OFFICE OF ENVIRONMENTAL HEALTH HAZARD ASSESSMENT

Public Health Goal

DRAFT

N-Nitrosodimethylamine in Drinking Water

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Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Proposed Public Health Goal for N-Nitrosodimethylamine in Drinking Water

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PREFACE

Public health goal (PHG) technical support documents provide information on health effects from contaminants in California drinking water. PHGs are developed for chemical contaminants based on the best available data in the scientific literature and using the most current principles, practices, and methods used by public health professionals. These documents and the analyses contained therein provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

Pursuant to the California Safe Drinking Water Act of 1996 (Health and Safety Code section 116365), the Office of Environmental Health Hazard Assessment (OEHHA) develops PHGs for drinking water contaminants in California based exclusively on public health considerations. PHGs published by OEHHA are used by the State Water Resources Control Board (SWRCB) in establishing primary drinking water standards (California Maximum Contaminant Levels, or CA MCLs). Whereas PHGs are based solely on scientific and public health considerations, MCLs adopted by SWRCB consider economic factors and technological feasibility. State law requires that MCLs be set at a level that is as close as feasible to the corresponding PHG, placing emphasis on the protection of public health. PHGs established by OEHHA are not regulatory and represent goals that SWRCB and California's public water systems strive to achieve if it is feasible to do so. Under federal law, CA MCLs established by SWRCB must be at least as stringent as the corresponding federal MCL if one exists.

OEHHA periodically reviews PHGs and revises them as necessary based on the occurrence of the respective contaminant in California drinking water supplies and the availability of new scientific data. This document presents an update for n-nitrosodimethylamine (NDMA), for which a PHG was established in 2006 (OEHHA, 2006).

CONTENTS

List of Commonly Used Abbreviations

ADD – acceptable daily dose

ASF – age sensitivity factor

BMD – benchmark dose

BMDL – 95% lower confidence limit of the benchmark dose

BMR – benchmark response

BMDS – Benchmark Dose Software

CAS # – Chemical Abstract Service number

CI – confidence interval

CSF – cancer slope factor

CYP – cytochrome p450 enzyme

DWI – daily water intake

GD – gestation day

hrs/day – hours per day

HR – hazard ratio

IARC - International Agency for Research on Cancer

ip – intraperitoneal

iv – intravenous

Kp – permeability coefficient

log K_{ow} – logarithm of the octanol-water partition coefficient

L/kg-day – liters per kg body weight per day

LOAEL – lowest-observed-adverse-effect level

MCL – maximum contaminant level

µg/L – micrograms per liter

µg/m^3 – micrograms per cubic meter

µg/g – micrograms per gram

mg/kg – milligrams per kilogram

mg/kg-day – milligrams per kilogram body weight per day

mM – millimolar

mmol/kg – millimoles per kilogram

nmol/mg – nanomoles per milligram

NCI – National Cancer Institute

NDMA – N-nitrosodimethylamine

ng/g – nanograms per gram

NOAEL – no-observed-adverse-effect level

NTP – National Toxicology Program

OEHHA – Office of Environmental Health Hazard Assessment

OR – odds ratio

PHG – public health goal

PND – postnatal day

POD – point of departure

ppb – parts per billion

ppm – parts per million

SWRCB – State Water Resources Control Board

UF – uncertainty factor

UF_A – interspecies uncertainty factor

UF_H – intraspecies uncertainty factor

US EPA – United States Environmental Protection Agency

SUMMARY

This document presents an update of the public health goal (PHG) for N-nitrosodimethylamine (NDMA). OEHHA published a PHG of 0.003 parts per billion (ppb), equivalent to 0.003 micrograms per liter (µg/L), for NDMA in 2006 (OEHHA, 2006). OEHHA's PHG was based on bile duct tumors induced by oral administration of NDMA to female rats (Peto et al., 1991a; Peto et al., 1991b).

In this PHG update, the Peto et al. (1991a, b) studies are retained as critical studies. The proposed updated PHG of 0.0005 ppb is based on bile duct, liver cell, and mesenchymal tumors in male rats induced by oral administration of NDMA. An updated dose-response assessment, updated drinking water intake rates, and age sensitivity factors to account for increased susceptibility of infants and children to carcinogens are incorporated into the derivation of this updated PHG.

INTRODUCTION

The Office of Environmental Health Hazard Assessment (OEHHA) performs health risk assessments and develops public health goals (PHGs) for drinking water contaminants in California. A PHG is the concentration of a contaminant in drinking water that is estimated to pose no significant health risk to individuals consuming the water on a daily basis over a lifetime. This document presents a PHG update for n-nitrosodimethylamine (NDMA). This update was initiated in March 2020, and incorporates a thorough review of the current scientific literature and the most current risk assessment practices and methods, as well as relevant chemical-specific toxicity data.

NDMA (Chemical Abstracts Service Registry Number 62-75-9), also known as dimethylnitrosamine, is a chemical formed in industrial or natural processes. NDMA is also a byproduct of water disinfection; the chlorination or chloramination process in the presence of nitrogen-containing organic matter during water treatment forms NDMA. Additionally, NDMA is created from reactions between dimethylamine and nitrates/nitrites in the human gastrointestinal tract.

NDMA is not currently produced or commercially used in the United States (ATSDR, 2023). The Drinking Water Program of the California Department of Public Health established a notification level of 0.01 ppb for NDMA in 2002,[1] which is a health-based advisory level for chemicals in drinking water that lack a regulatory standard or maximum contaminant level (MCL). NDMA has been detected in some California public drinking water supply wells within the last five years, at levels above the notification level.[2] This update of the risk assessment for NDMA considers the toxicology literature

[1] https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/NotificationLevels.html, accessed March 20, 2024

[2] Data accessed with GeoTracker GAMA, March 13, 2024: http://geotracker.waterboards.ca.gov/gama/

since the publication of the PHG in 2006 and incorporates updated risk assessment methodologies.

SYSTEMATIC LITERATURE SEARCH

OEHHA conducted a systematic literature search of multiple open literature databases (PubMed, Embase, Scopus, and SciFinder) in August 2021, using a search string intended to identify all studies that mention NDMA in the title or abstract. Because the original PHG was published in 2006, the current literature search was conducted from 2005 onward. An additional literature search was conducted in March 2024 to capture any studies that were published after the initial systematic literature search. The search terms used for each database are presented in Appendix I.

From the initial search, OEHHA identified 3,016 individual studies that met the search criteria. OEHHA uploaded the identified references into DistillerSR® systematic review software and conducted inclusion/exclusion screening for relevant toxicological studies against a PECO (populations, exposures, comparators, and outcomes) statement designed to capture relevant toxicological data (Appendix I). Two independent reviewers conducted both Tier 1 (title/abstract) and Tier 2 (full-text) reference evaluations against the PECO statement. Tier 1 screening resulted in 60 individual references identified, and Tier 2 reduced the number of included (cited) references to 24. References were categorized as animal toxicity studies, human epidemiology studies, toxicokinetics studies, or mechanistic studies. During study evaluation, as studies were identified that were not captured in the original literature search, or as new studies became available after the date of the original literature search, they were added to OEHHA's reference library and evaluated.

METHODOLOGY

Development of an updated PHG for a chemical in drinking water entails a two-part process:

1. Toxicological evaluation

The toxicological evaluation of a chemical starts with a thorough review of the PHG being updated and its toxicological basis, as well as a review of the relevant scientific literature published subsequent to its issuance. Relevant studies and toxicity endpoints are identified. The data and study findings are critically evaluated, and the quality of each study is assessed. In evaluating toxicity studies, consideration is given to the potential molecular and cellular mechanisms by which toxicity is induced (modes of action), toxicokinetics, corroborating data from different studies, and the relevance of toxicity endpoints to humans.

2. PHG derivation

After a review of the toxicity studies of sufficient quality, the most sensitive endpoints from studies determined to be relevant to human health are selected, and analyses of the dose-response relationships are performed. The adverse effect or a physiological change that leads to an adverse effect that occurs at the lowest dose is selected as the critical effect from which the PHG is derived.

If a chemical has been identified as a human or animal carcinogen, health-protective water concentrations are determined for both cancer and noncancer endpoints, and the lower of the two values is selected as the PHG. However, due to a lack of adequate noncancer studies and data for NDMA, a noncancer health-protective concentration could not be determined in this update.

Deriving Health-Protective Concentrations for Cancer Effects

Calculation of a health-protective concentration for cancer effects involves a three-step approach: determination of a cancer potency, estimation of an average daily dose, and calculation of a health-protective drinking water concentration (C).

Cancer Dose-Response Analyses and Cancer Potency Derivation

Standard methods for estimation of lifetime theoretical cancer risks are employed in the development of cancer potencies based on animal studies (OEHHA, 2009; US EPA, 2005; US EPA, 2012). The estimated cancer potency, also referred as the cancer slope factor (CSF), is a measure of the carcinogenic potential of a compound. It is often reported in units of 1/(mg/kg-day) or $(mg/kg\text{-}day)^{-1}$ and is derived by fitting the tumor incidence data from an animal carcinogenicity bioassay with the Multistage-Cancer model[3] from US EPA's Benchmark Dose Software (BMDS; US EPA, 2012), followed by linear low-dose extrapolation.

Development of cancer potency estimates from animal bioassays includes consideration of:

- the quality, suitability, and sensitivity of the available animal bioassay studies; for example, the thoroughness of the experimental protocol, the temporal exposure pattern, the degree to which dosing resembles the expected manner of human exposure, the duration of the study, the purity of test material, the number and size of exposed groups, and the extent of tumor occurrence
- the cancer sites and types from the selected experiments most appropriate for characterizing the cancer potency; where there are multiple independent sites with significant tumor findings in a selected experiment, a multisite analysis is performed to describe the overall carcinogenic potential

[3] https://www.epa.gov/bmds

- whether a dose-response model that assumes the absence of a carcinogenic threshold dose should be used or whether there are compelling mechanistic data to support an alternative approach
- interspecies scaling of animal cancer potency to human cancer potency
- physiologic, toxicokinetic and metabolic information for possible use in extrapolating from test animals to humans, from high to low dose, and from one exposure route to another.

Calculating Average Daily Dose

A mathematical model is fit to dose-response data from animal studies. For studies that do not involve daily administration of a fixed mg/kg amount, an average daily dose "d" (in units of mg/kg-day) is calculated. This is done by adjusting the administered or nominal dose, accounting for days of dosing during the week and total dosing weeks during the experimental period. For studies using variable doses, the weighted mean dose is calculated, considering the dosing frequency and duration of the various administered doses.

Dose-Response Model

Information on the mode of action involved in the carcinogenesis of a chemical is evaluated to determine whether human cancer risk should be estimated using the default assumption of low dose linearity or otherwise. Unless there is sufficiently compelling evidence, OEHHA uses a non-threshold approach and a linearized multistage (LMS) cancer model to calculate the chemical's CSF, or potency. This is accomplished by using the BMDS Multistage-Cancer model developed by US EPA. The model calculates the lifetime probability of developing a tumor (p) induced by an average daily dose (d) using the following equation:

$$p(d) = \beta + (1- \beta) \times \exp[-(q_1 d + q_2 d^2 + ... + q_i d^i)]$$

The q_i are parameters of the model, which are taken to be constants and are estimated from the animal cancer bioassay data. As recommended by US EPA (2012), $q_i \geq 0$ for all i. For example, with four dose groups, the Multistage-Cancer model can have a maximum of four parameters, β, q_1, q_2, and q_3. When dose is expressed in units of mg/kg-day, q_1 is given in units of $(\text{mg/kg-day})^{-1}$. The q_1 parameter is, for small doses, the ratio of excess lifetime cancer risk to the average daily dose received. The parameter β provides the basis for estimating the background lifetime probability of the tumor (i.e., when dose d is zero, the probability of cancer, p, is equal to β).

The Multistage-Cancer model defines the probability of developing a tumor at a single site. For carcinogens that induce tumors at multiple sites and/or in different cell types at the same site in a particular species and sex, US EPA's BMDS can be used to derive maximum likelihood estimates (MLEs) for the parameters of the multisite carcinogenicity model by summing the MLEs for the individual multistage models from the different sites

and/or cell types. This multisite model provides a basis for estimating the cancer potency of a chemical that causes tumors at multiple sites.

Adjusting for Human-Animal Differences

In the absence of reliable pharmacokinetic information, the human cancer slope factor (CSF_{human}) is estimated by assuming the chemical dose per body weight scaled to the three-quarters power produces the same degree of effect in different species. Under this assumption, the CSF_{animal} is multiplied by the ratio of human to animal body weights raised to the one-fourth power when animal cancer potency is expressed in units of $(mg/kg\text{-}day)^{-1}$:

$$CSF_{human} = CSF_{animal} \times (\text{body weight}_{human} \div \text{body weight}_{animal})^{1/4}.$$

Daily Water Intake

Daily water intake (DWI) includes intake from ingestion, inhalation, and dermal contact with contaminants in tap water from household uses (e.g., drinking, cooking, bathing, and showering). Inhalation exposure can take place when a chemical volatilizes out of the water during cooking or showering. Dermal absorption of the chemical can occur during bathing and other household uses of tap water. However, for NDMA, inhalation and dermal exposures were considered negligible due to its very low Henry's law constant and dermal permeability constant (ATSDR, 2023).

For oral intake rates, the PHG program uses age-specific water ingestion estimates (OEHHA, 2012) derived from a nationwide survey of food and beverage intake from approximately 20,000 people (US Department of Agriculture's Continuing Survey of Food Intake of Individuals 1994-1996, 1998 dataset). These age-specific intake rates are normalized to body weight and expressed as L/kg-day. The updated water ingestion rates indicate that drinking water ingestion per unit body weight is higher in infants than in adults. Previous PHGs using ingestion rates of 2 L/day for adults and 1 L/day for a 10 kg child are being updated with these more refined estimates. For noncancer endpoints, the time-weighted average daily water ingestion rate for a 70-year lifetime for the general population is generally used. However, if there is a particularly sensitive age group or other subgroup, the high-end estimates of the age-specific water ingestion rate for the subgroup will be used in the PHG calculations (OEHHA, 2012). OEHHA is mandated to consider sensitive subgroups, such as children and infants, who may be at greater risk of adverse health effects due to their greater exposure to drinking water contaminants on a body weight basis than the general population.

Accounting for Increased Susceptibility During Early-in-Life Exposures

When determining cancer risk, OEHHA applies age sensitivity factors (ASFs, unitless) to account for the increased susceptibility of infants and children to carcinogens (OEHHA, 2009). A weighting factor of 10 is applied for exposures that occur from the 3rd trimester to <2 years of age, and a factor of 3 is applied for exposures that occur from 2 through 16 years of age (Table 1). These factors are applied regardless of the mechanism of action, unless chemical-specific data exist to better guide the risk assessment.

Table 1. Duration and age sensitivity factors for different life stages

Life Stage	Fractional Duration[a] (d)	Age Sensitivity Factor (ASF)[b]
3rd Trimester	0.25/70	10
Infant (0-2 yrs)	2/70	10
Child (2-16 yrs)	14/70	3
Adult (16-70 yrs)	54/70	1

[a] An average lifetime of 70 years is assumed for the general population
[b] Age sensitivity factors for different life stages adopted by OEHHA (2009)

ASFs for each life stage are multiplied by the fractional duration (d) of each life stage and the DWI. This generates the ASF-adjusted exposure at each life stage, as shown in Appendix II. The sum of the ASF-adjusted exposures across all life stages is the lifetime exposure value for the chemical.

The health-protective water concentration (C) for carcinogenic effects can be calculated using the following equation, which combines the separate calculations for each exposure period (shown in Appendix II) into a single bracket:

$$C = \frac{R}{CSF_{oral} \times (\sum_j [ASF_j \times d_j \times DWI^{oral}_j])}$$

Where:

R	=	default risk level of one in one million, or 10^{-6}
CSF_{oral}	=	oral cancer slope factor, in $(mg/kg\text{-}day)^{-1}$
$\sum_j$	=	sum of contributions at each age range
ASF_j	=	age sensitivity factors for the 3rd trimester + infants, children, and adults
d_j	=	duration of exposure for the 3rd trimester + infant, child, and adult life stages
DWI^{oral}_j	=	equivalent water exposure values for each age range.

BASIS FOR THE 2006 PHG

In 2006, OEHHA developed a PHG of 0.003 ppb (µg/L) for NDMA in drinking water, based on cancer endpoints from drinking water studies in rats (Peto et al., 1991a,

1991b). Male and female Colworth (Wistar-derived) rats (60/dose/sex for treatment groups, 240/sex for controls) were administered NDMA in drinking water in 16 exposure groups (ranging from 0 to 16.9 parts per million, or ppm) for a period of up to 3.5 years. The treatment doses were estimated by the study authors to range from 0.001 to 0.697 mg/kg-day for males and 0.002 to 1.224 mg/kg-day for females. A linearized multistage model was constructed using the occurrence of bile duct tumors in female rats. The model was based on the assumption of a 10% increased incidence of tumors over the background incidence level, a lifetime extra cancer risk of 10^{-6}, and the extrapolation from rats to humans using the ratio of rat and human body weights to the ¾ power. The PHG was based solely on the oral route of exposure because inhalation and dermal exposures were considered negligible due to the very low Henry's law constant and dermal permeability constant for NDMA. The exposure assessment assumed a 70 kg adult body weight and oral water consumption rate of 2 L/day. Age sensitivity factors (ASFs) were not applied in the assessment. OEHHA did not calculate a health-protective concentration for noncancer endpoints due to the lack of adequate noncancer studies.

UPDATED TOXICOLOGICAL REVIEW

Studies in experimental animals showed that NDMA is an animal carcinogen. NDMA is considered a likely human carcinogen by the World Health Organization (WHO, 2008) and it is considered as "reasonably anticipated to be a human carcinogen" by the National Toxicology Program based on sufficient evidence of carcinogenicity from studies in experimental animals (NTP, 2016).

OEHHA conducted a systematic literature search of multiple open literature databases (PubMed, Embase, Scopus, and SciFinder) in August 2021. Since the original PHG was published in 2006, all studies that were published after 2005 were reviewed. A total of 3,016 studies were identified during the search; among them, 60 studies met the PECO (population, exposure, comparator, outcome) criteria (presented in Appendix I) and were evaluated. OEHHA conducted additional literature searches and reviews periodically after the initial systematic literature search and new information was incorporated into the update. The details of the literature search and review are presented in Appendix I. Selected studies are discussed below.

Exposure assessment

As indicated in OEHHA (2006), important sources of exposure to NDMA include the consumption of food and beverages (ATSDR, 2023). The ingestion of drinking water that contains NDMA appears to contribute only a small fraction of the overall NDMA exposure (Environment Canada, 2001). Rough estimates of the exposure to various sources of NDMA in Canada indicate that water contributes less than 10 percent of the overall exposure (IPSC, 2002).

NDMA has been detected in a variety of different foods, but given its low octanol/water partition coefficient, NDMA would not be expected to bioaccumulate to any great extent

(IPSC, 2002). Nitrates and nitrites appear to be converted to NDMA or other nitrosamines in the gastrointestinal tract (Mirvish, 1975; Pignatelli et al., 1993; Bartsch and Montesano, 1984).

As this assessment is based on lifetime excess cancer risk of one in one million associated with drinking water source, no attempt is made here to formally document the contribution of drinking water relative to other sources (e.g.. food, beer, formation from nitrates and nitrites in the GI tract).

Pharmacokinetics

NDMA is primarily absorbed in the small intestine after oral administration. It is metabolized by cytochrome P450 2E1 (CYP2E1) in the liver to hydroxymethyl nitrosamine. Methylamine is the major urinary metabolite in rats after oral exposure. NDMA can be produced endogenously through both acid-based nitrosation of amine precursors in the stomach or biologically-based nitrosation in other tissues. Since the publication of the 2006 PHG, a physiologically based pharmacokinetic (PBPK) model was developed for NDMA in male and female rats (Kang et al., 2024). The model accommodates intravenous (i.v.) and oral doses and comprises multiple compartments, including blood, gastrointestinal (GI) tract, liver, kidney, brain, lung, and heart. The authors conducted toxicokinetics studies of NDMA in Sprague-Dawley rats and derived model parameters from the resulting data. Sensitivity analyses were used to validate the model and the model predictions were compared with the observed values from the animal experiments, but the model was not validated using external data. Therefore, this model was not considered for use in this assessment. For more information on the toxicokinetics of NDMA, please refer to the original PHG (OEHHA, 2006).

Noncancer studies

Human studies

The current literature search did not find relevant human studies for noncancer endpoints.

Animal studies

Shortly after OEHHA's publication of the 2006 NDMA PHG (OEHHA, 2006), US EPA published its *Provisional Peer Reviewed Toxicity Values for N-Nitrosodimethylamine* (US EPA, 2007). Both OEHHA (2006) and US EPA (2007) reviewed the same noncancer animal studies, such as Anderson et al. (1978), Desjardins et al. (1992), Peto et al. (1991b), and others. Both agencies recognized the limitations of the noncancer animal studies, including incomplete results, inaccurate dosing information, and the lack of dose-related responses.

Noncancer studies published after 2006 are also limited in both quantity and quality. Among the five noncancer studies evaluated, the majority of the studies focused on the

protective effects of other chemicals on NDMA-induced toxicity. Oftentimes, a single dose of NDMA was used, the dose was generally high, and there were very small numbers of animals in each treatment group. A summary of these studies is given below. However, these studies are not suitable for developing a noncancer health-protective concentration due to the aforementioned limitations.

Sharma and Singh studied the protective effects of *Operculina turpethum* root extract and its isolated glycoside on the hematological effects of NDMA in male mice. An NDMA-only group of 6 Swiss albino mice was treated with 10 mg/kg-day NDMA by oral gavage, three days a week for a total of three weeks. NDMA was shown to cause reduced body weight, decreased red blood cell (RBC) and platelet counts, increased white blood cell (WBC) count, and reduced hemoglobin content (Sharma and Singh, 2014).

Sheweita et al. (2014) treated 10 male Sprague-Dawley rats per dose group with 0 or 0.2 mg/kg-day of NDMA in drinking water for 2 weeks. NDMA was seen to increase levels of free radicals and decrease the activity of antioxidant enzymes in the liver. In a separate study, Sheweita et al. (2017) studied the effects of nitrosamines on the liver and testes of male rabbits. Male New Zealand rabbits were given NDMA daily in drinking water at 0 or 0.5 mg/kg-day (five rabbits per group) for up to 2 weeks. NDMA increased the level of free radicals, and at the same time reduced glutathione levels and antioxidant enzyme activities in both liver and testes. Testosterone levels were reduced, while estradiol levels were increased in the plasma of NDMA-treated rabbits. The authors indicated that the decrease in testosterone and increase in estradiol levels might play a role in the infertility of male rabbits. Histopathological examinations also revealed morphological damage such as degenerative changes in the liver and testes of NDMA-treated rabbits.

Two studies from the same group demonstrated protective effects of α-lipoic acid on NDMA-induced toxicity in mice (El Shenawy et al., 2017; Hamza et al., 2016). In both cases, only male mice (strain not specified) were studied and NDMA was given orally at 0, 2, or 4 mg/kg-day for four weeks (8 mice per group). El Shenawy et al. (2017) observed elevated lipid peroxidation, reduced antioxidant enzyme activities, and histological alterations in the spleen of NDMA-treated mice. Similar effects were observed by Hamza et al. (2016) in the kidney of NDMA-treated mice. However, deficiencies in the reporting of the histopathological findings precluded their use in dose-response assessment.

Due to the lack of quality studies of noncancer endpoints, with limitations such as inaccurate dosing information, lack of dose-related responses, and findings that cannot be verified or supported by other studies, the existing data are inadequate to quantitatively evaluate the noncancer health effects for NDMA.

Cancer studies

Human studies

There are several cancer epidemiology studies regarding dietary intake of NDMA. These studies reported positive associations between self-reported NDMA intake and the occurrence of gastrointestinal cancers. Limitations of the studies include uncertainties associated with the estimate of exposure, such as meat consumption and NDMA intake estimates by using self-administered questionnaires (dietary recall), and other confounding factors such as other nitrosamines or carcinogens in the diet. Examples of studies with better overall quality, such as larger sample size, better design for confounding factors, etc., are presented below.

A prospective cohort study of 61,433 Swedish women with 18 years of follow-up found that high consumption of processed meat rich in NDMA was associated with an increased risk of stomach cancer; stomach cancer risk was two-fold higher in the top-quintile of NDMA intake compared to the bottom quintile (hazard ratio (HR) = 1.96; 95% confidence interval (CI) = 1.08-3.58; P-trend = 0.02). Based on their review of the literature, the authors believed that dietary nitrosamines could be responsible for the positive association, since processed meat is the major dietary source of nitrosamines in Sweden, and NDMA is the most commonly found nitrosamine in food (Larsson et al., 2006).

A cohort study in Norfolk, United Kingdom, examined the relationship between N-nitroso compounds and cancer risk. The study recruited 23,363 men and women ages 40-79 years with an average follow-up time of 11.4 years. Dietary NDMA intake was positively associated with gastrointestinal cancers (HR = 1.13; 95% CI = 1.00-1.28; P-trend = 0.04) per one standard deviation increase in NDMA. The positive association is more significant with rectal cancer (HR = 1.46; 95% CI = 1.16-1.84; P-trend = 0.001) than the combined gastrointestinal cancers. The study also showed that endogenous N-nitroso compounds and dietary nitrite were not associated with an increased risk of cancer overall or any specific cancers. The dietary NDMA and nitrite were estimated by comparing food items on the food frequency questionnaire (FFQ) with an existing food database of potential carcinogens. The endogenous N-nitroso compounds were estimated by using dietary iron value and the fecal excretion of N-nitroso compounds, measured as apparent total N-nitroso compounds (ATNC). The authors suggested that dietary NDMA is associated with increased risk of gastrointestinal cancers, especially rectal cancer (Loh et al., 2011).

A case-control study in Newfoundland and Labrador, Ontario, Canada, examined the association between dietary N-nitroso compounds and the risk of colorectal cancers. The study included a total of 1,760 cases and 2,481 population controls. The dietary intake of NDMA was determined by using self-administered food frequency questionnaires. Dietary intake of NDMA is associated with increased incidence of colorectal cancers. The OR (odds ratio) of highest vs. lowest quintiles for overall colorectal cancer is 1.42 (95% CI = 1.03-1.96; P-trend = 0.005). The risk estimate was greater for rectal carcinoma (OR = 1.61; 95% CI = 1.11-2.35; P-trend = 0.01) than for cancer of the proximal or distal colon. The authors indicated that NDMA intake is positively associated with colorectal cancer risk in humans in this study (Zhu et al., 2014).

A prospective cohort study in the Netherlands (Keszei et al., 2013) examined the association between dietary intake of N-nitroso compounds, such as NDMA based on food-frequency questionnaire, and risks of esophageal and gastric cancers. A total of 120,852 men and women ages 55-69 years were recruited and subsequently followed for 16.3 years. A positive association was observed between NDMA intake and the risk of esophageal squamous cell carcinoma (ESCC) and gastric noncardia adenocarcinoma (GNCA) in men. The HR for 0.1 µg/day increase in intake is 1.15 (95% CI = 1.05-1.25; P-trend = 0.01) for ESCC and 1.06 (95% CI = 1.01-1.10; P-trend = 0.09) for GNCA, respectively. The authors stated that no convincing positive associations were observed in women and concluded that NDMA intake may increase the risk of ESCC and may be positively associated with GNCA in men (Keszei et al., 2013).

In addition to the dietary intake of NDMA, studies were also conducted on exposure via NDMA-contaminated medicines (Joung et al., 2022; Mansouri et al., 2022; Wang et al., 2022; Gomm et al., 2021; Pottegard et al., 2018). The use of NDMA-contaminated medicines was not shown to be associated with increased cancer risk. For example, a Danish nationwide cohort study did not find any link between NDMA-contaminated valsartan, a drug used to control high blood pressure, and the risk of cancer, though the authors indicated that the study is limited by the short term of assessment without long-term follow-up, the limited use of valsartan in Denmark, and the uncertainty associated with the assumption about NDMA content in valsartan (Pottegard et al., 2018). A cohort study in Germany also failed to identify any association between NDMA-contaminated valsartan and the overall risk of cancer. However, when individual cancer types were studied, a statistically significant association (HR = 1.16; 95% CI = 1.03-1.31; P = 0.017) between any exposure to NDMA-contaminated valsartan and liver cancer was found, though no dose-dependent effect was observed (Gomm et al., 2021).

In general, the human studies are supportive of increased cancer risk following oral exposure to NDMA. However, uncertainties associated with the estimate of exposure and many confounding factors that were not considered and addressed in the studies made it difficult for these studies to be considered for the quantitative assessment of cancer risk.

Animal studies

The original PHG, which was published in 2006, discussed cancer studies in experimental animals such as Peto et al. (1991a, b). Very few animal cancer studies were discovered in the current literature search. The only relevant study identified is discussed below.

Latropoulos et al. (2008) studied the protective effects of the dietary matrix metalloproteinase inhibitor, BAY 12-9566N (BAY), on neoplastic growth induced by NDMA and two other carcinogens in Wistar CrL:(WI)BR rats. Two groups of male rats (24 rats per group) were given NDMA by gavage at 15 mg/kg once per week for 10 weeks. After 10 weeks, one group was given BAY at 240 mg/kg-day in the diet for another 42 weeks, while the other group received regular diet during the same period of

time. NDMA treatment induced pulmonary adenomas and carcinomas in male rats. BAY was shown to reduce NDMA-induced pulmonary adenomas from 38% to 21% ($p<0.01$) and carcinomas from 21% to 4% ($p<0.01$) (Latropoulos et al., 2008). A group of 24 male rats that received no NDMA or BAY (Room controls) did not develop any pulmonary adenoma or carcinoma. The Latropoulos et al. (2008) study is not considered a study of sufficient quality for quantifying cancer risk since a relatively small number of rats were exposed to only one dose of NDMA for ten weeks, and almost half of the animals had unscheduled deaths.

In summary, no high-quality animal cancer studies since 2006 were identified. It is worth noting that Peto et al. (1991a, b), the study used by OEHHA to develop the 2006 PHG for NDMA (OEHHA, 2006), remains the best animal cancer study due to the wide range of concentrations that were used, the large number of animals and dose groups, and the better overall quality of the study.

Genotoxicity

As discussed in the 2006 PHG document (OEHHA, 2006), the genotoxicity of NDMA has been extensively studied in both in vitro and in vivo animal systems, and the results demonstrate that NDMA is genotoxic in most assays.

Newer studies published since 2006 further support the genotoxicity of NDMA. For example, Lynch et al. (2024) evaluated NDMA-induced mutagenicity and liver toxicity in a 28-day transgenic mouse model. While NDMA was positive in the transgenic rodent (TGR) gene mutation assay as demonstrated by the dose-dependent increases in mutant frequency (MF) in the lacZ reporter transgene in DNA extracted from liver, lung, and kidney, no significant changes were observed in some other tissues such as bone marrow, stomach, spleen, or bladder. Liver appeared to be the most sensitive tissue in NDMA mutagenesis (Lynch et al., 2024). Most of these studies were reviewed by ATSDR (2023). Tables 2 and 3 below are adapted from ATSDR (2023) genotoxicity summaries to show some of the newer studies since 2006.

Table 2. Genotoxicity of NDMA In Vivo [a,b]

Species and tissue/cell type	Endpoint	Results[c]
Mouse (transgenic Big Blue®) liver	Mutations	+
Drosophila melanogaster	Mutations	+
Fish liver	Mutations	+
Rat and mouse liver	Micronuclei	+
Rat bone marrow	Micronuclei	–
Rat peripheral blood	Micronuclei	–
Rat stomach and colon	Micronuclei	–
Rat liver	DNA adducts	+
Human placenta	DNA adducts	–
Rat liver	DNA damage	+

Species and tissue/cell type	Endpoint	Results[c]
Rat stomach	DNA damage	–

a. + = positive results; – = negative results
b. Adapted from ATSDR (2023)
c. Results from each row may represent multiple studies reviewed by ATSDR (2023)

Table 3. Genotoxicity of NDMA In Vitro [a,b]

Species (test system)	Endpoint	Results[c]	
		Metabolic activation	
		With	Without
Salmonella typhimurium	Gene mutation	+	NT or -
Human peripheral blood lymphocytes	Micronuclei	-	NT
Human lymphoblasts (TK6) and peripheral blood lymphocytes	Micronuclei	NT	-
Mouse embryo fibroblast (NIH3T3) cells	Micronuclei	NT	-
Human hepatoma (HepG2, HepaRG) cells	DNA damage	NT	+
Human lung or kidney cells	DNA damage	NT	+
Rat lung or kidney cells	DNA damage	NT	+
Human lymphoblasts (TK6)	DNA damage	-	+
Chinese hamster ovary cells	DNA damage	+	-
Mouse embryo fibroblast (NIH3T3) cells	DNA damage	NT	-

a. + = positive results; - = negative results; NT = not tested
b. Adapted from ATSDR (2023)
c. Results from each row may represent multiple studies reviewed by ATSDR (2023)

DOSE-RESPONSE ASSESSMENT

Human cancer studies are generally supportive of the positive association between dietary NDMA exposure and cancer risk, though the uncertainties associated with the estimates of exposure and many confounding factors precluded the use of these studies to assess the quantitative risk of cancer. Animal cancer studies are therefore used for the dose-response assessment of NDMA. Among the animal studies, Peto et al. (1991a, b) remains the best available based on the quality of the study, thus it is retained as the critical study for estimating the cancer risk of NDMA.

Male and female Wistar-derived Colworth rats (60/sex/dose for treatment groups, 240/sex for control) were administered NDMA in drinking water in 16 dose groups (doses are shown in Tables 4 and 5) from six weeks of age for a period of up to 3.5 years (Peto et al., 1991a, b). Liver tumors were observed in both males and females. Among the liver tumors from four cell types examined (hepatocyte, bile duct, mesenchyme, and Kupffer cell), Kupffer cell tumors in the males were less sensitive,

while mesenchymal and Kupffer cell tumors were less sensitive in the females, compared to other cell types in the liver. Therefore, bile duct, hepatocyte, and mesenchymal tumors in male rats (Table 4) and bile duct and hepatocyte tumors in female rats (Table 5) were used as the basis for updating the PHG for NDMA.

Table 4. Bile duct, hepatocyte, and mesenchymal tumor incidence in male rats (from Table 7 of Peto et al., 1991a)

Dose group	NDMA in drinking water (ppm)	NDMA in drinking water (mg/kg-day)	Animals with bile duct tumors[a,d]	Animals with hepatocyte tumors[b,d]	Animals with mesenchymal tumors[c,d]
1	0	0	3/240	10/240	0/240
2	0.033	0.001	2/60	4/60	0/60
3	0.066	0.003	3/60	3/60	0/60
4	0.132	0.005	2/60	2/60	1/60
5	0.264	0.011	2/60	4/60	1/60
6	0.528	0.022	1/60	4/60	0/60
7	1.056	0.044	1/60	5/60	1/60
8	1.584	0.065	4/60	8/60	0/60
9	2.112	0.087	7/60	7/60	7/60
10	2.640	0.109	13/60	13/60	5/60
11	3.168	0.131	12/60	14/60	12/60
12	4.224	0.174	12/60	19/60	10/60
13	5.280	0.218	16/60	27/60	3/60
14	6.336	0.261	18/60	32/60	7/60
15	8.448	0.348	8/60	44/60	4/60
16	16.896	0.697	0/60	46/60	10/60

[a] The numerator is the number of animals with bile duct tumors and the denominator is the total number of animals within each treatment group.
[b] The numerator is the number of animals with liver tumors and the denominator is the total number of animals within each treatment group.
[c] The numerator is the number of animals with mesenchymal tumors and the denominator is the total number of animals within each treatment group.
[d] Trend test result for the first 12 dose groups that were used for multisite analysis: $p < 0.0001$

Table 5. Bile duct and hepatocyte tumor incidence in female rats (from Table 7 of Peto et al., 1991a)

Dose group	NDMA in drinking water (ppm)	NDMA in drinking water (mg/kg-day)	Animals with bile duct tumors[a,c]	Animals with hepatocyte tumors[b,c]
1	0	0	4/240	11/240
2	0.033	0.002	1/60	2/60
3	0.066	0.005	4/60	2/60
4	0.132	0.010	1/60	4/60
5	0.264	0.019	4/60	2/60

Dose group	NDMA in drinking water (ppm)	NDMA in drinking water (mg/kg-day)	Animals with bile duct tumors[a,c]	Animals with hepatocyte tumors[b,c]
6	0.528	0.038	4/60	6/60
7	1.056	0.076	9/60	6/60
8	1.584	0.115	39/60	3/60
9	2.112	0.153	33/60	7/60
10	2.640	0.191	44/60	7/60
11	3.168	0.229	48/60	4/60
12	4.224	0.306	46/60	7/60
13	5.280	0.382	44/60	13/60
14	6.336	0.459	38/60	20/60
15	8.448	0.612	10/60	40/60
16	16.896	1.224	1/60	41/60

[a] The numerator is the number of animals with bile duct tumors and the denominator is the total number of animals within each treatment group.
[b] The numerator is the number of animals with liver cell tumors and the denominator is the total number of animals within each treatment group.
[c] Trend test result for the first 8 dose groups that were used for multisite analysis: $p < 0.0001$

Multisite tumor analysis was performed on the data in Tables 4 and 5 using the BMDS (version 3.3) Multistage Cancer model with a benchmark response (BMR) of 5% to estimate the cancer potency of NDMA. Detailed BMDS model outputs are presented in Appendix III.

Due to the lack of a monotonic dose-response relationship in the higher dose groups for the bile duct tumors in female rats, an acceptable fit of the multistage polynomial could only be achieved after removing the top eight dose groups. Therefore, in performing multisite analysis of the hepatocyte and bile duct tumors, both tumors were modeled using the remaining eight lowest dose groups. For the mesenchymal tumors in male rats, no model could be fit when more than 12 doses were used. Therefore, for the bile duct, hepatocyte, and mesenchymal tumors, only the lowest 12 dose groups in male rats were used for modeling. The 95% lower confidence limit of the benchmark dose (BMDL) for tumors in male and female rats at a BMR of 5% extra risk were determined to be 0.012 and 0.017 mg/kg-day, respectively. The corresponding animal cancer slope factors (CSF_{animal}) were determined to be 4.16 and 2.88 $(mg/kg\text{-}day)^{-1}$, respectively; they were calculated by dividing the BMR by the BMDL. The human cancer slope factor (CSF_{human}) was calculated based on the following equation using body weight scaling between animals and humans:

$$CSF_{human} = CSF_{animal} \times (BW_{human}/BW_{animal})^{1/4}$$

where the default human body weight was 70 kg and the average body weights for male and female rats were 0.44 and 0.24 kg, respectively (Peto et al., 1991b). The resulting CSF_{animal} and CSF_{human} are listed in Table 6.

Table 6. Calculation of cancer slope factors (CSFs) for NDMA

	Male Rats	Female Rats
Type of tumors included in calculation	hepatocyte, bile duct, mesenchyme	hepatocyte, bile duct
Number of doses modeled	12	8
BMDLs (mg/kg-day)	0.01203	0.01737
CSF_{animal} $(mg/kg\text{-}day)^{-1}$	4.16	2.88
CSF_{human} $(mg/kg\text{-}day)^{-1}$	**14.8**	11.9

Male rats were most sensitive to the carcinogenic effects of NDMA as seen in Table 6. The human cancer slope factor of 14.8 $(mg/kg\text{-}day)^{-1}$ based on liver tumors in male rats is therefore used to derive the PHG for NDMA.

HEALTH-PROTECTIVE DRINKING WATER CONCENTRATION

NDMA has very low volatility and skin permeability; both the Henry's law constant (2.63×10^{-7} atm-m^3/mol at 20°C and 1.99×10^{-6} atm-m^3/mol at 37°C) and the dermal permeability constant (Kp) (0.000265 cm/hour) are very low (ATSDR, 2022; OEHHA, 2006). Therefore, inhalation and dermal exposures are expected to be insignificant compared to the oral route and are not included in the current assessment.

When determining cancer risk, OEHHA applies age sensitivity factors (ASFs) to account for the increased susceptibility of infants and children to carcinogens (OEHHA, 2009). A factor of 10 is applied for exposure that occurs from the 3rd trimester to <2 years of age, while a factor of 3 is applied for the ages of 2 through 16 years. ASFs are incorporated into the total daily exposure by multiplying the ASF by the total daily water intake (DWI) and the fractional duration of the life stage. The sum of the ASF-adjusted DWIs is the lifetime daily exposure (in L/kg-day) used to derive the PHG (Table 7).

Table 7. ASF-adjusted oral exposures

Life Stage	Age Sensitivity Factor (ASF)[a]	Fractional Duration (d)[b]	Daily Water Intake (DWI, L/kg-day)[c]	ASF × d × DWI (L/kg-day)
3rd trimester Fetus	10	0.25/70	0.047	0.002
Infant (0-2 yrs)	10	2/70	0.196	0.056
Child (2-16 yrs)	3	14/70	0.061	0.037
Adult (16-70 yrs)	1	54/70	0.045	0.035
			Total Lifetime Daily Exposure	**0.130**

[a] Based on OEHHA (2009)
[b] An average lifetime of 70 years is assumed for the general population
[c] Based on OEHHA (2012)

The total lifetime daily exposure of 0.130 L/kg-day is used to derive the PHG for NDMA, along with the human cancer slope factor of 14.8 $(mg/kg\text{-}day)^{-1}$ and the de minimis lifetime excess individual cancer risk of one in one million (10^{-6}). The following equation is used to calculate the health-protective concentration (C) for NDMA in drinking water:

$$C = \frac{1\times10^{-6}}{14.8\ (^{mg}/_{kg-day})^{-1} \times 0.130\ ^{L}/_{kg-day}} = 0.52 \times 10^{-6}\ ^{mg}/_{L} \approx 0.0005\ ^{\mu g}/_{L}\ \text{(ppb)}$$

Thus, an updated PHG of 0.0005 ppb based on liver tumors is proposed by OEHHA. This PHG incorporates a number of methodological updates involving dose-response analysis, drinking water ingestion rates, and ASFs to protect infants and children exposed to carcinogens.

RISK CHARACTERIZATION

As discussed above, noncancer studies are limited in both quantity and quality. The lack of high quality noncancer studies makes it difficult for OEHHA to develop a noncancer health-protective concentration for NDMA. It is worth noting that other regulatory agencies such as US EPA (US EPA, 2007) also have not developed noncancer guidance values for NDMA due to the absence of quality studies.

The comparison between the 2006 PHG for NDMA and the updated PHG is summarized in Table 8. The updated PHG is lower than the original PHG due to a new dose-response analysis, incorporation of OEHHA's current drinking water ingestion rates, and the application of ASFs.

Table 8. OEHHA 2006 NDMA PHG vs. 2024 updated NDMA PHG

	2006 PHG	2024 PHG
Critical study	Peto et al. (1991a, b)	Peto et al. (1991a, b)
Endpoint	Bile duct tumors in female rats	Bile duct, hepatocyte, and mesenchymal tumors in male rats
Human cancer slope factor $(mg/kg\text{-}day)^{-1}$	12.8	14.8
Lifetime daily exposure (L/kg-day)	0.03[a]	0.13[b]
PHG (ppb)	0.003	0.0005

[a] based on a default body weight of 70 kg and daily water ingestion of 2 L/day
[b] based on a time-weighted average of daily water ingestion rates for a 70-year lifetime (OEHHA, 2012)

The World Health Organization (WHO) established a guideline value for NDMA in drinking water associated with an upper-bound excess lifetime cancer risk of 10^{-5} at 0.1 µg/L (or ppb) based on bile duct tumors in female rats from the Peto et al. (1991a, b) study (WHO, 2008). The proposed updated PHG of 0.0005 ppb by OEHHA is based on bile duct, hepatocyte, and mesenchymal tumors induced by oral administration of NDMA in male rats from Peto et al. (1991a, b). The updated PHG is based on an estimated lifetime excess cancer risk of one in one million.

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APPENDIX I. LITERATURE SEARCH TERMS AND PECO STATEMENT

PubMed – Search executed 8.31.2021

Search Terms	Results
(62-75-9[rn] OR "Dimethylnitrosamine"[mh] OR "n-nitrosodimethylamine"[tiab] OR "dimethylnitrosamine"[tiab] OR "N,N-Dimethylnitrous amide"[tiab] OR "Methanamine, N-methyl-N-nitroso-"[tiab] OR "NDMA"[tiab])	1,316

EMBASE – Search executed 8.31.2021

Search Terms	Results
(62-75-9:rn OR 'Dimethylnitrosamine'/de OR 'n-nitrosodimethylamine':ti,ab OR 'dimethylnitrosamine':ti,ab OR 'N,N-Dimethylnitrous amide':ti,ab OR 'Methanamine, N-methyl-N-nitroso-':ti,ab OR 'NDMA':ti,ab)	607

SCOPUS – Search executed 8.31.2021

Search Terms	Results
CASREGNUMBER(62 75 9) OR TITLE-ABS-KEY("Dimethylnitrosamine" OR "n nitrosodimethylamine" OR "dimethylnitrosamine" OR "N N Dimethylnitrous amide" OR "Methanamine N methyl N nitroso " OR "NDMA")	648

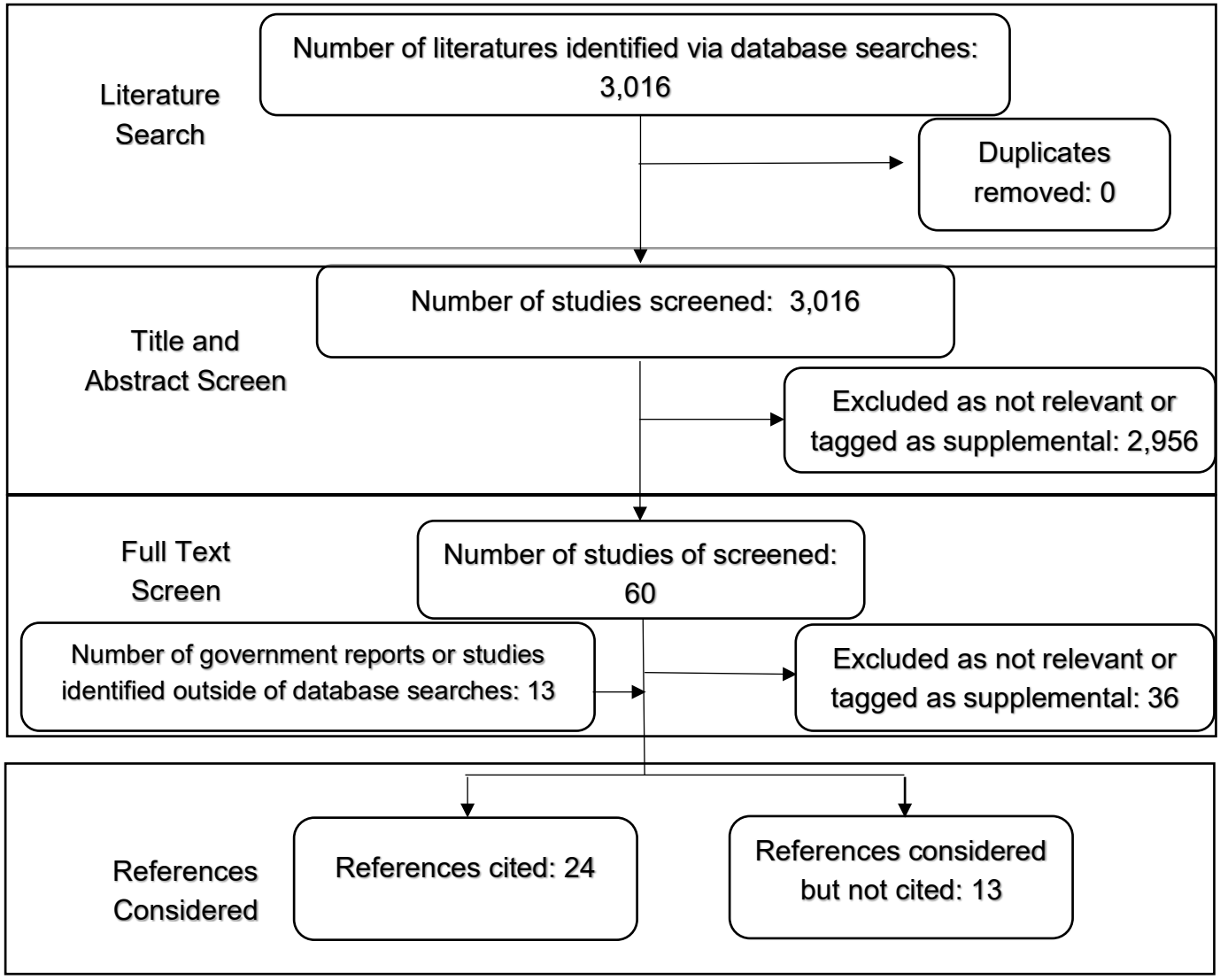
SciFinder – Search executed 8.31.2021

Search Terms	Results
62-75-9 PubMed references excluded Limit to biological studies	445

PECO statement used for Tier 1 and Tier 2 literature screening

PECO element	Evidence
Populations	**Human:** Studies of any population and lifestage (occupational or general population, including children and other sensitive populations). **Exclude:** biomonitoring studies and exposure studies (unless specifically relevant to California). **Animal:** Non-human mammalian animal species of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages). Zebrafish studies will be tagged as "potentially relevant supplemental information." **Mechanistic:** Studies of any human or animal (mammalian and non-mammalian) cell type, and mechanistic/genomic/in silico data with any biological significance.
Exposures	**Relevant forms:** N-nitrosodimethylamine (NDMA), also known as dimethylnitrosamine (CAS 62-75-9), and any synonyms. If uncertain about chemical identity, please look it up. **Human:** Any exposure to NDMA via any route for all the included studies described in the Populations section above. **Animal:** Any exposure to NDMA via the oral route. Studies involving intraperitoneal, inhalation, or dermal exposures, or exposure to mixtures will be tagged as "potentially relevant supplemental information." **Mechanistic:** Any cell type exposed to NDMA alone. Studies involving exposures to mixtures will be tagged as "potentially relevant supplemental information."
Comparators	**Human:** A comparison or reference population exposed to lower levels (or no exposure/exposure below detection limits) of NDMA, or exposure to NDMA for shorter periods of time. Case reports and case series will be tracked as "potentially relevant supplemental information." **Animal:** A concurrent control group exposed to vehicle-only treatment or untreated control. **Mechanistic:** A concurrent control group of cells exposed to vehicle-only treatment or untreated control.
Outcomes	All health outcomes (both cancer and noncancer) and toxicokinetics. **Exclude:** ecological studies, animal biomonitoring studies, and reviews.
PBPK models	Studies describing PBPK models for NDMA will be included. Studies describing toxicokinetic data and absorption, distribution, metabolism/biotransformation, and excretion (ADME) will also be included.

Flowchart of literature screen



APPENDIX II. ADJUSTMENT FOR EARLY-IN-LIFE EXPOSURES

OEHHA accounts for the increased susceptibility of children and infants to carcinogens by applying age sensitivity factors (ASFs) (OEHHA, 2009). Age-specific cancer risk is calculated for each age group by multiplying the cancer potency, age-specific exposure estimates (duration × intake rate), the concentration in drinking water and the ASF, where:

R	=	Total risk
C	=	Concentration in water
p_{oral}	=	Oral cancer potency
ASF_1	=	Age sensitivity factor for 3rd trimester + infancy, value 10
ASF_2	=	Age sensitivity factor for childhood (ages 2-16), value 3
ASF_3	=	Age sensitivity factor for adult (ages 16-70), value 1.

For this calculation, the duration (d) of sensitive periods is expressed as fractions of the standard lifetime of 70 years as follows:

d_0	=	3rd trimester, value 0.25/70
d_1	=	infancy, value 2/70
d_2	=	childhood, value 14/70
d_3	=	adult, value 54/70.

The equivalent water exposure values (Daily Drinking Water Intake or DWI, expressed in terms of L/kg-day) for each age range are expressed as follows:

DWI^o_1	=	Oral route, infancy
DWI^o_2	=	Oral route, childhood
DWI^o_3	=	Oral route, adult.

For the risk equation, the overall lifetime risk is the sum of the cancer risk for each age bin. Note that for the third trimester of pregnancy, the ASF_1 for early-in-life exposures is applicable, but the consumption rate is assumed to be that of the pregnant woman. Then,

$$\begin{aligned} R = {} & (p_{oral} \times ASF_1 \times d_0 \times DWI^o_3 \times C) + \\ & (p_{oral} \times ASF_1 \times d_1 \times DWI^o_1 \times C) + \\ & (p_{oral} \times ASF_2 \times d_2 \times DWI^o_2 \times C) + \\ & (p_{oral} \times ASF_3 \times d_3 \times DWI^o_3 \times C) \end{aligned}$$

Equation 1

Equation 1 can be rearranged as follows:

$$C = \frac{R}{p_{oral} \times \left(\begin{aligned} & ASF_1 \times d_0 \times DWI^o_3 + \\ & ASF_1 \times d_1 \times DWI^o_1 + \\ & ASF_2 \times d_2 \times DWI^o_2 + \\ & ASF_3 \times d_3 \times DWI^o_3 \end{aligned} \right)}$$

Equation 2

The PHG is determined by solving Equation 2 for $R = 10^{-6}$.

Reference

OEHHA (2009). Technical Support Document for Cancer Potency Factors: Methodologies for Derivation, Listing of Available Values, and Adjustments to Allow for Early Life Stage Exposures. Office of Environmental Health Hazard Assessment, California Environmental Protection Agency, Sacramento, CA. Accessed at: https://oehha.ca.gov/air/crnr/technical-support-document-cancer-potency-factors-2009.

APPENDIX III. BENCHMARK DOSE ANALYSIS RESULTS FOR CANCER ENDPOINTS

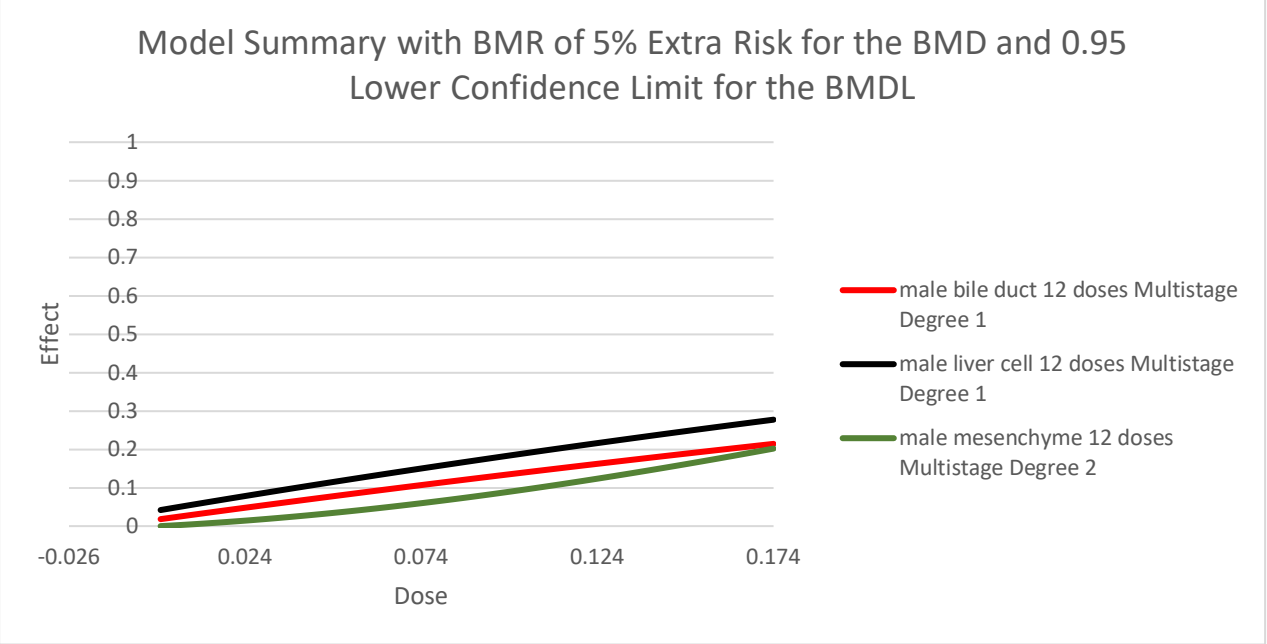
This appendix provides the BMDS modeling outputs for data from Peto et al. (1991a, b). A multisite analysis is performed, which provides an estimate of the cumulative risk for treatment-related tumors at multiple sites or originating from different cell types. Tumor types are first modeled individually to determine the best fit model, then are combined to derive a multisite potency factor. All models were run with default parameters and a BMR of 5% extra risk. Model selection criteria (US EPA, 2012) when comparing outputs of different models or the multistage model with different degrees of polynomials for the same endpoint/dataset were: the lowest Akaike's information criterion (AIC), goodness of fit p-value ≥ 0.05, scaled residual ≤ the absolute value of 2, and visual inspection of the dose-response curve. For female rats, tumors were modeled using the eight lowest dose groups because the acceptable fit of the multistage polynomial could only be achieved after removing the top eight dose groups for the bile duct tumors. For male rats, only the first 12 dose groups were used for modeling because no model could be fit when more than 12 doses were used for the mesenchymal tumors.

The model outputs for male and female rats are presented below in Table A1 and Figure A1, and Table A2 and Figure A2, respectively.

Table A1. Multi-tumor BMDS modeling of bile duct, liver cell (hepatocyte), and mesenchymal tumors in male rats exposed to NDMA in a lifetime oral study (Peto et al., 1991a, b)

Tumor types	Model	BMD (mg/kg-day)	BMDL (mg/kg-day)	P Value	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group
	Multi-tumor (MS_Combo)	0.015	0.012				
Bile Duct	Multistage Degree	0.040	0.031	0.44	399.95	-1.60	-0.65
Liver Cell (hepatocyte)	Multistage Degree	0.032	0.025	0.98	547.74	-0.25	-0.01
Mesenchyme	Multistage Degree	0.065	0.045	0.17	241.62	-1.73	-0.00

Figure A1. Multi-site Cancer Model output for NDMA – liver cell, bile duct, and mesenchymal tumors in male rats from a lifetime oral study (Peto et al., 1991a, b)



Data

male bile duct 12 doses		
[Add user notes here]		
Dose	N	Incidence
Dose	N	Effect
0	240	3
0.001	60	2
0.003	60	3
0.005	60	2
0.011	60	2
0.022	60	1
0.044	60	1
0.065	60	4
0.087	60	7
0.109	60	13
0.131	60	12
0.174	60	12

Degree: 1
Background: Estimated

male liver cell 12 doses		
[Add user notes here]		
Dose	N	Incidence
Dose	N	Effect
0	240	10
0.001	60	4
0.003	60	3
0.005	60	2
0.011	60	4
0.022	60	4
0.044	60	5
0.065	60	8
0.087	60	7
0.109	60	13
0.131	60	14
0.174	60	19

Degree: 1
Background: Estimated

male mesenchyme 12 doses		
[Add user notes here]		
Dose	N	Incidence
Dose	N	Effect
0	240	0
0.001	60	0
0.003	60	0
0.005	60	1
0.011	60	1
0.022	60	0
0.044	60	1
0.065	60	0
0.087	60	7
0.109	60	5
0.131	60	12
0.174	60	10

Degree: 2
Background: Estimated

MS_Combo

User Input

Info	
Model	frequentist Multi-tumor v1.0

Model Options	
Risk Type	Extra Risk
BMR	0.05
Confidence Level	0.95

Model Results

Benchmark Dose	
BMD	0.014840041
BMDL	0.012026999
BMDU	0.019639006
Slope Factor	4.157312898
Combined Log-Likelihood	-588.6521487

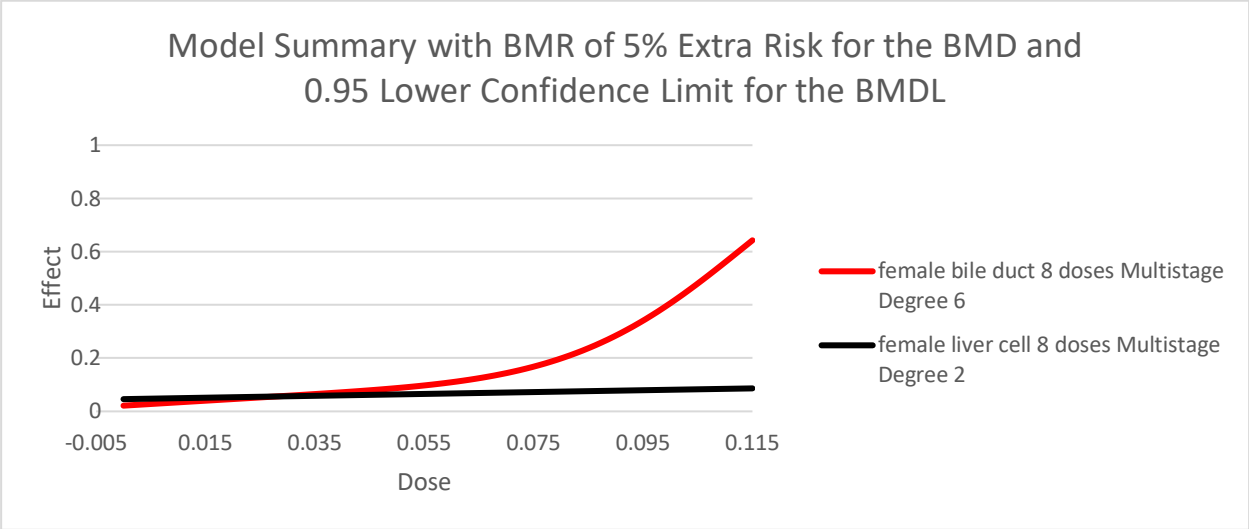
Summary of Results

Model	Analysis Type	Restriction	RiskType	BMD	BMDL	BMDU	P Value	AIC
Multi-tumor (MS_Combo)	frequentist	-	Extra Risk	0.01484	0.012027	0.019639		-
Multistage Degree 1	frequentist	Restricted	Extra Risk	0.040073	0.030889	0.0542305	0.4393047	399.9470518
Multistage Degree 1	frequentist	Restricted	Extra Risk	0.031661	0.024622	0.0426473	0.9824139	547.7402306
Multistage Degree 2	frequentist	Restricted	Extra Risk	0.064974	0.044599	0.0887468	0.1689976	241.6170157

Table A2. Multi-site BMDS modeling of bile duct and liver cell tumors in female rats exposed to NDMA in a lifetime oral study (Peto et al., 1991a, b)

Tumor types	Model	BMD (mg/kg-day)	BMDL (mg/kg-day)	P Value	AIC	Scaled Residual for Dose Group near BMD	Scaled Residual for Control Dose Group
	Multi-tumor (MS_Combo)	0.031	0.017		-	-	-
Bile Duct	Multistage Degree 6	0.039	0.021	0.41	288.01	-0.07	-0.51
Liver Cell	Multistage Degree 2	0.136	0.053	0.62	281.82	-0.96	-0.01

Figure A2. Multi-site Cancer Model output for NDMA – liver cell and bile duct tumors in female rats from a lifetime oral study (Peto et al., 1991a, b)



Data

female bile duct 8 doses		
[Add user notes here]		
Dose	N	Incidence
Dose	N	Effect
0	240	4
0.002	60	1
0.005	60	4
0.01	60	1
0.019	60	4
0.038	60	4
0.076	60	9
0.115	60	39

Degree: 6
Background: Estimated

female liver cell 8 doses		
[Add user notes here]		
Dose	N	Incidence
Dose	N	Effect
0	240	11
0.002	60	2
0.005	60	2
0.01	60	4
0.019	60	2
0.038	60	6
0.076	60	6
0.115	60	3

Degree: 2
Background: Estimated

MS_Combo

User Input

Info	
Model	frequentist Multi-tumor v1.0

Model Options	
Risk Type	Extra Risk
BMR	0.05
Confidence Level	0.95

Model Results

Benchmark Dose	
BMD	0.030755151
BMDL	0.017369248
BMDU	0.059618785
Slope Factor	2.878650812
Combined Log-Likelihood	-279.913545

Summary of Results

Model	Analysis Type	Restriction	Risk Type	BMD	BMDL	BMDU	P Value	AIC
Multi-tumor (MS_Combo)	frequentist	-	Extra Risk	0.030755	0.017369	0.0596188	-	-
Multistage Degree 6	frequentist	Restricted	Extra Risk	0.039	0.020816	0.0649744	0.413475	288.008239
Multistage Degree 2	frequentist	Restricted	Extra Risk	0.13645	0.053269	-9999	0.6159745	281.8188511