	5 µg/L

Recommendations and Conclusions

The Department of Health Services recommends use of the EPA reference dose for calculation of an enforcement standard for perchlorate. The US EPA used this reference dose to develop an interim subchronic drinking water health advisory for pregnant women of 15 µg/L. To develop a groundwater enforcement standard that will be protective of fetal development as well as long-term exposures at all stages of growth and development, an additional uncertainty factor of 10 is recommended. Because perchlorate has demonstrated carcinogenic effects in animals, a 10% PAL is proposed.

$$\frac{0.0007 \text{ mg/kg/day} \times 10\text{-kg}}{10 \times 1 \text{ liter/day}} = 0.0007 \text{ mg/L or rounded to } 1.0 \text{ µg/L}$$

Recommended Enforcement Standard	1.0 µg/L
Recommended Preventive Action Limit	0.1 µg/L

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PROPAZINE

Propazine is a triazine herbicide that is currently registered only for indoors on container-grown ornamentals in greenhouses. Propazine has no existing registered uses in the U.S. on agricultural crops. There is an import tolerance for propazine on sorghum. There are no registered residential uses of propazine in the U.S. These limited uses are unlikely to result in groundwater contamination. However, historical uses or chemical disposal may contribute to ongoing problems. Propazine is available in wettable powder, liquid and water dispersible granular formulations.

CAS #:	139-40-2
Molecular weight	229.7
Physical State	Colorless, crystalline solid
Specific gravity:	1.162
Water solubility:	8.6 ppm at 20 degrees C (1, 9, 20)
Log Kow:	2.94
Synonyms	GEIGY 30,028, Gesamil, Milogard, Plantulin, Primatol P, Propasin, Propazin, Propazine, Prozinex

Occurrence

Triazines are environmentally persistent and leach readily to groundwater. Propazine has been detected in drinking water supplies in areas of use on agricultural cropland. However, the current uses of propazine are limited to indoor greenhouse applications and the chemical is detected much less frequently than atrazine and its residues. In a USDA study published in 1990, propazine was detected in 33 out of 1,097 surface water samples and in 15 out of 906 groundwater samples. Contaminated groundwater samples have been collected from eight states. The maximum concentration found in any sample was 13 ug/l (ppb) for surface water and 300 ug/l (ppb) for groundwater (USDA 1990).

Occurrence data provided by the Wisconsin Department of Agriculture, Trade and Consumer Protection, confirm that propazine is an uncommon contaminant of Wisconsin's groundwater having been detected in only six water supply wells to date.

Toxicity

Propazine is classified as moderately toxic. Administration of lethal or near lethal doses to rats has caused symptoms of lethargy, muscular weakness, runny nose, emaciation, diarrhea, and labored breathing. It is mildly irritating to the skin, eyes, and upper respiratory tract. Contact dermatitis has been reported among workers manufacturing propazine. No cases of poisoning from human ingestion of this herbicide have been recorded.

Principal and Supporting Studies (Oral RfD)

EPA's current reference dose of 0.02 mg/kg/day was developed in 1987 and is based on a 2-yr rat feeding study completed by Ciba-Geigy in 1980 in which the critical effect was a decrease in body weight.

Two hundred and sixty males and 260 female CD rats were selected randomly and given 0, 3, 100 or 1000 ppm of propazine in their diets for 2 years. Seventy animals of each sex were placed in the control and high dose group. Sixty animals of each sex were placed in the low and mid-dose groups. At 1000

ppm there was a significant decrease in body weight in both sexes. There was a significant increase in mammary tumors in females at 1000 ppm. The NOEL for systemic effects was 100 ppm (5 mg/kg/day). The US EPA used the NOEL from this study as the point of departure to develop an oral reference dose. The agency applied an uncertainty factor of 300 which included a factor of 3 to account for the lack of a chronic toxicity study in a second mammalian species and factors of 10 each to account for intra- and inter- species differences. The agency noted that use of a subchronic dog NOEL of 5 mg/kg/day and a 1000 UF, to account for inter- and intraspecies differences and a subchronic-to-chronic extrapolation, would yield a value similar to the RfD.

When given daily to rabbits for one to four months, oral doses of 500 mg/kg propazine were reported to cause a type of anemia (Gosselin et al, 1984). No gross signs of toxicity or pathologic changes were evident in rats that received daily doses of 250 mg/kg for 130 consecutive days. No clinical or physical toxic symptoms were observed in beagle dogs fed 1.25, 5, or 25 mg/kg of propazine formulation in 90-day feeding studies (Worthing, 1983).

The National Academy of Science has established an Acceptable Daily Intake (ADI) of 0.0464 mg/kg/day for propazine (NRC, 1977; USDA, 1990).

Reproductive Effects

There was an increase in the number of deaths of newborns produced by female rats that were given 5 mg/kg of propazine during 18 days of pregnancy (Shepard, 1980). Consumption of propazine at high levels well above the Lifetime Health Advisory level over a long period of time has caused decreased fetal weight gain and delayed fetal bone development in animal studies (USDA, 1990). Maternal doses of 500 mg/kg/day resulted in maternal toxicity and developmental toxicity expressed as increased incidence of extra ribs, incomplete bone formation, and decreased fetal body weights (US EPA, 1988). In a 3-generation study with rats fed 0, 0.15, 5 or 50 mg/kg/day, no effects on fertility, length of pregnancy, pup viability or pup survival were observed. At 50 mg/kg, pup body weights on day 21 of lactation were reduced, and there were pathological changes in organ weights in the 2nd and 3rd generation (US EPA, 1988).

Teratogenic Effects

No teratogenic effects were observed in rats fed 500 mg/kg/ day, the highest dose tested (US EPA, 1988).

Mutagenic Effects

Propazine has shown no mutagenic effects in tests conducted on human and rat liver cells and in live hamsters.

Carcinogenicity

EPA Cancer Classification: N – Not likely to be carcinogenic in humans

No evidence of increased tumor frequency was detected in a 2-year study in mice fed doses up to 450 mg/kg of propazine each day. When rats were fed 0. 0.15, 5, or 50 mg/kg of propazine each day for 2 years, there was an increase in the incidence of mammary gland tumors at the highest dose level. EPA initially classified propazine as a possible human carcinogen. However this classification was changed in 2005 based on mode of action studies.

The Fourth Report of the Cancer Assessment Review Committee stated the following: "In accordance with the EPA Final *Guidelines for Carcinogen Risk Assessment* (March 29, 2005), the Committee classified propazine as "Not Likely To Be Carcinogenic To Humans." This decision was based on the following weight-of-evidence that propazine is not genotoxic and operates via a mode of action for the development of mammary tumors in the female SD rat similar to atrazine and simazine. Atrazine's mode of action of tumor formation appears to be specific to female rats (which maintain constant estrus) and does not appear to have a counterpart in humans, and thus the mammary gland tumors found in atrazine or propazine treated SD female rats are qualitatively not relevant for human risk assessment.

Environmental Fate

Terrestrial

Propazine does not adsorb as strongly to soil particles as other commercial triazine herbicides. In most soils, it binds only weakly to soil particles (Koc = 154 g/m), and, depending on soil temperature, moisture and pH, it can become unbound. Its movement with soil moisture is limited by partial adsorption to soil particles, as well as its low water solubility (Worthing, 1983). Propazine is persistent, moderately mobile in most soils, and it is resistant to breakdown. For these reasons, propazine is one of the pesticide compounds considered by the EPA to have the greatest potential for leaching into groundwater (US EPA, 1987).

A significant portion of the herbicide may be broken down by soil microbes. Several soil microorganisms utilize propazine as a source of energy or nitrogen. Photolysis and volatilization are not important factors in propazine degradation (Worthing, 1983).

Aquatic

Propazine is resistant to breakdown by hydrolysis. After 28 days, at pH 5, 60% of applied propazine remained unhydrolyzed; at pH 7, 92% remained; and at pH 9, 100% remained (USDA 1990).

US EPA Regulatory Position

NOAEL	5 mg/kg/day
Reference Dose	0.02 mg/kg/day
MCL	None
MCLG	None
Lifetime Health Advisory	10 µg/L
Cancer Classification	N,- Not Likely

State Drinking Water Standards and Advisories

Florida	10 µg/L
Maine	14 µg/L
New York	16 µg/L
Vermont	10 µg/L

Recommendations and Conclusions for Propazine

The Wisconsin Department of Health Services recommends adoption of the US EPA Lifetime Health Advisory for use as a groundwater enforcement standard. Since propazine has been determined to be

unlikely to cause cancer in humans and is not teratogenic or mutagenic, a 20% preventive action limit is appropriate.

Recommended enforcement standard 10 μg/L
Recommended preventive action limit 2 μg/L

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TERTIARY BUTYL ALCOHOL

t-Butyl alcohol is used as a denaturant for ethanol, in the manufacture of flotation agents, flavors and perfumes, as a solvent, as an octane booster in gasoline as well as its use as a dehydrating agent and in the manufacture of methyl methacrylate. t-Butyl alcohol is also a likely degradation product of methyl tert-butyl ether (MTBE) and has been detected in MTBE contaminated wells.

CAS No	75-65-0
Molecular Weight	74.12
Physical State	Colorless liquid
Solubility	Freely soluble in water
Synonyms	T-butanol

Occurrence

t-Butyl alcohol was identified, but not quantified in drinking water samples from at least one of the following cities: Cincinnati, OH, Miami, FL, Ottumwa, IA, Philadelphia, PA, and Seattle, WA(1). t-Butyl alcohol was detected in methyl tert-butyl ether (MTBE) contaminated wells in the US (1993-1998) at concentrations of 5.5-397 μg/L (HSDB, 2005).

Toxicity

Numerous acute toxicity tests are available on t-butyl alcohol. Oral, dermal and inhalation tests all meet OECD and EPA test guidelines. t-Butanol has low acute toxicity. The oral LD50 is 2733 mg/kg; the dermal LD50 is > 2000 mg/kg. By inhalation, the LC50 is >14,100 ppm from a 4 hour whole body exposure to t-butanol vapor; ataxia and dyspnea were seen immediately post exposure at 9700 or 14,100 ppm.

NTP (1995) performed short term and chronic carcinogenesis studies in both mice and rats by administration in drinking water. In rats t-butanol caused kidney toxicity at concentrations of 1.25 to 5 mg/l and increased kidney tumors in male rats at 5 mg/L (420 mg/kg/day). In mice t-butanol caused thyroid toxicity at concentrations of 10 to 20 mg/L and marginally increased thyroid tumors in females at 20 mg/L (US EPA, 2004).

Mutagenesis

There are two Ames assays; both are negative. There are two mouse lymphoma assays; both are negative. There is an *in vitro* sister chromatid exchange assay that was positive without activation, but negative with activation. Blood taken from mice in the 90 day NTP study were analyzed for micronuclei; TBA did not induce an increase in MN. The mutagenicity battery is satisfactory; no further mutagenicity testing was recommended.

Developmental/Reproductive Toxicity

A developmental toxicity study is available in rats. Maternal toxicity (decreased weight gain and feed consumption at 5000 ppm; unsteady gait at 3500 and 5000 ppm and decreased locomoter activity at 2000 ppm) was seen at all exposure concentrations. Developmental delay (reduced fetal weight, reduced ossification) occurred in offspring of dams exposed during gestation to 2000 ppm or greater; however, no increase in malformations was seen. Results from two developmental toxicity studies in mice are available. Neither of the studies, which failed to meet EPA guidelines for developmental toxicity testing, demonstrated increased malformations.

No studies of the effect of t-butanol on reproductive function were available. No adverse effects were observed in sex organs in rats or mice in the subchronic or chronic studies of t-butanol conducted by NTP. However, several observations (*i.e.*, decreased fetal body weights in teratology studies, altered postnatal development) suggest that further study of reproductive toxicity is warranted.

An enhanced study on t-butanol was conducted in which t-butanol was administered by gavage to F_0 male and female Sprague-Dawley rats for 4 weeks premating. Males were treated for a total of 9 weeks, after which sperm were analyzed for total number, abnormal morphology, and motility. Females were treated through mating, through day 20 gestation and lactation days 5-21 (US EPA, 2004). In males at 1000 mg/kg/day, there was an initial reduction in body weight gain, which remained as a 5-7% deficit in weight until termination. During late gestation, there was a reduction in weight gain in females. At 1000 mg/kg/day, there was transient lethargy, and ataxia. At 400 mg/kg/day similar effects were seen in a few females during weeks 2-4. There was no effect on mating or fertility; 11-12 females in each group became pregnant and all delivered a live litter. All but three females mated at the first estrus (one each in 0, 64, and 160 mg/kg/day groups). There was a questionable increase in gestation length at 400 and 1000 mg/kg/day. All females delivered within the normal range of 21-23 days; however, 6 of 11 females at 1000 mg/kg/day and 5 of 12 at 400 mg/kg/day vs. no more than 20% in any of the control and lowest two treatment groups delivered on day 23.

There was no effect on sperm motility or sperm morphology. There was no effect on the number of implantation sites per pregnancy. At 1000 mg/kg/day, there was a significant reduction in the number of live born pups and an increase in the number of still born pups. The NOAEL for paternal and maternal toxicity was 160 mg/kg/day t-butanol. Maternally toxic doses of t-butanol (1000 mg/kg/day) resulted in decreased survival and body weight of pups. The NOAEL for reproduction/development was 400 mg/kg/day.

Carcinogenicity

USEPA, Cancer classification: Not classified.

Male and female F344/N rats and B6C3F1 mice were given t-butyl alcohol (>99% pure) in drinking water for 2 yr.

Groups of 60 F344/N rats were given 0, 1.25, 2.5, or 5 mg/ml t-butyl alcohol (males) or 0, 2.5, 5, or 10 mg/ml t-butyl alcohol (females) in drinking water for 2 yr. These correspond to average daily doses of approximately 90, 200, or 420 mg t-butyl alcohol/kg body weight for males and 180, 330, or 650 mg t-butyl alcohol/kg body weight for females. Groups of 60 male & 60 female B6C3F1 mice were given 0, 5, 10, or 20 mg/ml t-butyl alcohol in drinking water for 2 yr. Exposure levels of 5, 10, or 20 mg/mL delivered average daily doses of approx 540, 1,040, or 2,070 mg t-butyl alcohol/kg to males & approx 510, 1,020, or 2,110 mg/kg to females. Under the conditions of these studies, there was evidence of carcinogenic activity in male rats based on increased incidences of renal tubule adenoma or carcinoma (combined). There was no evidence of carcinogenic activity in female rats. There was equivocal evidence of carcinogenic activity of t-butyl alcohol in male B6C3F1 mice based on the marginally increased incidence of follicular cell adenoma or carcinoma (combined) of the thyroid gland. There was some evidence of carcinogenic activity of t-butyl alcohol in female B6C3F1 mice based on an increased incidence of follicular cell adenoma of the thyroid gland (NTP, 1995).

The California EPA used the NTP feeding studies to develop a cancer slope factor of 3.0E-3 for t-butyl alcohol (Alexeef, 1999). Using this cancer slope factor, CalEPA developed a drinking water guideline of 12 ug/L.

Environmental Fate

Aquatic

If released into water, t-butyl alcohol is not expected to adsorb to suspended solids and sediment in water based upon the estimated Koc. Volatilization from water surfaces is expected to be an important environmental fate process based upon this compound's Henry's Law constant. Estimated volatilization half-lives for a model river and model lake are 2 and 29 days, respectively. The biodegradation half-life of t-butyl alcohol was reported to range from about 28 to 180 days in aerobic water and 100 to 500 days in anaerobic water. BCF values of less than 5 measured in fish suggest that bioconcentration in aquatic organisms is low. Hydrolysis is not expected to be an important environmental fate process since this compound lacks functional groups that hydrolyze under environmental conditions.

Atmosphere

If released to air a vapor pressure of 40.7 mm Hg at 25° C indicates t-butyl alcohol will exist solely as a vapor in the ambient atmosphere. Vapor-phase t-butyl alcohol will be degraded in the atmosphere by reaction with photochemically-produced hydroxyl radicals; the half-life for this reaction in air is estimated to be 14 days.

Terrestrial

If released to soil, t-butyl alcohol is expected to have very high mobility based upon an estimated Koc of 37. Volatilization from moist soil surfaces is expected to be an important fate process based upon a Henry's Law constant of 9.05X10-6 atm-cu m/mole. t-Butyl alcohol may volatilize from dry soil surfaces based upon its vapor pressure. Screening tests using sewage or activated sludge inoculum have shown that t-butyl alcohol degrades slower than primary or secondary alcohols. The half-life of t-butyl alcohol under anoxic conditions in a non-amended soil was about 200 days, but the half-lives in the same soil amended with nitrate and sulfate nutrients were 100 and 50 days, respectively.

Regulatory Summary

MCL	None
MCLG	None
LOAEL	180 mg/kg/day
BMDL10	133 mg/kg/day (subchronic rat study)
RfD	None
Cancer class	Not classified by EPA; NTP found evidence of carcinogenicity

State Drinking Water Guidelines

California	12 µg/L
Florida	1,200 µg/L
Michigan	3,900 µg/L

Recommendations and Conclusions

The Department of Health Services recommends use of the cancer slope factor developed by CalEPA in the development of a groundwater standard for t-butyl alcohol. Because this substance has carcinogenic properties, a 10% preventive action limit is proposed.

$$\frac{10\text{-}6\ \text{LCR}^* \times 70\ \text{kg}}{3\text{x}10\text{-}3\ /\text{mg/kg/day} \times 2\ \text{liters/day}} = 12\ \mu\text{g/L}$$

*LCR = lifetime cancer risk of 1 in a million

Recommended Enforcement Standard 12 µg/L
Recommended Preventive Action Limit 1.2 µg/L

References

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