Environmental Guidelines and Regulations for Nitrosamines:

A Policy Summary

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Executive Summary

This report presents a summary of environmental and human health guidelines and regulations for nitrosamines, focusing on the United States and selected international contexts. Many nitrosamines are carcinogenic; the most frequently investigated by regulatory authorities are N-nitrosodimethylamine (NDMA) and N-nitrosodiethylamine (NDEA).

Both NDMA and NDEA have been classified by national and international regulatory authorities as probable human carcinogens. Numerous laboratory animal studies have linked exposure of these compounds to cancers. Some epidemiological evidence is available supporting a link to human cancers.

Historically, nitrosamines were of most regulatory interest due to their presence in food. However, recently NDMA has attracted renewed regulatory attention due to its presence as a drinking water contaminant. A number of studies measured NDMA near industrial sources. More recently, NDMA has been identified as a byproduct of drinking water disinfection. Regulatory development for NDMA concentrations in drinking water is ongoing under several authorities, including the United States, Canada and several European countries.

Assessment of the carcinogenic risk posed by nitrosamines follows a general methodology of risk assessment, where animal studies are extrapolated and associated with human risk levels. Several assumptions are made in the carcinogen risk assessment process, including the choice of animal study and endpoint used, extrapolation methods, and characterizations of exposure pathways. These assumptions are applied differently by different regulatory authorities, resulting in a range of concentrations that are calculated to be associated with human risk. Generally, a 10^{-5} or 10^{-6} risk level is applied to carcinogen risk assessments. Different risk assessments have calculated drinking water concentrations associated with these risks range between 0.7-100 ng/L.

Environmental measurements exist for nitrosamines in drinking water as well as air and natural waters. The chemical pathways of nitrosamine formation and degradation in the atmosphere (particularly in the aqueous phase) remain uncertain. One area of uncertainty is the relative importance of industrial vs. background sources.

1. Introduction

This report summarizes the environmental and human health guidelines and regulations in the United States and selected international contexts on nitrosamines. It includes: a summary of the health-related scientific information used in support of regulatory and risk analyses (Section 2); a historical analysis and timeline of environmental and public health actions and emerging data about nitrosamines (Section 3); background information on calculation of action or reporting levels in regulatory context (Section 4); a comparative analysis of levels of nitrosamine environmental concentrations at various sites and a survey of categories of sources of nitrosamines to the environment (Section 5). A brief summary of emerging issues is presented in section 6, and references to peer-reviewed literature and internet links to regulatory documentation are provided in Section 7.

Nitrosamines are compounds of the chemical form R_1NNOR_2 (see figure 1 for chemical structure). They are produced by the reaction of nitrite with secondary amines (Mirvish, 1995). While many nitrosamines are carcinogenic, some are not, and their potency varies depending on their molecular structure (Dai, 1998; Luan et al., 2005). N-nitrosodimethylamine (NDMA), a highly potent carcinogen, is commonly detected and often used as an indicator compound for nitrosamines. The degree of carcinogenicity among these compounds varies dramatically. N-Nitrosodiethylamine (NDEA) is the most potent carcinogen among the nitrosamines, and and N-nitrosodiphenylamine (NDP(h)A) being 15,000 times less potent. (European Commission, 2007).

The main compounds investigated by health and regulatory authorities have been NDMA (Figure 2) and NDEA. The United States Environmental Protection Agency has also developed an analytical measurement method covering seven nitrosamines, which are listed in Table 1 (Munch and Bassett, 2004). Following policy activities in national and international settings, this report will focus on regulations and supporting analyses produced for NDMA and NDEA, and will reference other nitrosamines, as appropriate and where information is available. It is important to note, however, that the use of a highly-potent carcinogen as an indicator could lead to overestimating nitrosamine risks (European Commission, 2007).

Table 1. Nitrosamines covered by EPA Method 521.

Nitrosamine Analyte	Chemical Abstract Services (CAS) Registry Number	Detection Limit for EPA Method 521 (ng/L)
N-Nitrosodimethylamine (NDMA)	62-75-9	0.28
N-Nitrosomethylethylamine (NMEA)	10595-95-6	0.28
N-Nitrosodiethylamine (NDEA)	55-18-5	0.26
N-Nitrosodi-n-propylamine (NDPA)	621-64-7	0.32
N-Nitrosodi-n-butylamine (NDBA)	924-16-3	0.36
N-Nitrosopyrollidine (NPYR)	930-55-2	0.35
N-Nitrosopiperidine (NPIP)	100-75-4	0.66

Figure 1. Structure of nitrosamines.

From Luan et al., 2005.

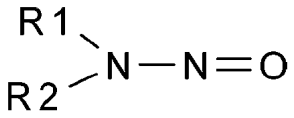
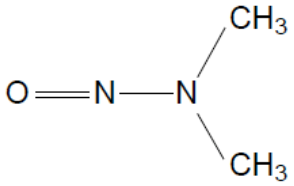


Figure 2. Structure of N-nitrosodimethylamine (NDMA).

From California Environmental Protection Agency, 2006.



2. Health Risks of Nitrosamines

The health risk of most concern for environmental levels of nitrosamine is carcinogenicity. Exposure to nitrosamine has been shown to form tumors in laboratory animals, and have been linked in epidemiological studies to human cancers including pancreatic cancer (Risch, 2003) and childhood brain tumors (Huncharek and Kupelnick, 2004).

Nitrosamines are classified by a number of international organizations and regulatory authorities as to their carcinogenicity. Under the International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO), NDMA and NDEA are classified as Group 2A substances (probably carcinogenic to humans). The European Union categorizes NDMA and NDEA as category 1B (Presumed to have carcinogenic potential for humans; largely based on animal evidence). In the US, the Environmental Protection Agency classifies both NDMA and NDEA as a "probable human carcinogen (category B2)" under its 1986 carcinogen assessment guidelines.

3. Nitrosamine Historical Analysis and Emerging Policies

Nitrosamines initially gained regulatory concern due to their levels in food. For example, nitrates intentionally added to food as preservatives react with amines in cooking to form nitrosamines (Shapley, 1976). Food products that can contain nitrosamines include bacon and other cured meats, fish, cheese, and malt beverages including beer (ATSDR, 1989). Consumption of meats and foods with elevated levels

of nitrosamines have been linked in epidemiological studies to increased risk of cancer. Concentrations of nitrosamines in food have decreased over the last few decades due to regulation and decreases in added nitrates (Scanlan, 1995).

Internationally, the World Health Organization in 2008 added NDMA to the third edition of its guidelines for drinking water quality. In addition to industrial processes, the WHO noted the recent identification of NDMA as a disinfection byproduct of water treatment processes as background to its substance profile. A background scientific assessment document was developed in 2006 for this guideline process.

Industrial sources and emissions of NDMA produced a renewed interest in the compound in the 1990s. Nitrosamine formation has been associated with the production of rocket fuel. In 1998, NDMA was detected in a drinking water well near a facility in California, USA that used unsymmetrical dimethylhyrazine (UMDH)-based rocket fuel (California DPH, 2010a; Mitch et al., 2003). Oxidation of UMDH produces NDMA. Surveys of drinking water in noncontaminated areas following this discovery also revealed the presence of nitrosamine in these water supplies. The production of NDMA in treated drinking water primarily results from chloramination processes. In Canada, a drinking water survey found nitrosamines in treated drinking water in 1989, and a similar survey in California detected nitrosamines in 2001. Some drinking water samples showed concentrations greater than 10 ng L^{-1}, though most fell below that level (Mitch et al., 2003). High concentrations have also been found in wastewater effluents.

Few firm regulatory limits exist for the concentration of nitrosamines in the environment and in particular in drinking water (Mhlongo et al., 2009). However, regulatory guideline or assessment levels for environmental media and in particular for drinking water have been set by a number of international, national and subnational authorities. In addition, growing concern about the presence of nitrosamines as disinfection byproducts (i.e. substances produced as a result of processes used to reduce water bacteria levels) has prompted renewed interest in setting regulatory standards for these substances in North America and internationally.

Nitrosamines are listed in a number of national regulations in the United States. Under the U.S. Clean Water Act, which regulates surface water quality, nitrosamines are listed as a toxic pollutant. The U.S. EPA has issued, pursuant to the Clean Water Act, national recommended water quality criteria for the presence of N-Nitrosodimethylamine (0.00069 μg L^{-1}, considering an endpoint of water and organism consumption, or 3.0 μg L^{-1} for the endpoint of organism consumption only); N-Nitrosodi-n-Propylamine (0.0050 μg L^{-1} for water+organism or 0.51 for organism only); and N-Nitrosodiphenylamine (3.3 μg L^{-1} for water+organism or 6.0 for organism only) (U.S. Environmental Protection Agency, 1980). These levels are based on a 10^{-6} carcinogenic risk level, and represent a non-regulatory, scientific assessment of ecological and health effects.

With respect to drinking water regulation in the United States, six nitrosamines (those listed in Table 1, with the exception of NPIP) have been listed in the EPA's Unregulated Contaminants Monitoring Rule. This means that data were required to be collected between 2008-2010 on their presence in drinking water systems nationwide (Unregulated Contaminant Monitoring Regulation (UCMR) for Public Water Systems Revisions, 2007). This data may be used for future regulatory determinations for the substance (Richardson, 2006). As of October 2009, EPA listed five nitrosamines (NDEA, NDMA, NDPA, NPYR plus N-nitrosodiphenylamine) on its contaminant candidate list, which is a list of priority drinking water contaminants for which EPA will research whether regulations are needed. Data from the EPA Unregulated Contaminant Monitoring Regulation is presently available through October, 2010; over 100,000 samples have been analyzed.

Under the U.S. Toxics Release Inventory (TRI), both NDEA and NDMA are listed substances subject to reporting requirements. For environmental releases Under the Resource Conservation and Recovery Act, NDMA and NDEA are both listed as hazardous constituents of wastes, and under the Comprehensive Environmental Response, Compensation, and Liability Act, they are on a priority list of substances dangerous to human health.

The U.S. State of California has taken a number of actions regarding NDMA. In 1998, the California Department of Health Services set an action level of 0.002 μg $L^{-1}$for NDMA in drinking water (California Department of Public Health, 2010a). (At that time, detection limits were above this level). In California, action levels (now referred to as Notification Levels) are health-based advisory levels for drinking water contaminants for which there is no regulatory maximum (California Department of Public Health, 2010b). Drinking water systems are required to notify local authorities whenever these levels are exceeded (California Health and Safety Code, 2004). This level was raised in 1999 to 0.02 μg L^{-1}, to reflect the presence of NDMA in treated drinking water. In 2006, after a risk assessment process, California established a Public Health Goal of 0.003 μg $L^{-1}$for NDMA in drinking water; this is a first step towards regulation of the substance through a drinking water standards. For other nitrosamines, the California Department of Health Services has a notification level of 0.01 μg $L^{-1}$for NDEA since 2004, and for NDPA since 2005 (California Department of Public Health, 2010a). If any of these chemicals reach response levels corresponding to a calculated 10^{-4} cancer risk level (100 ng/L for NDEA, 300 ng/L for NDMA, and 500 ng/L for NDPA), the California Department of Public Health recommends that drinking water sources should be taken out of service (California Department of Public Health, 2010c).

Several other U.S. states have also addressed NDMA. For example, the U.S. state of Massachusetts has set a guideline level of 0.00001 mg L^{-1} for NDMA in drinking water, based on the analytical detection limit of NDMA (Mass. DEP, 2010a), as state policy is to minimize concentrations of carcinogens as much as feasible (Mass. DEP, 2010b). The state of Arizona requires monitoring of NDMA concentrations under

the state-administered National Pollutant Discharge Elimination System permit program, and set a maximum water quality criterion of 30 ng L^{-1} (Sedlak and Kavanaugh, 2006).

In Canada, NDMA is considered to be "toxic" according to the Canadian Environmental Protection Act of 1999 (Environment Canada and Health Canada, 2001). In March 2010, Health Canada proposed a maximum acceptable concentration for NDMA in drinking water of 0.04 µg L^{-1} (Health Canada, 2010). Public comments are now being reviewed on the draft guideline, and a final guideline is expected to be issued. N-Nitrosodiphenylamine is currently listed under the Canadian National Pollutant Release Inventory; NDMA is not currently listed.

In the European Union, nitrosamines are not specifically listed in the Drinking Water Directive (Council Directive 98/93/EC), but a few EU member states have regulated their presence in drinking water, as higher or more stringent standards are allowed under the directive. The regulatory authorities of the UK and Germany have classified NDMA as a suspected human carcinogen (Health Council of the Netherlands, 1999). In the UK, regulation of NDMA in drinking water takes the form of a four-tiered approach (UK DWI, 2000). At any concentration (Tier 1), it considered as a potential hazard and considered as part of risk assessments. At levels > 1 ng L^{-1}, Tier 2 notification and monitoring requirements are initiated. At levels > 10 ng L^{-1}, measures are put in place to reduce concentrations (Tier 3), and at levels > 200 ng L^{-1}, urgent measures are to be put in place to reduce concentrations within days (Tier 4). In Germany, 10 ng L^{-1} concentrations trigger the initiation of remedial actions to reduce NDMA concentrations. While such actions are taking place, acceptable concentrations can be up to 200 ng L^{-1} for up to 3 years, and 60 ng L^{-1} for up to 10 years (UK DWI, 2000). In other European Union regulations, the presence of nitrosamine in cosmetics, balloons and rubber teats has been addressed.

Table 2. Timeline of Scientific Evidence and Policy Action on nitrosamines

1956	J. Barnes and P. Magee report N-Nitrosodimethylamine (NDMA) has a carcinogenic effect on rats (Andrzejewski et al., 2005)
1970	Scientists suspect connection between nitrosamines & urban cancer (Lijinsky and Epstein, 1970)
1973	USDA panel of experts meets on nitrosamines in food (Shapley, 1976)
1975	Nitrosamines measured at elevated levels in urban atmosphere (Shapley et al, 1976)
1978	IARC classifies NDMA as "possibly carcinogenic to humans" (Group 2B)

1980	U.S. EPA publishes ambient water quality criteria document for nitrosamines
1989	High levels of NDMA found in drinking water in Canada following disinfection treatment (Mlongo et al., 2009).
1987	NDMA classification by IARC upgraded to "probably carcinogenic to humans" (Group 2A)
1998	NDMA found in drinking water well near industrial site in Sacramento, CA. (California DPH, 2010a)
2001	NDMA found in treated drinking water samples in California, USA (Mitch et al., 2003); NDMA considered "toxic" under Canadian Environmental Protection Act
2004	U.S. EPA Method 521 published on detection of nitrosamines (Munch and Bassett, 2004).
2006	California establishes Public Health Goal for NDMA in drinking water
2008	WHO proposes guideline level for NDMA in drinking water
2010	Canada proposes maximum acceptable concentration for NDMA in drinking water

4. Calculation of Health-related Risk Levels: Health-related carcinogenicity guidelines

Deriving carcinogenic risk levels often requires extrapolating from available testing data, a process that requires regulators to make a variety of different assumptions. Various regulatory authorities may make different judgments about data quality and extrapolation methods in their calculations in conducting a risk assessment for a carcinogenic substance, and these judgments can change over time based on the emergence of new scientific information. Based on this risk assessment, they may choose to regulate the substance (risk management) at a particular level.

In assessment of cancer risks, regulatory authorities generally do not take into account contributions of risk from different sources in a comparative way. This type of comparison is generally only considered appropriate where a carcinogen is only active after exposure to a concentration over a threshold. Relative source contributions, which compare contributions to risk from different sources, are customarily not used for carcinogen assessment. The rationale for this is that carcinogen risk assessment is based on extra risk, and already includes conservative

assumptions (California Environmental Protection Agency, 2006). Calculations based on a relative source contribution method is most appropriate in risk assessment where there exists a threshold below which no adverse effect is expected. This is not the case with the linear dose-response assumptions applied for nitrosamines.

In the case of nitrosamines, because existing epidemiological studies examining humans have thus far not been comprehensive enough on which to base quantitative risk assessments, such risk assessments must extrapolate from animal studies to human exposure levels. The choices made by risk assessors to conduct hazard assessment, dose-response evaluation, and exposure assessment include the following:

Choice of animal study: There are a number of studies establishing carcinogenicity of nitrosamines in laboratory animals. The judgment about which animal study to use for extrapolation is based on the species involved (often rats), data availability, the range of doses, number of test subjects, routes of exposure, and the specificity of carcinogenic endpoints. For NDMA, most risk assessments have chosen to use the studies on drinking water exposure in rats by Peto et al. (1991) as a basis for risk assessment, based on its wide concentration range and large number of experimental subjects (World Health Organization, 2008).

Low-dose extrapolation: The risk assessor must determine the nature of the relationship between dose and health endpoints for the data involved. For example, this relationship can be linear or non-linear and various curve-fitting methods can be applied. Risk assessors then extrapolate beyond the lowest data point to doses that might be relevant for human doses.

Interspecies extrapolations: Some risk assessments often use scaling factors to account for differences in toxicologically equivalent doses between laboratory animals and humans, based on physiological differences (U.S. EPA, 2005). The U.S. EPA, for example, scales equivalent dose by body weight to the three-fourths power. Others use an uncertainty factor to take into account interspecies differences, and still others do not use a correction or scaling factor for these extrapolations.

Exposure assessment: To go from a human dose corresponding to a particular risk level, to a concentration in environmental media such as air or water associated with that risk level, assumptions are required about both humans and exposure patterns. For example, a standard human weight (60 or 70 kg) is often used, as is a standard amount of air intake or water intake per day. Risk assessments vary on whether and how they might take into account populations that, because of their age, genetics or lifestyle, might be more susceptible to such risks.

Risk threshold: Regulatory agencies choose to regulate concentrations to minimize risks to below a certain set threshold. The levels of 1 in 100,000 (10^{-5}) or 1 in 1,000,000 (10^{-6}) are commonly chosen. 10^{-6} is recommended by European

regulators for general population exposure, while risk levels >10^{-5} are not commonly used. The choice of risk threshold is a political or management decision, based on policy judgments about how to define a *de minimis* risk level.

A comparative analysis of regulatory guidelines of NDMA in drinking water for set by different authorities is presented in Table 2. Most regulatory authorities apply a risk level of 1 in 100,000 or 1 in 1,000,000. Even considering the same risk level, though, different choices and assumptions in carcinogen risk assessment result as summarized above in very different guideline levels (a factor of 4 or more).

In the United States, the Environmental Protection Agency regulates carcinogenic hazards at risk levels between 10^{-6} and 10^{-4}, corresponding to between a 1 in 1,000,000 and 1 in 10,000 incidence of cancer (US EPA, 2007, Chapter 3). In regulating water systems, EPA instructs U.S. states that risk levels less protective than 1 in 100,000 require substantial documentation and justification (US EPA 2007, Chapter 3). The European Union has not set a specific 'tolerable' risk level for carcinogens. However, guidelines for assessing substances under its Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) regulation note that based on values previously applied within and outside the EU, cancer risk levels of 10^{-5} and 10^{-6} can be considered indicative tolerable risks for workers and the general population, respectively (European Chemicals Agency, 2010).

The US EPA guidelines for carcinogen risk assessment (US EPA 2005) outline its process for dose-response assessment. Dose-response assessment as used by EPA is a two-step process. First, animal, human effect or other data are used to create a model relating doses to biological responses. This data and model are used to determine a point of departure below which extrapolations will be made to doses lower than those observed. These extrapolations are conducted in the second step; extrapolation methodology depends on what is known about the mode of action of the carcinogenic agent.

In the case of NDMA, the US EPA Integrated Risk Information System (IRIS) was developed using the older (1986) carcinogenic risk guidelines. These resulted in NDMA being categorized as "Probably carcinogenic to humans" (Group B2), meaning that animal data providing a causal relationship of carcinogenicity is available, but human data is limited. The 1986 methodology assumed a linear relationship between dose and carcinogenic risk. The risks are derived from the study of Peto et al. (1984), who exposed rats with NDMA in drinking water. In that study, the cumulative incidence (CI) of tumors at all sites in the liver in the female rat followed the relationship:

$$CI=51.45(d+0.1)^{6}t^{7}$$

Where d=dose in mg/kg-day, and t=time in years.
The incidence of liver tumors in female rats was used to derive a linear slope factor for rats of 7.8 per (mg/kg)/day. From this level, a drinking water unit risk was

defined as $1.4x10^3$ per μg L^{-1}, and an associated drinking water concentration at 10^{-6} risk level of $7x10^{-4}$ μg L^{-1}.

In developing its Public Health Goal for NDMA in 2006, the U.S. state of California used two approaches: a time-to-tumor model and a linearized multistage model. For the time-to-tumor model, they also judged the data from Peto et al. (1991) on liver tumors in female rats to be most appropriate for use in extrapolating dose-response relationships to humans. This data and the above CI equation was used to derive a dose associated with a 10% incidence of liver tumors during a rat's two-year lifetime of 0.06 mg/kg-day. The equivalent dose in humans, 0.0145 mg/kg-day, was derived from the ratio of rat to human body weight to the ¾ power. Deriving a linear slope from this 10% risk level results in a slope of 6.9 (mg/kg-day)-1, and thus a 10^{-6} risk of $1.4x10^{-7}$ mg/kg-day. For the linearized multistage model, the incidence of bile duct tumors from the Peto et al. (1991) study was chosen as the most appropriate endpoint for lower doses. After testing a variety of models to fit the dose groups in the data, the linearized multistage model was chosen as the best fit to the greatest number of dosage groups. Based on this fit, the dose associated with a 10% incidence of tumors was 0.032 mg/kg/day in rats, corresponding to 0.0078 mg/kg-day in humans, and a slope of 12.8 $(mg/kg\text{-}day)^{-1}$. This results in a 10^{-6} risk of $7.8x10^{-8}$ mg/kg-day, or lower than the first methodology. Based on this comparison, the linearized multistage model was chosen in development of the public health goal, as it described a lower bound of dose.

Canadian guidelines recommend regulation of carcinogens in drinking water at a level at which additional cancer risk over a lifetime is essentially negligible. This is interpreted as a 10^{-5} to 10^{-6} cancer incidence level (Health Canada, 2010). In developing its proposed maximum contaminant level for NDMA, Health Canada chose to use a 10^{-5} risk level. Health Canada calculated unit risks from NDMA using the same Peto et al. (1991) data. They used as their point of departure the dose at which tumor incidence was 5% (TD_{05}, as opposed to 10% for the calculation in California). They used a multistage model to calculate the TD_{05}, and these values were used to calculate unit risks based on the ranges and 95% lower confidence limits from tumor data. An animal-to-human scaling factor of $(0.35/70)^{\wedge 1/4}$ was used, intending to account for interspecies differences in susceptibility. Considering uncertainties in the animal studies used, they proposed a maximum contaminant level of 0.04–0.1 μg L^{-1} based on these calculations.

The World Health Organization, in developing their drinking water guideline for NDMA, used a methodology similar to that used by Canada. However, the major difference was that they chose not to use an animal-to-human scaling factor.[1] They chose a risk level of 10^{-5}, and calculated a guideline value of 100 ng L^{-1} for drinking water, based on a 60 kg adult consuming 3 L of water per day.

[1] WHO argues that scaling based on the ratio between surface area to body weight for rodents vs. humans is inappropriate for NDMA because of the probably mechanism of carcinogenicity.

The Health Council of the Netherlands (1999) conducted an exposure assessment to investigate occupational risk associated with NDMA. For this purpose, they used data from a study by Klein et al. in rats where the route of exposure was inhalation. They used a linear assumption to relate the lowest reported dose to a risk factor per µg m^{-3} concentration, they derived an estimated incidence range of 0.057-0.1 per µg m^{-3} (the range is due to two different assumptions about the reported exposure period). Based on this incidence, a health risk to humans is derived through multiplying the calculated incidence by concentration and amount of exposure to air in an occupational setting.

Figure 3 summarizes different dose-response relationships used in NDMA risk assessment. Blue dots indicate values used as points of extrapolation associating dose with tumor incidence for laboratory animals, used by different authorities. Black lines indicate slope factors for unit risk associating dose with tumor incidence. The steeper the slope of the line is, the higher the risk is thought to be associated with a given dose. These unit risks are then associated with guideline risk concentrations (shown in Table 3) through assumptions about human body weight and daily consumption.

Figure 3: Dose-response relationships used in NDMA risk assessment

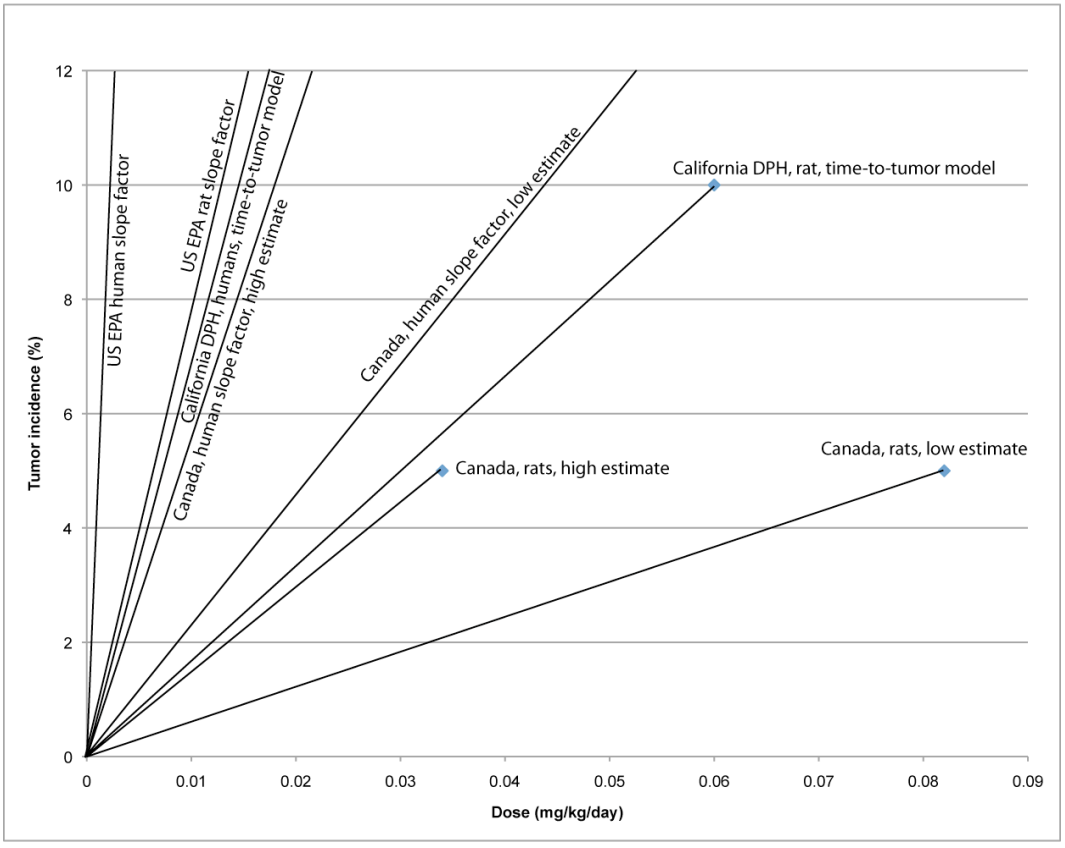


Table 3: NDMA Drinking water guideline values and associated risks

Authority	Concentration (ng L^{-1})	Comment
U.S. Environmental Protection Agency IRIS Database	0.7	10^{-6} cancer $_{risk}$
Canada proposed Maximum Acceptable Concentration (MAC)	40-100[2]	10^{-5} cancer risk
U.S. State of California Public Health Goal	3	10^{-6} cancer risk
US EPA Regions 3 & 6 non-enforceable screening level in tap water (2007)	0.42	
World Health Organization Guideline Value	100	10^{-5} cancer risk

5. Environmental Levels: A Survey

The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) notes that the potential exists for release of NDMA into the environment for industrial situations where alkylamides come into contact with nitrogen oxides, nitrous acids, or nitrite salts. Examples include industries such as tanneries, pesticide manufacturing plants, rubber and tire manufacturers, alkylamine manufacturing or use sites, fish processing industries, foundries and dye manufacturers (ATSDR, 1989). NDMA can also be formed in the environment, through reactions of amines in the presence of nitrite. Canada reports that major releases of NDMA to the environment have been associated with the manufacture of pesticides, rubber tires, alkylamines and dyes (Environment Canada and Health Canada, 2001).

Under the U.S. Toxics Release Inventory, NDMA is a listed substance with a reportable quantity of 10 lb (4.5 kg)(US Department of Health and Human Services, 2005). The last year in which a release of NDMA was reported to the US TRI was 1999, comprising 5 lbs (2.3 kg) of nitrosamine reported by one company in California. For NDEA, releases reported totaled 17,540 lbs (7960 kg) in 2009, 651 lbs in 2008, 650 lbs in 2007, and 500 lbs each in 2006 and 2005. Canadian estimates of the amount of NDMA released through the use of herbicides contaminated with NDMA total approximately 200 g (World Health Organization, 2002).

NDMA was measured in the atmosphere in several studies in urban areas such as New York City and Baltimore the 1970s (Mitch et al., 2003), prompting suggestions that there may be a link between atmospheric concentrations and high rates of

[2] The range is based on differences in the animal studies used to calculate unit risk. The lower unit risk was based on biliary cistadenomas and the higher for carcinomas.

cancer in these areas (Shapley, 1976). The concentrations measured in these studies were on the order of 0.1-1 μg m^{-3}. At the time, there was some concern that NDMA could be formed in the polluted atmosphere. However, these elevated concentrations were later explained by direct emission from a previously unknown source (Mitch et al., 2003). In addition, further atmospheric investigations indicated that photolysis reactions were rapid, leading to a lifetime of NDMA in full sunlight around 30 minutes (Hanst et al., 1977). This led to the conclusion that contamination was unlikely to be a problem in the ambient atmosphere, without the influence of direct emissions. Surveys conducted in Ontario, Canada in 1990 at industrial and urban locations indicated concentrations of NDMA mostly below detection limits (limits were between 0.0034 to 0.0046 μg m^{-3}) (Health Canada, 2010).

Recent measurements of NDMA in fogs and clouds in the western and eastern United States showed unexpectedly high concentrations (7.5-397 ng L^{-1}), suggesting NDMA photolysis may be much less efficient in the aqueous phase than in the gas phase (Hutchings et al., 2010). This means that NDMA could persist in the atmosphere longer at sunrise and sunset than its rapid gas-phase photolysis might imply. These recent results raise some questions about the atmospheric fate of nitrosamines, and further research is needed to explain the significance of these results.

High concentrations of NDMA have been measured in ground water near rocket engine testing facilities, as mentioned above (Mitch et al., 2003). Concentrations in surface waters near the Baltimore, MD facility that used NDMA to produce UDMH were present at up to 940 ng L^{-1} (ATSDR, 1989). In 2004, the U.S. EPA published a method for determining the presence of seven nitrosamines (including NDMA and NDEA) in drinking water (Munch and Bassett, 2004). Concentrations in drinking water supplies in 2008-2010 monitored as part of the. EPA's Unregulated Contaminants Monitoring Rule For NDMA, mean detected values are 0.009 μg L^{-1}, while maximum detected is 0.6 μg L^{-1}. For NDEA, the mean is 0.015 μg $L^{-1}$and maximum 0.1 μg L^{-1}.

Recent studies have shown that nitrosamines are present in chlorinated swimming pools at levels up to 500 times those found in drinking water. In a study by Walse and Mitch (2008), median NDMA levels in indoor pools were 32 ng L^{-1} and outdoor pools were 5.3 ng L^{-1}, while median levels in hot tubs were 313 ng L^{-1}.

6. Summary and Analysis

Nitrosamines are a well-known category of carcinogenic substances, and have been subject to much analysis and assessment over the past several decades. In the 1970s and 1980s, nitrosamines were mainly of concern due to their presence in foods, including smoked meats and fish and malt beverages. Releases to the environment due to industrial contamination, especially due to production of rocket fuel, have

garnered additional regulatory attention. More recently, environmental levels, particularly in drinking water, are of most regulatory interest. It is likely that a number of authorities will regulate these substances in the near future. In addition, some recent measurements have shown that further research is needed on the chemical formation and transformation of nitrosamines in the environment.

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