Office of Environmental Health Hazard Assessment (OEHHA)
California Environmental Protection Agency

Meeting of the
Carcinogen Identification Committee (CIC)
Safe Drinking Water and Toxic Enforcement Act of 1986
(Proposition 65)
October 17, 2003

Acrylamide Briefing Binder
(Outline and Availability of Contents)

Background Materials for CIC Consultation on OEHHA Proposed Acrylamide Workplan

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Tab 1. Introduction: consultation of proposed acrylamide workplan with the CIC

Recent research has shown that acrylamide can form during the cooking of certain foods at high temperatures. Accordingly, OEHHA, as the lead agency for the implementation of Proposition 65, was requested by interested parties to interpret the applicability of Proposition 65 regulations to acrylamide in foods. On May 12, 2003, OEHHA held a public workshop to explore appropriate Proposition 65 regulatory options regarding acrylamide created by cooking foods. Subsequent to the workshop, OEHHA developed a draft workplan (under this tab, Tab 1), which reflects input received at the workshop, public health considerations, and the need for clear guidance to facilitate Proposition 65 compliance concerning acrylamide in foods.

OEHHA has incorporated into this workplan a consultative role for the CIC. This is consistent with the CIC's role as the State's Qualified Experts and its general powers and duties as set forth in Title 22, California Code of Regulations (CCR), Section 12305(a)(5), and noted in Title 22, CCR, Section 12302(e). At the October 17, 2003, meeting OEHHA is seeking advice and counsel from the CIC on the workplan and on the scientific basis for the proposed workplan activities. Under the proposed workplan OEHHA would develop a series of regulations to provide guidance to facilitate Proposition 65 compliance concerning acrylamide in foods.

One workplan item on which OEHHA is seeking advice from the CIC is whether the No Significant Risk Level (NSRL) for acrylamide should be updated. A NSRL of 0.2 µg/d was proposed for acrylamide in February 1990, and subsequently adopted in regulation, based on a cancer potency estimate of 4.5 $(mg/kg\text{-}d)^{-1}$ developed by the U.S. EPA (1989) (documented in Tab 2). Acrylamide has been listed on California's Proposition 65 list of chemicals "known to the State to cause cancer" since January 1, 1990 (documentation in Tab 3). Since then, three Proposition 65 authoritative bodies have issued or reissued documents consistent with this finding (Tab 4). This briefing book also includes the following reports and studies of acrylamide: the institutional reactions to the discovery in food (Tab 5), animal cancer bioassays (Tab 6), recent epidemiological reports (Tab 7), studies of genotoxicity (Tab 8), and pharmacokinetic and bioavailability investigations (Tab 9). Acrylamide concentrations measured in foods are given under Tab 10, along with researchers estimates of two-day and four-day average consumption levels.

Historically, toxicity concerns over acrylamide centered on worker health and safety, primarily neurological and cancer effects in workers. However, in April 2002 Swedish researchers announced findings that acrylamide is present in many human foods, and published these findings in Tareke *et al.* (2002) (provided in Tab 5). Since that time research has confirmed that acrylamide is a common byproduct of high-temperature cooking, which is present in many foods and some beverages. Thus, the focus of concern over acrylamide has shifted from occupational exposures of workers to dietary exposures of the general population.

Worldwide efforts have been undertaken to understand the extent of dietary exposure and its public health ramifications as well as ways to minimize acrylamide formation during cooking and food processing. For example, the World Health Organization (WHO), together with the United Nations Food and Agriculture Organization (FAO) convened an Expert Consultation on the Health Implications of Acrylamide in Food June 25-27, 2002. Their report is provided in Tab 5. The Consultation recommended that an international network on acrylamide in food be established, to facilitate the sharing of data and information on ongoing investigations. In response the FAO/WHO Acrylamide in Food Network and Infonet website was established (www.acrylamide-food.org/index.htm) (see Tab 5). At the national level, the U.S. Food and Drug Administration (U.S. FDA) has initiated an action plan to address the issue of acrylamide in food (Tab 5).

Following the discovery of acrylamide in foods, several lawsuits were filed in California against food manufacturers for failure to provide "clear and reasonable" warnings as required under Proposition 65. Foods named in the suits include French fries, and other fried or baked foods. The lawsuits contend that the food manufacturers have failed to warn the public of a significant cancer risk of acrylamide in their products.

In a letter from U.S. FDA Deputy Commissioner Dr. Lester Crawford, received July 14, 2003, U.S. FDA expressed concerns over possible actions California may take. That letter, and OEHHA's response to it, are included under Tab 5.

Due to the public health importance of the issue, OEHHA is seeking advice and counsel from the CIC on the scientific basis for proposed workplan activities, including a recommendation whether OEHHA should update the NSRL for acrylamide, and if so, the factors OEHHA should consider in doing so.

Links to contents for Tab 1

- OEHHA's proposed workplan for acrylamide in foods, located at http://www.oehha.ca.gov/prop65/docs_state/pdf/Acrylwrkpln.pdf.

Tab 2. Chronology of OEHHA actions under Proposition 65 regarding the carcinogenicity of acrylamide

- **January 1, 1990 – Placed on the Proposition 65 list of carcinogens, via the authoritative body listing mechanism**

  Acrylamide (CAS # 79-06-1) was added to the Proposition 65 list of carcinogens on January 1, 1990. This listing was based on formal identification of acrylamide as causing cancer by two authoritative bodies: the International Agency for Research on Cancer (IARC, 1987) and the U.S. Environmental Protection Agency (U.S. EPA, 1989).

  The IARC (1987) and U.S. EPA (1989) documents are provided in Tab 3.

- **1990 – adoption of a No Significant Risk Level (NSRL) for acrylamide, based on the 1989 U.S. EPA cancer assessment and cancer potency value**

  The cancer potency estimate of 4.5 $(mg/kg\text{-}d)^{-1}$ for acrylamide developed by the U.S. EPA (1989) was utilized in the calculation of a daily intake level associated with a 10^{-5} cancer risk (NSRL = 0.2 µg/d). This value was adopted into regulation (Title 22, California Code of Regulations, Section 12705(c)). This action is documented in a February 27, 1990 memorandum from Dr. Steven Book, Science Advisor to the Secretary, Health and Welfare Agency, Department of Health Services (a predecessor agency to OEHHA).

  Provided in Tab 2.

- **May 12, 2003 – OEHHA holds a workshop on acrylamide in foods**

  After requesting public input on possible Proposition 65 regulatory options to address the issue of acrylamide in foods on March 14, 2003, OEHHA convened a public workshop May 12, 2003 in Sacramento.

  Related notices and the workshop agenda are provided at Tab 2. Presentations from the workshop are available on OEHHA's website, http://www.oehha.ca.gov/prop65/CRNR_notices/acrylamidewrkshp2.html.

Documents or links to contents of Tab 2.

- February 27, 1990 memorandum from Dr. Steven Book, Science Advisor to the Secretary, Health and Welfare Agency, Department of Health Service (Scanned copy of document attached).

- March 14, 2003 Notice to Interested Parties. Located at http://www.oehha.ca.gov/prop65/CRNR_notices/pdf_zip/Acrylamideworkshop.pdf

- April 25, 2003 Notice to Interested Parties. Located at http://www.oehha.ca.gov/prop65/CRNR_notices/pdf_zip/Acrylamideworkshop2.pdf

- Workshop Agenda, May 12, 2003. Proposition 65 Regulatory Options Regarding Acrylamide in Foods. Located at http://www.oehha.ca.gov/prop65/public_meetings/AcrylamidePres.html

RCHAS-B

State of California

Department of Health Services

Memorandum

To : Steven A. Book, Ph.D.
Science Advisor to the Secretary
Health and Welfare Agency
1600 Ninth Street, Room 460

Date : FEB 27 1990

Subject: Intakes Posing 10^{-5} Cancer Risk for 11 Proposition 65 Carcinogens

From : Public Health
714 P Street, Room 1253
445-2927

The Environmental Protection Agency (EPA) has published cancer potency evaluations for several chemicals listed as carcinogens under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65; California Health and Safety Code, Section 25249.5 et sq.). Staff of the Cancer Unit of the Reproductive and Cancer Hazard Assessment Section (RCHAS) have calculated intake levels associated with 10^{-5} cancer risk based on the EPA assessments. These intake levels are given below.

Chemical	Cancer Potency $(mg/kg\text{-}d)^{-1}$	Risk Specific Intake Level* ($\mu g/d$)	Reference
Acrylamide	4.5	0.2	1
Aniline	0.0057	100	2
Azobenzene	0.11	6	3
Dichlorvos	0.29	2	4
Folpet	0.0035	200	5
Furmecyclox	0.030	20	6
Hydrazine sulfate	3.0	0.2	7
4,4'-Methylene bis (N,N'-dimethyl)aniline	0.046	20	8
N-Nitrosodiethanolamine	2.8	0.3	9
N-Nitroso-N-methyl-ethylamine	22	0.03	10
N-Nitrosopyrrolidine	2.1	0.3	11

*Intake levels associated with a 10^{-5} risk of cancer.

For your convenience we have attached the EPA Integrated Risk Information System (IRIS) document for each chemical. Please contact Wai Nang Choy, Ph.D. at 8-571-2005 if you have any questions about the derivation of the risk specific intake levels presented here.

ORIGINAL SIGNED BY
HARVEY F. COLLINS, Ph.D

Harvey F. Collins, Ph.D.
Deputy Director

Attachments

References

1. Environmental Protection Agency (1989). Integrated Risk Information System: *Acrylamide*. *CASRN 79-06-1*. EPA Environmental Criteria and Assessment Office, Cincinnati, OH, June 1.

2. Environmental Protection Agency (1989). Integrated Risk Information System: *Aniline*. *CASRN 62-53-3*. EPA Environmental Criteria and Assessment Office, Cincinnati, OH, August 1.

3. Environmental Protection Agency (1989). Integrated Risk Information System: *Azobenzene*. *CASRN 103-33-3*. EPA Environmental Criteria and Assessment Office, Cincinnati, OH, September 1.

4. Environmental Protection Agency (1989). Integrated Risk Information System: *Dichlorvos*. *CASRN 62-73-7*. EPA Environmental Criteria and Assessment Office, Cincinnati, OH, December 1.

5. Environmental Protection Agency (1988). Integrated Risk Information System: *Folpet*. *CASRN 133-07-3*. EPA Environmental Criteria and Assessment Office, Cincinnati, OH, August 22.

6. Environmental Protection Agency (1989). Integrated Risk Information System: *Furmecyclox*. *CASRN 60568-05-0*. EPA Environmental Criteria and Assessment Office, Cincinnati, OH, December 1.

7. Environmental Protection Agency (1989). Integrated Risk Information System: *Hydrazine*. *CASRN 302-01-2*. EPA Environmental Criteria and Assessment Office, Cincinnati, OH, December 1.

8. Environmental Protection Agency (1989). Integrated Risk Information System: *4,4'-Methylene bis(N,N'-dimethyl)aniline*. *CASRN 101-61-1*. EPA Environmental Criteria and Assessment Office, Cincinnati, OH, August 1.

9. Environmental Protection Agency (1988). Integrated Risk Information System: *N-Nitrosodiethanolamine*. *CASRN 1116-54-7*. EPA Environmental Criteria and Assessment Office, Cincinnati, OH, March 1.

10. Environmental Protection Agency (1989). Integrated Risk Information System: *N-Nitroso-N-methylethylamine*. *CASRN 10595-95-6*. EPA Environmental Criteria and Assessment Office, Cincinnati, OH, December 1.

11. Environmental Protection Agency (1988). Integrated Risk Information System: *N-Nitrosopyrrolidine*. *CASRN 930-55-2*. EPA Environmental Criteria and Assessment Office, Cincinnati, OH, March 1.

Tab 3. Basis of 1990 Proposition 65 acrylamide cancer listing via authoritative body mechanism: U.S. EPA and IARC

In 1990, two authoritative bodies, namely the U.S. Environmental Protection Agency (U.S. EPA) and the International Agency for Research on Cancer (IARC), had formally identified acrylamide as causing cancer. Following regulatory procedures given in Title 22, California Code of Regulations Section 12306, acrylamide was listed as a Proposition 65 carcinogen.

The U.S. EPA and IARC reports that served as the bases for the 1990 listing are provided at Tab 3.

- U.S. EPA IRIS file (carcinogenicity assessment, June 1, 1989): Group B2 – "probable human carcinogen"

  The U.S. EPA (1989) assessment cited the following as evidence of the carcinogenicity of acrylamide: limited or inadequate human data, benign and/or malignant tumor formation at multiple sites in rats, cancer formation in one-year studies in mice by multiple routes of exposure, positive genotoxicity data, DNA adduct formation, and structure-activity relationships to other carcinogens. An oral cancer slope factor was derived.

- IARC (1987) Monograph Suppl. 7: Group 2B - "possibly carcinogenic to humans"
  - IARC (1986) Monograph Vol. 39: "sufficient evidence" in animals (as cited by IARC (1987))

  The summary of data in IARC (1986) cites the following evidence: increased tumor incidences in oral cancer studies in male and female rats (Johnson et al., 1986), tumor-initiating activity in mouse skin by multiple routes, induction of lung tumors in mice from oral or i.p. administration (Bull et al., 1984a), and findings of chromosomal damage from *in vitro* and *in vivo* studies. In its overall evaluation of the carcinogenicity of acrylamide, IARC (1987) concluded that acrylamide was possibly carcinogenic to humans (Group 2B), based on sufficient evidence in animals.

Documents or links to contents of Tab 3.

- 1989 U.S. EPA IRIS file for acrylamide (scanned copy attached (selected pages))

- 1987 IARC Monograph Supplement 7, page 56, information on obtaining copies of IARC Monographs is located on the IARC website at http://193.51.164.11/default.html.

- 1986 IARC Monograph Volume 39, pages 41-66, information on obtaining copies of IARC Monographs is located on the IARC website at http://193.51.164.11/default.html.

Environmental Protection Agency (1989). Integrated Risk Information System: Acrylamide. CASRN 79-06-1. EPA Environmental Criteria and Assessment Office, Cincinnati, OH, June 1.

Acrylamide; CASRN 79-06-1 (06/01/89)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Acrylamide

File On-Line 09/26/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	09/26/88
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	06/01/89
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	

medium only because of the lack of a sensitive measure of the critical effect for chronic exposure.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Agency RfD Work Group Review: 02/24/88

Verification Date: 02/24/88

___I.A.7. EPA CONTACTS (ORAL RfD)

Charles O. Abernathy / ODW -- (202)382-5374 / FTS 382-5374

Edward V. Ohanian / ODW -- (202)382-7571 / FTS 382-7571

------<<< Acrylamide >>>------

__I.B. REFERENCE DOSE FOR CHRONIC INHALATION EXPOSURE (RfDi)

Not available at this time

_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Acrylamide
Primary Synonym -- 2-Propenamide
CASRN -- 79-06-1
Last Revised -- 06/01/89

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2

(Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Acrylamide >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen

Basis -- Based on inadequate human data and sufficient evidence of carcinogenicity in animals; significantly increased incidences of benign and/or malignant tumors at multiple sites in both sexes of rats, and carcinogenic effects in a series of one-year limited bioassays in mice by several routes of exposures. The classification is supported by positive genotoxicity data, adduct formation activity, and structure-activity relationships to vinyl carbamate and acrylonitrile.

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___II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. There are two studies on the relationship of workers exposed to acrylamide and cancer mortality. A basic limitation of both studies is that the design is insufficient to derive inference of relative risk.

In the first study (Collins, 1984), a standardized proportionate mortality ratio (SPMR) was used to analyze the data on two study groups: a long duration exposure group of 10 individuals and a short duration/ intermittent exposure group of 52 individuals. Results from the study indicated no significant excesses of mortality from cancer (all types combined) in either group. The mortality from cancer of the lung and CNS appeared to be slightly elevated; however, the SPMRs were not significantly different from expected values, due to the small size of the groups. Other limitations in this study include under representation of the worker population potentially at risk for exposure related effects, incomplete ascertainment of causes of death for group members, and incomplete acrylamide exposure data.

In another study (Sobel et al., 1986), the mortality experience of 371 employees assigned to acrylamide monomer and polymerization operations during the late 1950s and 1960s was examined. Whereas 38 deaths were expected (based on the U.S white male mortality rates), a total of 29 deaths had been observed up until 1982. The mortality in the total cohort from cancer was somewhat in excess (11 observed vs. 7.9 expected); however, this appeared due to excess cancer mortality in the subgroup with previous exposure to organic dyes. The epidemiologic evidence of this study is considered insufficient to assess the carcinogenicity of acrylamide because of the small cohort, multiple chemical exposures and limited follow-up; furthermore, 167 cohort members had <1 year

employment and another 109 had only 1-4 years of employment.

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___II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. In an adequately designed 2-year carcinogenesis bioassay (Johnson et al., 1984, 1986), acrylamide (>98% purity) was administered in drinking water to F344 rats (60/sex/dose) at doses of 0, 0.01, 0.1, 0.5 and 2.0 mg/kg bw/day. An MTD appeared to have been achieved based on decreased body weight gain, decreased survival and the observance of several toxic effects in the high dose group. There were transient symptoms of a viral infection (sialodacryoadenitis virus) in some rats beginning on day 210 of the study; however, all animal groups were equally affected. This viral infection did not significantly affect the body weight, survival or tumor incidences of F344 rats (Rao et al., 1988).

Acrylamide induced significantly ($p<0.05$) increased incidences of several tumor types in test rats of both sexes when compared to control animals. In males, significantly increased incidences of tumors included the following: scrotal mesotheliomas in the two highest doses (3/57 control; 11/53 and 10/54 two highest doses), adrenal pheochromocytomas in the high dose (3/57; 10/54), and thyroid adenomas in the high dose (1/57; 7/54). In high dose females, gliomas and astrocytomas of the CNS (1/60 control; 9/61 high dose), adenomas and adenocarcinomas of the mammary gland (10/60; 28/60), adenomas and adenocarcinomas of the thyroid gland (1/54; 5/50), adenocarcinomas of the uterus (1/56; 5/49), and papillomas and carcinomas of the oral cavity (0/60; 8/60) were significantly increased.

A series of mouse skin papilloma and lung adenoma assays showed that acrylamide initiated skin tumorigenesis in both SENCAR and Swiss-ICR mice, and induced lung tumors in mice of SENCAR, Swiss-ICR and A/J strains (Bull et al., 1984a,b; Robinson et al., 1986). Administration of a total of 0, 75, 150 and 300 mg acrylamide/kg during 6 applications over a 2-week period by gavage, i.p. or dermal route to groups of female SENCAR mice followed by triweekly applications of 1 ug TPA (12-0-tetradecanoyl-phorbal-13-acetate) for 20 weeks, caused a dose-response increase of skin tumors in the mice (Bull et al, 1984a). Significant increases of skin and lung tumors were noted in SENCAR mice administered 50 mg/kg of acrylamide by a single i.p. injection followed by treatment with TPA (Robinson et al., 1986). Acrylamide also initiated skin tumorigenesis in Swiss-ICR mice (by gavage) and induced lung neoplasms in Swiss-ICR mice (by gavage) and A/J mice (by gavage and i.p.). Skin tumor development was dependent on promotion by TPA whereas lung tumor induction was not (Bull et al., 1984 a,b).

<<< Acrylamide >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Acrylamide has been shown to be a clastogenic agent, inducing chromosomal aberrations, dominant lethality, sister-chromatid exchanges and unscheduled DNA synthesis in various in vivo and in vitro systems. Acrylamide also produces cell transformation in vitro and causes amplification of SV40 DNA inserts of SV40-transformed Chinese hamster cells. Furthermore, there is evidence that [C14]-acrylamide binds covalently to DNA and protein in rodents (Dearfield et al., 1988).

Acrylamide is structurally analogous to the carcinogens vinyl carbamate and acrylonitrile; they all contain a vinyl group which may interact with cellular macromolecules via activation to an epoxide.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE
<<< Acrylamide >>>

___II.B.1. SUMMARY OF RISK ESTIMATES

Oral Slope Factor -- 4.5/mg/kg/day

Drinking Water Unit Risk -- 1.3E-4/ug/L

Extrapolation Method -- Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	8E-1 ug/L
E-5 (1 in 100,000)	8E-2 ug/L
E-6 (1 in 1,000,000)	8E-3 ug/L

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___II.B.2. DOSE-RESPONSE DATA (CARCINOGENICITY, ORAL EXPOSURE)

Tumor Type -- CNS, Mammary and thyroid glands, uterus, oral cavity (combined)
Test Animals -- rat/Fischer 344, female
Route -- Drinking water
Reference -- Johnson et al., 1986

---- Dose ----- Administered (mg/kg/day)	Human Equivalent (mg/kg/day)	Tumor Incidence
0	0	13/60
0.01	0.001	18/60
0.1	0.015	14/60
0.5	0.076	21/60
2.0	0.305	46/60

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___II.B.3. ADDITIONAL COMMENTS (CARCINOGENICITY, ORAL EXPOSURE)

Tumors at a particular site were added into the pool only when the tumor site had statistically significantly increased incidence at least at the high dose level (treated vs. control). The dose response curves for each sex based on the pooled tumor incidence (benign and malignant) data comprise the data sets of choice for risk assessment. The female was the more sensitive sex (as there were significantly increased tumor incidences at a greater number of sites than in the males) and was, therefore, chosen for the risk estimate. A transpecies conversion factor of 7.05 was used (the cube root of the ratio of human to rat body weights, or 70 kg/0.2 kg).

There was no indication that the doses used should be adjusted to reflect different patterns of distribution or metabolism; the distribution of acrylamide appears to be quantitatively the same regardless of route of exposure (Dearfield et al., 1988).

The unit risk should not be used if the water concentration exceeds 8E+1 ug/L, since above this concentration the slope factor may differ from that stated.

<<< Acrylamide >>>

___II.B.4. DISCUSSION OF CONFIDENCE (CARCINOGENICITY, ORAL EXPOSURE)

Four doses over a reasonable range and a sufficient number of animals were tested. Many of the tumors were malignant, among which were gliomas and astrocytomas of the CNS which rarely occur in rats.

Slope factors calculated from six data sets based on tumor incidences at individual sites in males and females ranged from 2.9E-1/mg/kg/day to 2.3/mg/kg/day.

Tab 4. Reports on the carcinogenicity of acrylamide published by Proposition 65 authoritative bodies since the 1990 listing: U.S. EPA, IARC, NTP

U.S. EPA

- U.S. EPA IRIS file (carcinogenicity assessment, July 1, 1993): Group B2 – "probable human carcinogen". Provided here at Tab 4.

  The U.S. EPA (1993) assessment cited as carcinogenicity evidence: limited or inadequate human data, benign and/or malignant tumor formation at multiple sites in rats, cancer formation in one-year studies in mice by multiple routes of exposure, positive genotoxicity data, DNA adduct formation, and structure activity relationships to other carcinogens. As in the U.S. EPA's 1989 assessment, an oral cancer slope factor is provided in the 1993 assessment, the same value as in earlier U.S.EPA documentation and updated under Proposition 65.

IARC

- IARC (1994) Monograph Vol. 60: Group 2A – "probably carcinogenic to humans". Provided at Tab 4.

  IARC (1994) upgraded the listing of acrylamide from 2B to 2A based in part on new data from humans and rodents on acrylamide uptake, metabolism, and hemoglobin adducts. The evidence evaluated included drinking water cancer studies in male and female rats (Johnson et al., 1986); oral, i.p. and dermal cancer studies in male and female A/J and SENCAR mice (Bull et al., 1984a); an oral cancer study in female Swiss mice (Bull et al., 1984b), many new studies showing gene mutations and chromosomal damage in mammalian cells *in vivo* and *in vitro*; DNA adducts measured *in vivo* in rats and mice in all tissues examined, and extensive new data from humans and rodents on uptake, metabolism, and formation of hemoglobin adducts.

The National Toxicology Program (NTP)

- NTP 6th Annual Report on Carcinogens (1991): Acrylamide is "reasonably anticipated to be a human carcinogen." Provided at Tab 4.

- NTP 10th Report on Carcinogens (2002): Acrylamide is "reasonably anticipated to be a human carcinogen." Provided at Tab 4.

  Acrylamide was first listed in 1991 as "reasonably anticipated to be a human carcinogen" in the NTP's 6th Report on Carcinogens. The 10th, and most recent Report on Carcinogens, continues to classify acrylamide as "reasonably anticipated to be a human carcinogen." The evidence cited in the NTP Report on Carcinogens includes formation of tumors at multiple sites in rats following acrylamide administration via drinking water, lung tumors in mice following oral or i.p. administration, and skin tumor initiation by three routes of exposure in mice.

Documents or links to contents of Tab 4.

- Current U.S. EPA IRIS file for acrylamide (carcinogenicity assessment, July 1, 1993), located at http://www.epa.gov/iris.

- 1994 IARC Monograph Volume 60, pages 389-433. Summary located online at http://www-cie.iarc.fr/htdocs/monographs/vol60/m60-11.htm.

- Information on obtaining full copies of IARC Monographs is located on the IARC website at http://193.51.164.11/default.html.

- NTP (1991). 6th Annual Report on Carcinogens. Acrylamide, pages 80-85. Copies of scanned document are attached.

- NTP (2002). 10th Annual Report on Carcinogens. Acrylamide, pages III-4 to III-6. Located at http://ehp.niehs.nih.gov/roc/tenth/profiles/s003acry.pdf.

NTP (1991) 6th Report on Carcinogens

REGULATIONS

EPA regulates 2-acetylaminofluorene under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), the Resource Conservation and Recovery Act (RCRA), and the Superfund Amendments and Reauthorization Act (SARA). 2-Acetylaminofluorene has been designated as a hazardous constituent of waste and a potential human carcinogen under RCRA. Based on this designation, a reportable quantity (RQ) of 1 lb has been established under CERCLA. 2-Acetylaminofluorene is subject to reporting requirements under SARA. OSHA has promulgated a standard designating protective clothing and hygiene procedures for anyone handling, storing, or working with 2-acetylaminofluorene, and special engineering requirements for its manufacture and processing. OSHA regulates 2-acetyl-aminofluorene under the Hazard Communication Standard and as a chemical hazard in laboratories.

ACRYLAMIDE
CAS No. 79-06-1

CARCINOGENICITY

There is sufficient evidence for the carcinogenicity of acrylamide in experimental animals (IARC V.39, 1986; IARC S.7, 1987). When administered in the drinking water, acrylamide increased the incidences of adrenal pheochromocytomas and mesotheliomas of the tunica of the testes in male rats; pituitary adenomas, mammary adenomas and adenocarcinomas, oral cavity papillomas, uterine adenocarcinomas, and clitoral gland adenomas in female rats; and follicular adenomas of the thyroid in rats of both sexes. When administered by gavage or by intraperitoneal injection, acrylamide increased both the incidence and multiplicity of lung adenomas in mice of both sexes. When administered topically, by gavage, or by intraperitoneal injection followed by long-term topical treatment with 12-O-tetradecanoylphorbol 13-acetate, acrylamide induced skin squamous cell papillomas and squamous cell carcinomas in female mice.

An IARC Working Group reported that there were no adequate data available to evaluate the carcinogenicity of acrylamide in humans (IARC V.39, 1986; IARC S.7, 1987).

PROPERTIES

Acrylamide occurs in crystalline form and in aqueous solution. The solid monomer is a colorless-to-white, free-flowing crystal that is soluble in water, methanol, ethanol, dimethyl ether, and acetone and is insoluble in benzene and heptane. It melts at 84°-85° C and boils at 125° C. The crystalline acrylamide monomer is available as pellets of 98% and 95% purity. The 50% aqueous form is the preferred form for applications in which water can be tolerated. The monomer readily polymerizes at the melting point or under ultraviolet light. Solid acrylamide is stable at room temperature but may polymerize violently when melted or in contact with oxidizing agents. When heated to decomposition, acrylamide emits

acrid fumes and NO_x. Commercial acrylamide monomer contains residual levels of acrylonitrile (1-100 mg/kg) (IARC V.39, 1986). Residual acrylamide monomer is present in the polymer at approximately 0.01% (Fujiki et al., 1985; IARC V.39, 1986).

USE

Acrylamide is a chemical intermediate used in the production and synthesis of polyacrylamides (IARC V.39, 1986). These high-molecular weight polymers can be modified to develop nonionic, anionic, or cationic properties for specific uses. The principle end use of acrylamide is in water-soluble polymers used as additives for water treatment, enhanced oil recovery, flocculants, papermaking aids, thickeners, soil conditioning agents, sewage and waste treatment, ore processing, and permanent-press fabrics (Kirk-Othmer V.1, 1978; Sax and Lewis, 1987). Acrylamide is also used in the synthesis of dyes, in copolymers for contact lenses, and the construction of dam foundations, tunnels, and sewers (Kirk-Othmer V.6, 1979).

The largest use for polyacrylamide is in treating municipal drinking water and waste water (IARC V.39, 1986). The polymer is also used to remove suspended solids from industrial waste water before discharge, reuse, or disposal. Polyacrylamide used for potable water should not contain more than 0.05% residual monomer (Kirk-Othmer V.1, 1978). The polymers bind with particles and form heavy aggregates that rapidly settle out of solution and leave a clear supernatant (IARC V.39, 1986). Ten to thirty percent of the annual production volume is used in oil-recovery processes in which the polyacrylamides increase water viscosity. Acrylamides also find use in oil-drilling processes to control fluid losses. In the pulp and paper industry, polyacrylamides are used as binders and retention aids for fibers and to retain pigments on paper fibers. The paper industry uses approximately 20% of the annual U.S. production volume. Polyacrylamides are used to clarify waste water, recover tailings, and flocculate ores in mineral processing. They are incorporated in cement to slow the dehydration process to improve structural strength. Methylated polyacrylamide with subsequent radiation curing is used to produce waterproof concrete. Acrylamide is a soil stabilizer and also finds use in foundry operations to facilitate free sand flow into molds. Polyacrylamides are incorporated in coatings as dispersants and binders and in water-based paints for pigment suspension and flow. Home appliances, building materials, and automotive parts are coated with acrylamide resins and thermosetting acrylics. Acrylamides are formulated in cosmetics and soap preparations as thickeners and in dental fixtures, hair grooming preparations, and preshave lotions. In the textile industry, polyacrylamides are used to size and shrink-proof material and as water repellants. Minor uses of acrylamide are as latex thickeners, emulsion stabilizers for printing inks, gelling agents for explosives, binders in adhesives and adhesive tape; in

the production of diazo compounds; and for gel chromatography and electrophoresis (Sittig, 1985; IARC V.39, 1986). When added to herbicidal gels, polyacrylamides restrict herbicidal treatment to the bottom of lakes or reservoirs by allowing the herbicides to sink before they break up. The FDA has regulated the use of acrylamide and polyacrylamide in foods. Up to 10 mg polyacrylamide/L water can be used to wash or peel fruits and vegetables; acrylamide monomer should not exceed 0.2%. Acrylamide resins may be added to water for steam that will contact food; the monomer should not exceed 0.05% by weight. Polyacrylamide may be used in gelatin capsules, if no more than 0.2% of the monomer is present. Acrylamide polymers may be used in food packaging adhesives, and acrylamide resins, containing <0.2% monomer, may be used in food packaging paper and paperboard if the resin is ≤2% of the weight of the paper.

PRODUCTION

Three U.S. producers of acrylamide monomer were identified for 1988 and two for 1987, with no production figures available (USITC, 1989, 1988). Four U.S. producers reportedly manufactured 47.1 million lb in 1986 (USITC, 1987). An estimated 70 million lb was produced in 1974 (Sitting, 1985).

The import and export volumes of acrylamide reported for 1972, 1975, and 1983 are negligible or not available (HSDB, 1989).

EXPOSURE

Acrylamide can be absorbed through unbroken skin (Merck, 1989), mucous membranes and lungs, and the gastrointestinal tract (Klaassen et al., 1986). NIOSH estimates that approximately 20,000 workers were potentially exposed to acrylamide in 1976 (IARC V.39, 1986). Human exposure to acrylamide is primarily occupational from dermal contact with the solid monomer and inhalation of dust and vapor (Kirk-Othmer V.1, 1978; Howard, 1990). Occupational exposure to the aqueous form is primarily confined to maintenance and repair operations and connection and disconnection for transport. Routine exposure is minimal for captive operations. Polymerized acrylamide is not toxic, but the monomer can cause peripheral neuropathy (Klaassen et al., 1986). Residual monomer in the polymers is a concern (Howard, 1990). Improvements in the polymerization process have reduced the monomer content of the nonpotable water-grade polymers from 5% to 0.3% (Brown et al., 1982).

Workers in the paper and pulp, construction, foundry, oil drilling, textiles, cosmetics, food processing, plastics, mining, and agricultural industries are potentially exposed to acrylamide. Although exposure levels have not been reported for grouters, the potential exposure for these personnel may be greater than for other workers because of the uncontrolled nature of the exposure (WHO, 1985). The National Occupational Health Survey (1972-1974) estimated that 10,368 workers were exposed to acrylamide (Howard, 1990). The National Occupational

Exposure Survey (1981-1983) estimated that 9,776 workers potentially were exposed (NIOSH, 1984). This estimate was based on observations of actual use of the chemical (43%) and as an ingredient of tradename products (57%).

Primary exposure occurs during the handling of the monomer. Two acrylamide manufacturing plants showed breathing zone concentrations of 0.1-3.6 mg/m^3 (IARC V.39, 1986). During normal operations, workers at another plant were exposed to not more than 0.3 mg/m^3. The ACGIH (1986) recommended that acrylamide be considered a suspected human carcinogen, worker absorption of acrylamide be limited to no more than 0.5 mg/kg per day, and the threshold limit value (TLV) be 0.03 mg/m^3 with no short-term exposure limit.

Although human exposure to acrylamide will primarily be occupational, the general public may be exposed through contaminated drinking water from polyacrylamide flocculants used in water treatment (Brown et al., 1980a; Howard, 1990). Residual acrylamide concentrations in 32 polyacrylamide flocculants approved for water treatment plants ranged from 0.5 to 600 ppm (Howard, 1990). Acrylamide may not be removed in many water treatment processes (Croll et al., 1974,). Acrylamide remains in water after flocculation with polyacrylamides because it is very water soluble and is not readily adsorbed by sediment (Brown et al., 1980b). Acrylamide and polyacrylamides are used in the manufacture of a number of consumer products, including textiles, contact lenses, appliances, building materials, cosmetic and soap preparations, food, and gelatin capsules (Kirk-Othmer V.6, 1979).

Acrylamide may be released into the environment from waste during acrylamide production and the manufacture of polyacrylamides and other polymers (Howard, 1990). Release to water also occurs from acrylamide-based sewer grouting and wastepaper recycling (Brown et al., 1980b, 1982; Howard, 1990). The most important environmental contamination results from the use of acrylamide in soil grouting (WHO, 1985). Acrylamide biodegrades in water in approximately 8-12 days (Howard, 1990). Acrylamide may not be completely degraded in sewage works and water treatment facilities if residence times are relatively short (Brown et al., 1982; Howard, 1990). Acrylamide degradation in a secondary sewage plant would be complete in approximately 10 days (Kirk-Othmer V.1, 1978). It has been detected in effluent from a sewage treatment plant. Adsorption to sediment and volatilization is not appreciable. Certain debris organisms that exist in anaerobic, light aerobic, or dark aerobic conditions in natural and polluted environments are able to degrade acrylamide (Brown et al., 1980b). Bacteriologic degradation will likely depend on temperature fluctuations in temperate climates. Although acrylamide is highly mobile in aqueous environments, readily leaches into soil, and is carried great distances in ground water of deep rock aquifers where biodegradability is reportedly absent (WHO, 1985), bioconcentration of acrylamide is

unlikely because it degrades easily in surface waters and is highly water soluble (Kirk-Othmer V.1, 1978). In an EPA study of five industrial sites (beyond plant site perimeters) of acrylamide and polyacrylamide producers and one polyacrylamide user, acrylamide (1.5 ppm) was found in only one sample downstream from a polyacrylamide producer; no acrylamide was detected in soil or air samples (WHO, 1985; Howard, 1990). An average acrylamide concentration in air was <0.2 $\mu g/m^3$ near six acrylamide or polyacrylamide plants (WHO, 1985). The vapor pressure of acrylamide is low, and the monomer is not expected to be distributed in the atmosphere (WHO, 1985).

Environmental contamination may result from disposal on land or from leaching of the residual monomer from polyacrylamides. The Toxic Chemical Release Inventory (EPA) lists 53 industrial facilities that produced, supplied, or otherwise used acrylamide monomer in 1988 (TRI, 1990). Thirty-six of these facilities reported releases of acrylamide to the environment which were estimated to total 909,000 lb. Based on experimental data, acrylamide would readily leach into the ground and biodegrade within a few weeks or would biodegrade within 8-12 days in water (Howard, 1990).

REGULATIONS

EPA regulates acrylamide under the Clean Air Act (CAA), Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Resource Conservation and Recovery Act (RCRA), Safe Drinking Water Act (SDWA), and Superfund Amendments and Reauthorization Act (SARA). Acrylamide is a toxic pollutant of air and water. EPA has established rules for regulating hazardous spills, general threshold amounts, and requirements for handling and disposal of wastes. A reportable quantity (RQ) of 5,000 lb has been established for acrylamide under CERCLA. Acrylamide is regulated as a hazardous constituent of waste under RCRA. EPA proposed a maximum contaminant level goal (MCLG) of 0 mg/l and a water treatment technique for acrylamide under SDWA. FDA regulates acrylamide as an indirect food additive as a component of single- and repeated-use food contact surfaces. The OSHA final rule permissible exposure limit (PEL) is 0.03 mg/m^3 for an 8-hr time-weighted average (TWA); the potential for skin absorption was noted. OSHA also regulates acrylamide under the Hazard Communication Standard and as a chemical hazard in laboratories.

ACRYLONITRILE
CAS No. 107-13-1

CARCINOGENICITY

There is sufficient evidence for the carcinogenicity of acrylonitrile in experimental animals (IARC V.19, 1979; IARC S.4, 1982; IARC S.7, 1987). When administered orally (by gavage or in drinking water), acrylonitrile induced increased incidences of forestomach squamous cell papillomas, central nervous system microgliomas, mammary gland carcinomas, and Zymbal gland carcinomas in rats of both sexes. Inhalation of acrylonitrile induced Zymbal gland carcinomas, forestomach papillomas and acanthomas, and central nervous system neoplasms in rats of both sexes.

An IARC Working Group reported that there is limited evidence for the carcinogenicity of acrylonitrile in humans (IARC V.19, 1979; IARC S.4, 1982; IARC S.7, 1987). An epidemiological study of textile-plant workers potentially exposed to acrylonitrile and observed for 20 years or more showed an increased incidence of cancers of the lung; further follow-up of this cohort revealed a continued excess of lung cancer, although during the actual 5-year follow-up period there was no excess. The follow-up also showed a significant excess of cancer of the prostate. In a similar study at another textile-fiber plant, an excess of prostatic cancer was observed, but there was no excess of lung cancer. Another occupational study of persons potentially exposed to acrylonitrile and followed for 10 years or more indicated an increased incidence of cancers of the stomach, colon, brain, and respiratory tract (IARC V.19, 1979). Among rubber workers exposed to acrylonitrile, excesses were noted for cancers of the lung and of the lymphatic and hematopoietic systems. Another study of rubber workers however, showed no association between exposure to acrylonitrile and lung cancer. One study of workers exposed to acrylonitrile in 12 different plants showed excesses of bronchial cancer and of tumors of the lymphatic system.

PROPERTIES

Acrylonitrile is a colorless, volatile liquid that is soluble in water and most common organic solvents such as acetone, benzene, carbon tetrachloride, ethyl acetate, and toluene. It melts at 84° C and boils at 77° C. Technical-grade acrylonitrile is more than 99% pure. The technical-grade product always contains a polymerization inhibitor. Acrylonitrile is a reactive chemical that polymerizes spontaneously and can explode when exposed to flame.

USE

Acrylonitrile is an important industrial chemical. It is used extensively in the manufacture of synthetic fibers, resins, plastics, elastomers, and rubber for a variety of consumer goods such as textiles, dinnerware, food containers, toys, luggage, automotive parts, small appliances, and telephones (SRIc, 1984). Acrylonitrile also is used in fumigants (DPIM, 1989). In 1986, about 40% of the acrylonitrile produced was used to produce acrylic and modacrylic fibers, 28% to produce acrylonitrile-butadiene-styrene (ABS) and styrene-acrylonitrile (SAN) resins, and 15% to produce adiponitrile, an intermediate used in nylon production. The remainder was used in the production of acrylamide (10%), nitrile elastomers, barrier resins, and miscellaneous specialty chemicals (4%) (Chem. Profile, 1986a).

PRODUCTION

Acrylonitrile ranks among the top 50 chemicals produced domestically. In 1988, more than 2.6 million lb of

Tab 5. Institutional reactions to acrylamide in food (i.e., findings of Tareke *et al.* (2002) Swedish study on acrylamide in food)

In April 2002 Swedish researchers announced findings that acrylamide is present in many human foods. These findings were later published as Tareke *et al.* (2002), which is provided here in Tab 5.

Since that discovery, worldwide efforts have been undertaken to understand the extent of dietary exposure and it public health ramifications as well as ways to minimize acrylamide formation during cooking and food processing. Reports of these processes are provided here in Tab 5 and include:

- World Health Organization (WHO)/United Nations Food and Agriculture Organization (FAO) Health Implications of Acrylamide in Food June 25-27, 2002.

- FAO/WHO Acrylamide in Food Network and Infonet website information

- U.S. Food and Drug Administration (U.S. FDA) Draft Action Plan for Acrylamide in Food – February 24, 2003 Update.

- U.S. FDA letter received July 14, 2003 from Dr. Lester Crawford, Deputy Commissioner, U.S. FDA to Dr. Joan Denton, Director, OEHHA regarding OEHHA's proposed workplan

- OEHHA's response letter dated August 5, 2003 from Dr. Joan Denton, OEHHA to Dr. Lester Crawford, U.S. FDA.

Citations or links to contents of Tab 5.

- Tareke E, Rydberg P, Karlsson P, Eriksson S, Tornqvist M (2002). Analysis of acrylamide, a carcinogen formed in heated foodstuffs. *J Agric Food Chem*. 50(17):4998-5006.

- WHO/FAO (2002). Health Implications of Acrylamide in Food, located at http://www.who.int/fsf/Acrylamide/Acrylamide_report.pdf.

- FAO/WHO Acrylamide in Food Network and Infonet website information. Located at http://www.acrylamide-food.org/index.htm.

- U.S. FDA (2003) Draft Action Plan for Acrylamide in Food. Located at http://www.cfsan.fda.gov/~dms/acrypla2.html.

- U.S. FDA – OEHHA correspondence. (Scanned copies of U.S. FDA letter and OEHHA response are attached)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Joan E. Denton, M.S., Ph.D.
Director
Office of Environmental Health Hazard Assessment
Proposition 65 Implementation
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Sacramento, California 95812-4010

Dear Dr. Denton:

Under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65), California currently has a no significant risk level (NSRL) for acrylamide of .2 micrograms per day. We understand that California intends to announce a revised approach to acrylamide in the near future. FDA believes that it is premature to set a level for acrylamide in food, and that California's current NSRL and future actions may frustrate federal purposes or even directly conflict with federal law. More information is needed on the risks to humans from acrylamide in foods and on whether and how acrylamide levels in food can be safely reduced. FDA has created an extensive Action Plan (which is attached*) outlining the steps FDA believes necessary to answer these questions. The Action Plan includes the following major goals, most of which relate to expanding the research base on acrylamide:

- Develop rapid or inexpensive screening methods and validate confirmatory methods of analysis.
- Identify mechanisms responsible for the formation of acrylamide in foods and identify means to reduce acrylamide exposure.
- Assess the dietary exposure of U.S. consumers to acrylamide by measuring acrylamide levels in various foods and estimating dietary exposure.
- Characterize the potential risks and uncertainties associated with exposure to acrylamide in foods by assessing the available information, by expanding research into acrylamide toxicology to reduce uncertainty, and by performing a quantitative risk assessment with the new information.
- Develop and foster public/private partnerships to gather scientific and technological information and data for assessing the human risk.
- Inform and educate consumers and processors about the potential risks associated with acrylamide throughout the assessment process and as knowledge is gained.
- Provide all the essential elements for risk analysis, i.e., risk assessment, risk communication, and risk management.

* See Tab 5

The FDA Food Advisory Committee, consisting of outside experts on food safety, has endorsed FDA's approach to acrylamide. Furthermore, the Food and Agriculture Organization (FAO) and World Health Organization (WHO) held a consultation on acrylamide on June 25-27, 2002, and did not suggest setting levels for acrylamide in food. The consultation concluded that the "information on the levels of acrylamide in food is far from complete." The consultation outlined needed research on acrylamide in foods, including methods of analysis for acrylamide, formation and fate of acrylamide in food, exposure assessment, non-cancer toxicology, genotoxicity, and carcinogenicity. The consultation also provided some advice to minimize whatever risk exists from acrylamide in foods, including avoiding excessive cooking of food (but cooking food thoroughly to destroy foodborne pathogens), choosing healthy eating, investigating possibilities for reducing levels of acrylamide in food, and establishing an international network on acrylamide in food to encourage sharing of data and ongoing investigations.

In addition, the Joint Expert Committee on Food Additives (JECFA), an international expert committee that evaluates food additives and contaminants for Codex Alimentarius, is scheduled to conduct a risk assessment on acrylamide in February 2005. Results of the JECFA risk assessment will be an invaluable part of a well-considered approach to any regulation of acrylamide in food.

Based on preliminary estimates provided by Grocery Manufacturers of America, many foods (including French fries, potato chips, cereals, breads, and coffee) might have to be labeled based on the present NSRL for acrylamide of 0.2 micrograms/day. FDA is concerned that premature labeling of many foods with warnings about dangerous levels of acrylamide would confuse and could potentially mislead consumers, both because the labeling would be so broad as to be meaningless and because the risk of consumption of acrylamide in food is not yet clear.

Furthermore, consumers may be misled into thinking that acrylamide is only a hazard in store-bought food. In fact, consumer exposure may be greatest through home cooking. Some of FDA's research will try to answer questions on the relationship between the degree of browning and acrylamide formation in home cooking. In addition, a requirement for warning labels on food might deter consumers from eating foods with such labels. Consumers who avoid eating some of these foods, such as breads and cereals, may encounter greater risks because they would have less fiber and other beneficial nutrients in their diets. For these reasons, premature labeling requirements would conflict with FDA's ongoing efforts to provide consumers with effective scientifically based risk communication to prevent disease and promote health.

In addition, any warning label requirements imposed under Proposition 65 might encourage manufacturers to take premature steps to remove acrylamide from food by introducing additives or changing cooking processes. Such steps could have unforeseen adverse consequences on public health if the consequences of these changes on the introduction of other health hazards are

not scientifically and thoughtfully considered. Currently, not enough is known about acrylamide formation to identify safe, effective, and practical modifications to food processing techniques that will clearly prevent or reduce formation. Studies on formation and methods to reduce acrylamide are currently underway in many labs around the world including at FDA's National Center for Food Safety and Technology.

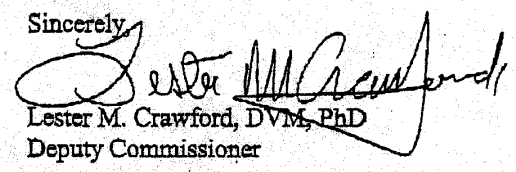
Also, California's current approach to acrylamide might discourage manufacturers from sharing data with FDA or with the Joint Institute for Food Safety and Applied Nutrition (JIFSAN), which is running the Acrylamide InfoNet for FAO/WHO. Such data would be helpful to FDA in its exposure and risk assessments for acrylamide.

FDA believes that California should not require warning labels for foods under Proposition 65 before completion of scientific studies adequate to assess the potential risk to consumers, as outlined in FDA's Action Plan, and until FDA determines appropriate risk management based on FDA's risk assessment. This approach will avoid confusing consumers and will assure that advice to consumers is scientifically founded. Although a precise time for the research and analysis cannot be predicted, it is expected to take 2–3 years.

Finally, FDA believes that California's current requirements for acrylamide under Proposition 65 and some actions that California may propose may be preempted by federal law to the extent that they frustrate federal purposes or create conflicts with federal law. For example, as discussed above, warning labels based on the presence of acrylamide in food might be misleading.

To ameliorate some of the concerns discussed above, California may wish to consider a regulatory approach for acrylamide which does not require warning labels on food. For example, Article 7, Section 12701, of the California Code of Regulations, "No Significant Risk Levels," defines the risk level which represents no significant risk as one that results in one excess cancer case per 100,000 population, with an exception applicable when "sound considerations of public health support an alternative level." The provision includes an example applicable "where chemicals in food are produced by cooking necessary to render the food palatable or to avoid microbiological contamination." California could designate acrylamide as a chemical "produced by cooking necessary to render the food palatable or to avoid microbiological contamination."

Sincerely,



Lester M. Crawford, DVM, PhD
Deputy Commissioner

Enclosure

cc: Mark B. McClellan, MD, PhD
Joseph A. Levitt, Esq.

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Winston H. Hickox
Agency Secretary

Gray Davis
Governor

August 5, 2003

Lester M. Crawford, DVM, Ph.D.
Deputy Commissioner
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Dear Dr. Crawford:

Thank you for your letter of July 14, 2003, regarding the treatment of acrylamide as a food contaminant under California's Safe Drinking Water and Toxic Enforcement Act of 1986, also known as Proposition 65. As the lead agency for implementing Proposition 65, the Office of Environmental Health Hazard Assessment (OEHHA) was requested by interested parties to interpret the applicability of Proposition 65 compliance concerning acrylamide in foods. In response, OEHHA has developed a draft work plan (enclosure) to provide clear guidance to facilitate Proposition 65 compliance concerning acrylamide. Recognizing the unique challenge posed by acrylamide's pervasiveness and the degree of exposure to it in the diet, OEHHA will seek input from the Proposition 65 "State's Qualified Experts," an appointed panel of scientists known as the Cancer Identification Committee (CIC), on the work plan. We also welcome your input at the CIC meeting on October 17, 2003, and as OEHHA proceeds with our regulatory initiatives on acrylamide. I firmly believe that collaboration between our departments will enhance public health protection and minimize potential confusion on this issue.

As you know, Proposition 65 is a "right-to-know" law designed to inform members of the public when they are exposed to carcinogens or reproductive toxicants. If a business knowingly exposes an individual to a carcinogen, it is exempt from the warning requirement if it can show the exposure poses no significant risk of cancer. You note that California's current no significant risk level (NSRL) for acrylamide of 0.2 micrograms per day is problematic. This level was adopted in 1990; considerable data on the carcinogenicity of acrylamide has been generated since then. Our NSRL is consistent with the current information on the carcinogenicity of acrylamide used by the U.S. Environmental Protection Agency in its quantitative risk assessments for acrylamide (see http://www.epa.gov/iris/subst/0286.htm), and is derived from that federal Agency's cancer unit risk value. However, more recent information suggests that the unit risk might warrant re-examination. As a first step in our work plan for acrylamide, we will seek advice from the CIC, about whether we should revise our dose response analysis and update the NSRL. We will also invite public comment on this and other issues at the October CIC meeting.

I agree with your statement that more information is needed on the risks to humans from acrylamide in food, and I am pleased about the fast-paced research effort being undertaken in this regard by the Food and Drug Administration (FDA), industry, other federal and international institutions, and academia. We understand that certain critical research projects on health effects will take years to complete. In the meantime, acrylamide is already listed under Proposition 65 (as it has been since January 1, 1990) as a carcinogen and, thus, is subject to applicable Proposition 65 requirements, including litigation. As you know, lawsuits have been filed in California and others are likely to follow if no additional regulatory clarity is forthcoming in the near term. In the interim, we should consider updating levels used to estimate risk. I believe such analyses will indicate that risks from acrylamide in certain foods are not a public health concern, and it would serve the public to make information available on those foods that fall below the Proposition 65 NSRL of one excess cancer per one hundred thousand people exposed (Title 22, California Code of Regulations, Section 12703). Making such information available would also facilitate Proposition 65 implementation and provide "safe harbor" for businesses subject to Proposition 65. This should prevent or greatly reduce the number of non-meritorious Proposition 65 lawsuits.

You note that the Joint Expert Committee on Food Additives is scheduled to conduct a risk assessment on acrylamide in February 2005. Should scientific information indicate a further update in the Proposition 65 NSRL is needed, a second revision could be undertaken at that time. A process to rapidly update the current NSRL will also result in better information for discussing foods potentially subject to the warning provisions of Proposition 65. Your letter cites a finding by the Grocery Manufacturers Association that given the current NSRL many foods might have to be "labeled" (i.e., subject to a Proposition 65 warning). While a clear and reasonable warning is specified in Proposition 65, labeling is just one means of providing a warning. As we have in the past, we look forward to working with the FDA in developing possible warning messages.

The second activity we are considering is providing additional guidance regarding the limit of detection. Those foods with levels falling below this level are deemed not to pose an exposure for purposes of Proposition 65. It is expected that this guideline will provide "safe harbor" for a number of foods. The hierarchy for determining the appropriate method is given in regulation (Title 22, California Code of Regulations, Section 12901). Your letter notes that the Food and Agriculture Organization and World Health Organization consultation found that the information on levels of acrylamide in foods is far from complete. We agree, but observe that several foods have low concentrations, perhaps too low to quantify, and are expected to pose minimal risk. Warnings on such foods would be misleading, an issue raised in your letter. It serves the public and provides "safe harbor" to businesses to provide information on foods not considered to pose an exposure under Proposition 65 as specified in this provision.

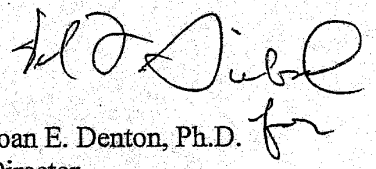
Average lifetime consumption of certain foods may result in exposures above the updated NSRL but, for reasons of public health, consumption of such foods should not be discouraged,

another issue raised in your letter. In such circumstances, as also noted in your letter, we should consider an alternative risk level, following Title 22, California Code of Regulations, Section 12703. Therefore, the third activity under consideration by OEHHA involves establishing alternative risk levels to the standard one per hundred-thousand risk level where sound considerations of public health support an alternative risk level. We believe this will bring greater clarity to the regulatory status of various foods that contain acrylamide and thus may provide further "relief" to segments of the regulated community.

Finally, the possibility remains that some foods may cause acrylamide exposures at levels high enough to require Proposition 65 warnings. OEHHA will develop a regulation regarding appropriate warning messages. The goal of any such warning message would be to provide consumers with meaningful health information concerning the presence of acrylamide in food. The guidance would be intended to forestall the dissemination of confusing, unduly alarming, or indiscriminate warnings.

As discussed over the telephone and in email messages between our staffs, my department would like to work closely with yours to facilitate actions that would best serve the public on this important health issue. We appreciate the effort Dr. Terry Troxell made, on our behalf, in presenting the FDA action plan at our May 2003 workshop to receive input on Proposition 65 regulatory options. Both our agencies have the mission of protecting public health, and I am confident that we will continue to work together to fulfill our respective mandates. I would like to coordinate with you to ensure that this is the case, and look forward to discussing this with you in the near future.

Sincerely,



Joan E. Denton, Ph.D. for
Director

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Tab 6. Animal cancer studies of acrylamide

- Long-term drinking water studies in rats

    1. Johnson *et al*. (1986). Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. *Toxicol Appl Pharmacol* **85**(2): 154-168.

    2. Friedman *et al*. (1995). A lifetime oncogenicity study in rats with acrylamide. *Fundam Appl Toxicol* **27**(1): 95-105, and

        - Damjanov and Friedman (1998) *In Vivo* 12:495-502 (a reanalysis of the pathology of acrylamide-induced testicular mesothelioma in male F344 rats).

Provided in Tab 6. These studies reported increased incidences of benign and/or malignant tumors at multiple sites in male and female rats exposed to acrylamide in drinking water for two years.

- Limited-term cancer studies in mice

    1. Bull *et al*. (1984a). Carcinogenic effects of acrylamide in Sencar and A/J mice. *Cancer Res* **44**(1):107-111.

    2. Bull *et al*. (1984b). Carcinogenic activity of acrylamide in the skin and lung of Swiss-ICR mice. *Cancer Lett* **24**(2):209-212.

    3. Robinson *et al*. (1986). A combined carcinogen bioassay utilizing both the lung adenoma and skin papilloma protocols. *Environ Health Perspect* **68**:141-145.

Provided in Tab 6. These studies reported increased incidences of lung tumors in female Swiss mice following six doses given by oral gavage, strong dose-related induction of lung tumors in both male and female A/J mice by oral gavage or i.p. administration, and increased incidences of skin tumors in mice treated by oral gavage, i.p. or dermal administration (followed by TPA promotion).

Tab 7. Recent human cancer studies of acrylamide

Since the last major review by an authoritative body (IARC, 1994), several notable epidemiological studies have been published, and are included here in Tab 7. They are:

Retrospective occupational cohort study

1. Marsh GM, Lucas LJ, Youk AO, Schall LC (1999). Mortality patterns among workers exposed to acrylamide: 1994 follow up. *Occup Environ Med* **56**(3):181-190.

    Comments on Marsh study

    - Granath *et al*. (2001): Cancer risk from exposure to occupational acryalmide. *Occup Environ Med* **58**(9): 608-9.
    - Schulz *et al*. (2001). Dose-response relation between acrylamide and pancreatic cancer. *Occup Environ Med* **58**(9): 609.

Two case-control dietary studies

1. Mucci LA, Dickman PW, Steineck G, Adami HO, Augustsson K (2003). Dietary acrylamide and cancer of the large bowel, kidney, and bladder: Absence of an association in a population-based study in Sweden. *Br J Cancer* **88**(1):84-89.
2. Pelucchi C, Franceschi S, Levi F, Trichopoulos D, Bosetti C, Negri E, La Vecchia C (2003). Fried potatoes and human cancer. *Int J Cancer* **105**(4):558-560.

Marsh et al. (1999) is an update to the largest existing retrospective cohort study of acrylamide-exposed workers (Collins et al., 1989), and reports on the mortality experience of 8508 workers with potential exposure to acrylamide at three plants in the United States. Comments on the study were also published by Granath et al. (2001) and Schulz et al. (2001).

A significant association of occupational acrylamide exposure and cancer of the pancreas was observed; however, the authors indicate that this finding may be confounded by smoking. As noted by Marsh et al. (1999), the study had limited power to detect cancer associations for nearly all sites, except possibly the lung.

Mucci et al. (2003) is a case-control study that compared consumption of acrylamide-containing foods and cancers at certain sites. Food consumption was assessed through a dietary questionnaire. Currently measured levels of acrylamide in various foods were applied to the food consumption data to estimate acrylamide intake. No associations with acrylamide intake and cancer were observed. Dybing and Sanner (2003, provided in Tab 10) concluded that the Mucci et al. (2003) study was too small to detect an association, assuming the risk estimates based on the animal tumor data represent true human risk to acrylamide.

Pellucchi et al. (2003) is a hospital-based case-control study comparing consumption of fried or baked potatoes and cancer. Potato consumption was ascertained with a food-frequency questionnaire. No association of cancer and fried or baked potato consumption was observed.

Tab 8. Recent studies of the genotoxicity of acrylamide

Since the 1994 IARC review, the following papers on acrylamide genotoxicity have been published:

1. Dearfield *et al*. (1995). Acrylamide: a review of its genotoxicity and an assessment of heritable genetic risk. *Mutat Res* **330**(1-2):71-99. **(major review)**

2. Segerback *et al*. (1995). Formation of N-7-(2-carbamoyl-2-hydroxyethyl)guanine in DNA of the mouse and the rat following intraperitoneal administration of acrylamide. *Carcinogenesis* **16** (5):1161-1165.

3. Sickles *et al.* (1995) Acrylamide arrests mitosis and prevents chromosome migration in the absence of changes in spindle microtubules. *J Toxicol Environ Health* 44:73-86.

4. Martenson *et al.* (1995). The effect of acrylamide and other sulfhydryl alkylators on the ability of dynein and kinesin to translocate microtubules *in vitro*. *Toxicol Appl Pharmacol* 133:73-81.

5. Generoso *et al*. (1996). Dominant lethal mutations, heritable translocations, and unscheduled DNA synthesis induced in male mouse germ cells by glycidamide, a metabolite of acrylamide. *Mutat Res* **371**(3-4):175-183.

6. Park *et al*. (2002). Acrylamide-induced cellular transformation. *Toxicol Sci* **65**(2):177-183.

7. Paulsson *et al*. (2002). Hemoglobin adducts and micronucleus frequencies in mouse and rat after acrylamide or N-methylolacrylamide treatment. *Mutat Res* **516**(1-2):101-111.

8. Paulsson *et al*. (2003). Induction of micronuclei in mouse and rat by glycidamide, genotoxic metabolite of acrylamide. *Mutat Res* **535**(1):15-24.

9. Abramsson-Zetterberg L (2003). The dose-response relationship at very low doses of acrylamide is linear in the flow cytometer-based mouse micronucleus assay. *Mutat Res* **535**(2):215-222.

10. Granath F, Tornqvist M (2003). Who knows whether acrylamide in food is hazardous to humans? *J Natl Cancer Inst* **95**(12): 842-843. (Commentary on Besaratinia and Pfeifer, 2003)

11. Besaratinia A, Pfeifer GP (2003). Weak yet distinct mutagenicity of acrylamide in mammalian cells. *J Natl Cancer Inst* **95**(12): 889-896.

These recent studies reported that acrylamide induces both mutations and clastogenic effects in mammalian cells. Some study authors hypothesized that acrylamide may cause DNA damage through direct DNA adduction, whereas others hypothesized that acrylamide binding to proteins involved in mitosis may be a mechanism of DNA damage. DNA adducts of glycidamide, the reactive epoxide of acrylamide, were measured in every tissue examined following exposure of rats and mice to acrylamide. Several studies (Segerback et al., 1995; Generoso et al., 1996; Paulsson et al., 2002; 2003) concluded that glycidamide is likely responsible for the observed genotoxicity; one study (Park et al., 2002) suggested that acrylamide itself may play a role in cellular transformation. With respect to dose-response, two sets of studies (Paulsson et al., 2002; 2003, and Abramsson-Zetterberg, 2003) reported a linear formation of micronuclei in blood lymphocytes over a wide range of in vivo dosing.

Tab 9. Recent studies on acrylamide pharmacokinetics and bioavailability

A. Metabolism and pharmacokinetics

Since the 1994 IARC review, several studies on the metabolism and pharmacokinetics of acrylamide have been published, as well as a review of the topic by Calleman (1996) and a pharmacokinetic model for acrylamide in the rat (Kirman et al., 2003). Recent studies on metabolism include Sumner et al. (1997; 1999) and Barber et al. (2001). Many additional biomarker studies have also been published, but are not listed or provided here.

1. Calleman CJ (1996). The metabolism and pharmacokinetics of acrylamide: implications for mechanisms of toxicity and human risk estimation. *Drug Metab Rev* **28**(4):527-590.

2. Sumner SC, Selvaraj L, Nauhaus SK, Fennell TR (1997). Urinary metabolites from F344 rats and B6C3F1 mice coadministered acrylamide and acrylonitrile for 1 or 5 days. *Chem Res Toxicol* **10**(10):1152-1160.

3. Sumner SC, Fennell TR, Moore TA, Chanas B, Gonzalez F, Ghanayem BI (1999). Role of cytochrome P450 2E1 in the metabolism of acrylamide and acrylonitrile in mice. *Chem Res Toxicol* **12**(11):1110-1116.

4. Barber DS, Hunt JR, Ehrich MF, Lehning EJ, LoPachin RM (2001). Metabolism, toxicokinetics and hemoglobin adduct formation in rats following subacute and subchronic acrylamide dosing. *Neurotoxicology* **22**(3):341-353.

5. Kirman C, Gargas M, Deskin R, Tonner-Navarro L, Andersen M (2003). A physiologically based pharmacokinetic model for acrylamide and its metabolite, glycidamide, in the rat. *J Toxicol Environ Health A* **66**(3):253-274.

Acrylamide is almost completely absorbed following either oral administration or i.p. injection, and is distributed widely throughout the body (Calleman, 1996). Sumner et al. (1999) reported that metabolism to the reactive metabolite glycidamide in mice is highly dependent on cytochrome P450 2E1.

B. Bioavailability of acrylamide from food

Two studies have directly examined the issue of bioavailability of acrylamide from food. They include an animal study by Tareke et al. (2000) and a human volunteer study by Sorgel et al. (2002).

6. Tareke E, Rydberg P, Karlsson P, Eriksson S, Tornqvist M (2000). Acrylamide: a cooking carcinogen? *Chem Res Toxicol* **13**(6):517-522.

7. Sorgel F, Weissenbacher R, Kinzig-Schippers M, Hofmann A, Illauer M, Skott A *et al*. (2002). Acrylamide: increased concentrations in homemade food and first evidence of its variable absorption from food, variable metabolism and placental and breast milk transfer in humans. *Chemotherapy* **48**(6):267-274.

Tareke et al. (2000) reported the formation of acrylamide in rat chow, upon frying. Tareke et al. (2000) reported a large increase in acrylamide-derived hemoglobin adducts in rats fed fried rat chow. Sorgel et al. (2002) reported that consumption by human volunteers of home-cooked potato chips resulted in increased levels of acrylamide in urine and breast milk.

Tareke et al. (2000) noted that human biomonitoring studies measure background levels of acrylamide-hemoglobin adducts in non-occupationally exposed individuals. Tareke et al. (2000) concluded that acrylamide in food is most likely the major source of background adducts observed among non-smoking, non-occupationally exposed individuals.

Tab 10. Acrylamide levels measured in foods and preliminary two- and four-day average intake estimates

1. **Acrylamide levels measured in U.S. foods by the U.S. FDA**

   The U.S. FDA published an initial compilation of acrylamide measurements in samples of certain foods on December 4, 2002. On March 12, 2003 the U.S. FDA released a second set of measurements of acrylamide based on testing of a second set of food products.

   These datasets are located at
   - http://www.cfsan.fda.gov/~dms/acrydata.html
   - http://www.cfsan.fda.gov/~dms/acrydat2.html.

2. The summary tables come from: Peterson, B. (2002). Exposure and biomarkers. JIFSAN/NCFST Acrylamide in Food Workshop. Located at http://www.jifsan/umd.edu/Acrylamide/acryalmide workshop.html, October 29-30, 2002, Rosemont, Illinois.
   - **Summary of acrylamide levels measured in foods of six different countries (as of October 2002) (**Numerous foods have been analyzed for acrylamide content in Norway, The Netherlands, Sweden, Switzerland, the U.K., and the U.S.) (Table 1, page 12)
   - **Two-day consumption estimates** (Table 2, page 13)

3. Dybing E, Sanner T (2003) Risk assessment of acrylamide in foods. *Toxicol Sci* 75: 7-15.
   - Estimates of average daily intake based on four-day food consumption from the 1997 Norway national food survey and acrylamide residue data from the Norwegian Food Agency.