

## Estimation of the total daily oral intake of NDMA attributable to drinking water

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### ABSTRACT

Disinfection with chlorine and chloramine leads to the formation of many disinfection by-products including N-Nitrosodimethylamine (NDMA). Because NDMA is a probable human carcinogen, public health officials are concerned with its occurrence in drinking water. The goal of this study was to estimate NDMA concentrations from exogenous (i.e., drinking water and food) and endogenous (i.e., formed in the human body) sources, calculate average daily doses for ingestion route exposures and estimate the proportional oral intake (POI) of NDMA attributable to the consumption of drinking water relative to other ingestion sources of NDMA. The POI is predicted to be 0.02% relative to exogenous and endogenous NDMA sources combined. When only exogenous sources are considered, the POI was predicted to be 2.7%. The exclusion of endogenously formed NDMA causes the POI to increase dramatically, reflecting its importance as a potentially major source of exposure and uncertainty in the model. Although concentrations of NDMA in foods are small and human exposure to NDMA from foods is quite low, the contribution from food is predicted to be high relative to that of drinking water. The mean concentration of NDMA in drinking water would need to increase from  $2.1 \times 10^{-3} \mu\text{g/L}$  to  $0.10 \mu\text{g/L}$ , a 47-fold increase, for the POI to reach 1%, relative to all sources of NDMA considered in our model, suggesting that drinking water consumption is most likely a minor source of NDMA exposure.

**Key words** | DBPs, disinfection by-products, drinking water, exposure assessment, NDMA, N-Nitrosodimethylamine

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### INTRODUCTION

To reduce concentrations of potentially pathogenic microorganisms in public drinking waters, the United States Environmental Protection Agency (EPA) requires drinking water treatment facilities to disinfect their water supplies and provide residual disinfection throughout the distribution system. Reactions of disinfectants with natural organic matter (NOM) in source water during drinking water treatment can generate a variety of chemicals known as disinfection byproducts (DBPs). Over 500 DBPs have been identified in treated waters (Richardson 2003); the types and ratios of DBPs formed depend primarily on the type of disinfectant used and the amount of NOM in the water. The occurrence of these complex mixtures results in

ubiquitous, chronic, low-level exposures in populations consuming chemically disinfected drinking water.

Some epidemiology studies report that exposure to DBPs increases the risk of developing colon, rectal and bladder cancers (Cantor *et al.* 1998; Hildesheim *et al.* 1998). To diminish these risks, the EPA has implemented regulations, such as the Stage 2 Disinfectant and Disinfection By-Product Rule (DBPR2), to reduce DBPs exposures (EPA 2006). To comply with the requirements of DBPR2, some United States (U.S.) drinking water suppliers are predicted to switch from free-chlorine, the primary disinfectant used in the U.S., to alternative disinfectants such as chloramine (Kirmeyer *et al.* 2004). Although chloramination

may reduce total DBP levels, it may result in the formation of nitrosamines such as N-Nitrosodimethylamine (NDMA) (CASRN 62-75-9) (Mitch *et al.* 2003); early studies indicated that chloramination led to higher levels of NDMA than chlorination (Siddiqui & Atasi 2001; Choi & Valentine 2002). Factors that influence NDMA formation in drinking water include the order of reagent addition in the disinfection process (Schreiber & Mitch 2005), contamination with the rocket fuel 1,1-dimethylhydrazine (CADHS 2002), the presence of precursor amines such as dimethylamine (DMA) (Choi & Valentine 2003), oxidation of cationic polymers (Najm *et al.* 2004) and reactions of tertiary amines (e.g., sulfur-containing carbamates) with nitrite (Choi *et al.* 2002).

Because NDMA is classified as a probable human carcinogen (IARC 1978; EPA 1993; NTP 2005), its occurrence in drinking water concerns public health officials. The EPA's Integrated Risk Information System (IRIS) estimates that a NDMA concentration of  $7 \times 10^{-4}$   $\mu\text{g/L}$  in drinking water is associated with a  $10^{-6}$  cancer risk (EPA 1993). The World Health Organization (WHO) (2006) estimates that 0.1  $\mu\text{g/L}$  NDMA in drinking water corresponds to an upper-bound  $10^{-5}$  cancer risk. The EPA has placed NDMA on the screening survey list (List 2)<sup>1</sup> of the Unregulated Contaminant Monitoring Rule (UCMR) for 2007-2010 (EPA 2005). The UCMR program collects data for contaminants suspected to be present in drinking water that do not have health-based standards. EPA Region 9 has set a Preliminary Remedial Goal<sup>2</sup> of  $1.3 \times 10^{-3}$   $\mu\text{g/L}$  for contaminated water at Superfund sites (EPA 1994). California (CADHS 2005) and Massachusetts (MADEP 2005) have set drinking water regulations at 0.01  $\mu\text{g/L}$ . Canada has established a drinking water quality standard of  $9 \times 10^{-3}$   $\mu\text{g/L}$  (OMOE 2003). In addition, the U.S. Food and Drug Administration (FDA) has established action levels for NDMA in malt beverages (5  $\mu\text{g/L}$ ) (FDA 1996), barley malt (0.01  $\mu\text{g/g}$ ) (FDA 1995a) and rubber baby-bottle nipples (0.01  $\mu\text{g/g}$ ) (FDA 1995b).

In this paper, we estimate NDMA concentrations in drinking water and food, calculate the average daily dose

(ADD) for ingestion route exposures for the U.S. population and estimate the proportional oral intake (POI) of NDMA attributable to the ingestion of drinking water relative to that of NDMA present in food and formed endogenously in the human body.

## SOURCES OF NDMA EXPOSURE

### Drinking water

Although studies have examined the occurrence of NDMA in some drinking water systems, there have not been any large-scale systematic evaluations of the occurrence of NDMA or other nitrosamines within drinking water distribution systems in the U.S. Elevated concentrations of NDMA were first observed in Canada where a survey of 145 Ontario drinking water plants reported levels greater than  $9 \times 10^{-3}$   $\mu\text{g/L}$  in chlorinated drinking waters, although most samples were less than the detection limit (DL) of  $5 \times 10^{-3}$   $\mu\text{g/L}$  (Jobb *et al.* 1995). Other studies have reported similar NDMA concentrations in treated drinking water (Tomkins *et al.* 1995; Tomkins & Griest 1996; CADHS 2002). A recent study of 21 U.S. and Canadian drinking water treatment plants reported a range of NDMA levels from below the minimum reporting level (MRL) of  $6 \times 10^{-4}$   $\mu\text{g/L}$  to  $2.4 \times 10^{-2}$   $\mu\text{g/L}$  (Valentine *et al.* 2006).

### Food

NDMA can form in food when secondary amines are exposed to nitrite during processing or preservation. Dietary sources of NDMA include beer, fish and fish products, dairy products including cheese, dried milk and infant formula, meat and cured meats, cereals and vegetables (Hotchkiss 1989; Tricker & Kubacki 1992). Although no systematic reviews of NDMA levels in U.S. or Canadian foods were identified, NDMA levels in specific foods have been reported by the FDA (Havery *et al.* 1976), the United States Department of Agriculture (Fiddler *et al.* 1973; Fiddler *et al.* 1975) and the Canadian Health Protective Branch (Sen 1972; Sen *et al.* 1973). The results of these and other North American studies, although dated, are similar to comprehensive systematic surveys conducted in Europe. Infants

<sup>1</sup> UCMR List 2 contaminants are those for which analytical methods have been recently developed and are not widely used, therefore, laboratory capacity may be insufficient to conduct the large scale monitoring studies (EPA, 2005).

<sup>2</sup> Preliminary Remedial Goals are used in superfund assessments to determine cleanup levels that are protective of human health.

may be exposed to trace quantities of NDMA in powdered infant formula (Westin 1990), rubber bottle nipples (Hile 1983) and breast milk (ATSDR 1989).

### Endogenous formation

In addition to NDMA exposure from these exogenous sources, NDMA can form endogenously from the nitrosation of secondary amines, such as DMA, contained in ingested meat and fish. Nitrosation involves the reaction of stomach acid with nitrite and nitrate found in foods as well as nitrate created in the stomach to form nitroso groups, which are free to react with amines in food to form NDMA (Mirvish 1974, 1992; Tricker *et al.* 1994). The amount of NDMA formed endogenously appears to depend on the relative concentrations of nitrate, nitrite, nitrosatable substances (Mirvish 1992), pH (Mirvish 1974), the presence of enhancing or inhibitory agents<sup>3</sup> (Chung *et al.* 2002) or the presence of nitrosating bacteria (Ralt & Tannenbaum 1981). Vegetables, primarily spinach, beets, cabbage, broccoli and carrots, are the predominant dietary source of nitrate, with additional exposures from cured meats, fish and, to a lesser extent, drinking water (NRC 1995). Reduction of nitrate by bacteria in the mouth is the predominate source of nitrite in humans (Shapiro *et al.* 1991). Many other factors may influence nitrosation reactions, making predictions of the quantities of NDMA formed endogenously uncertain.

Experimental data on endogenous formation of NDMA has been reported in animal and human studies *in vivo* and laboratory experiments *in vitro*. Several *in vivo* studies report maximum NDMA levels in urine of 1.3 µg/day after consumption of foods high in nitrite, nitrate and nitrosatable substances (Fine *et al.* 1977; Milligan *et al.* 1987; Vermeer *et al.* 1998). Spiegelhalter *et al.* (1982) reported that less than 0.5% of ingested NDMA is excreted unmetabolized in the urine if beverages containing ethanol are not consumed suggesting that the amount of NDMA formed in the stomach is likely higher than the quantities measured in urine.

*In vitro* studies have estimated NDMA concentrations formed under simulated gastric conditions with nitrite and

nitrate levels comparable to normal dietary intake levels (Groenen *et al.* 1980, 1982; Sen *et al.* 1985; Krul *et al.* 2004). These studies reported NDMA levels from less than the DL of 0.01 to 44 µg per portion of amine-rich food while adjusting for many factors not achievable during *in vivo* studies, such as pH and secondary amine concentration.

Although the chemistry and kinetics of *in vivo* NDMA formation are understood (Fine *et al.* 1982; Licht & Deen 1988; Leaf *et al.* 1989), inadequate data exist to accurately estimate the quantities of NDMA formed endogenously in humans. This decreases the precision and increases the uncertainty of estimates of endogenously formed NDMA and its contribution to total human NDMA exposure.

### Other sources

Non-dietary sources of NDMA include cutting oils, herbicides, pesticides and rubber products (NIOSH 1984). NDMA also has been found in sewage influent from industrial sources and from the chlorination of secondary effluent at wastewater treatment plants (Najm & Trussell 2001; Mitch & Sedlak 2004). NDMA has been detected in inhalable cigarette smoke (Hoffman *et al.* 1980; Tricker & Preussmann 1992) and environmental tobacco smoke (ETS) (Hoffmann *et al.* 1987).

## METHODS

Because ingestion rates vary with age, we examined exposures for three age groups: bottle-fed infants (<6 months), children (6 months to 17 years) and adults (≥18 years). We did not stratify the data by gender. To evaluate the magnitude of the contribution of NDMA intake through drinking water relative to total NDMA intake, the ADD was estimated for all oral route sources and only exogenous sources. Both measured and simulated data are used to estimate the levels of NDMA formed endogenously.

### Exposure model

Probabilistic exposure models allow for a robust examination of the factors leading to exposures and provide the

<sup>3</sup> Compounds such as thiocyanate, iodide and bromide, can catalyze nitrosation, whereas ascorbic acid, α-tocopherol and thiols can inhibit the reaction. Tannic acid, propyl gallate, vanillin, chlorogenic acid and thymol are phenols that may have an inhibitory effect on the formation of N-nitroso compounds.

ability to evaluate the impacts of parameter uncertainty and variability within the model as well as addressing high-risk populations. Consumption rates are highly variable in the population so using a single-point estimate for these variables instead of probability distributions ignores inherent variability that may influence exposure estimates. Monte Carlo methods lead to an approximation of a sampling distribution by statistically incorporating parameter probability distributions and treating observed data as if they were an unknown population (Cullen & Frey 1999). However, in the case of exposure to waterborne contaminants, Wilkes (1996) has shown that a strictly probabilistic framework fails to accurately estimate exposure and a more realistic approach combines probabilistic human behavior and physiological parameters with a deterministic calculation of water concentrations leading to exposure. We developed an exposure model that employed NDMA concentration point estimates for each source and parametric distributions of averaging times, exposure duration, intake rates and body weight under the assumption of independence of the parameters. Using the models shown in Equation 1 and 2, we computed the ADD and lifetime average daily dose (LADD), respectively, from the output of a Monte Carlo simulation consisting of 10,000 iterations, using SAS v 9.1.2<sup>®</sup> (SAS Institute, Cary, NC). POI was calculated (see Equation 3) from these ADD estimates.

$$ADD_{jk} = \frac{\sum_{i=1}^9 C_i \cdot IR_{ij}}{BW_j} \quad (1)$$

where:

$ADD_{jk}$  = Average Daily Dose ( $\mu\text{g}/\text{kg}\cdot\text{day}$ ) for the  $j$ th age group and  $k$  source

$C_i$  = NDMA Concentration ( $\mu\text{g}/\text{g}$  or  $\mu\text{g}/\text{L}$ ) for the  $i$ th source

$IR_{ij}$  = Intake rate ( $\text{g}/\text{day}$  or  $\text{L}/\text{day}$ ) for the  $i$ th source and  $j$ th age group

$BW_j$  = Body weight (kg) for the  $j$ th age group

$i$  = NDMA source (nine sources identified in Table 2);  $j$  = a (infant), b (child) and c (adult)  $k$  source categories = w (water), all (all oral route sources) and ex (exogenous sources only)

$$LADD_{jk} = \sum_{j=1}^3 \left( \frac{ED_j}{LT} \cdot ADD_{jk} \right) \quad (2)$$

where:

$LADD_k$  = Lifetime Average Daily Dose ( $\mu\text{g}/\text{kg}\cdot\text{day}$ ) for the  $k$ th source

$ED_j$  = Time (years) in the  $j$ th age group

$LT$  = Lifetime (75 years)

$ADD_{jk}$  = Average Daily Dose ( $\mu\text{g}/\text{kg}\cdot\text{day}$ ) for the  $j$ th age group and  $k$ th source

$j$  = a (infant), b (child) and c (adult)  $k$  source categories = w (water), all (all oral route sources) and ex (exogenous sources only)

$$POI = \left( \frac{ADD_{jw}}{ADD_{jk}} \cdot 100 \right) \text{ or } \left( \frac{LADD_w}{LADD_k} \cdot 100 \right) \quad (3)$$

where:

$POI$  = Proportional oral route intake attributable to Drinking Water (%)

$ADD_{jk}$  = Average Daily Dose ( $\mu\text{g}/\text{kg}\cdot\text{day}$ ) for the  $j$ th age group and  $k$ th source

$LADD_k$  = Lifetime Average Daily Dose ( $\mu\text{g}/\text{kg}\cdot\text{day}$ ) for the  $k$ th source

$j$  = a (infant), b (child) and c (adult)  $k$  source categories = w (water), all (all oral route sources) and ex (exogenous sources only)

## ASSUMPTIONS

The exposure models were based on the following assumptions:

- Individuals within a specific age group receive the same daily NDMA exposure from foods and drinking water during that exposure period
- The bioavailability of NDMA is constant regardless of the exposure source
- NDMA concentrations in foods (including those calculated from non-U.S. sources) and drinking water are representative of levels encountered in the U.S.
- Exposures from endogenous and exogenous sources are additive

- Food intake rates follow an empirical distribution (EPA 1997a)
- Water intake rates (Roseberry & Burmaster 1992), chemical concentrations (Singh *et al.* 1997) and body weights (Burmaster & Crouch 1997) follow a lognormal distribution
- Bottle-fed infants do not consume foods rich in amines, nitrites or nitrates and, consequently, do not form NDMA endogenously
- The average life expectancy in the U.S. is 75 years (CDC 1997).

## Parameters

### Food ingestion rates

Distributions of daily intake rates ( $IR_{ij}$ ) for cereals, dairy (powdered milk and cheese), fish, meat, and vegetables were developed from per-capita estimates of food-specific intake rates reported in the *Exposure Factors Handbook* (EFH) (EPA 1997b). An intake rate distribution for powdered infant formula was developed from a 1984 study on food intake of infants (Köhler *et al.* 1984). An intake rate distribution for beer was developed from data reported in the National Epidemiological Survey on Alcohol and Related Conditions (NESARC 2002). The distribution of intake rates for foods high in nitrite and nitrate levels was developed from estimates of per-capita intake rates for beets, lettuce, spinach and pork reported in the *CSFII Analysis of Food Intake Distributions* (EPA 2003). All intake rates used in this analysis are summarized in Table 1.

### Drinking water ingestion rates

Distributions of U.S. drinking water intake rates were developed for adults and children using mean and standard deviation values reported in Jacobs *et al.* (2000). Distributions of drinking water intake rates for infants, not accounting for water used to reconstitute powdered formula, were developed using mean and standard deviation values reported in a population-based study of drinking water intake in the U.S. conducted by Ershow & Cantor (1989).

### Body weight

Body weight distributions were developed using values reported in the EFH for infants ( $BW_a$ ) ( $\mu = 6.6$  kg  $\sigma = 0.09$ ), children ( $BW_b$ ) ( $\mu = 33.7$  kg  $\sigma = 6.6$ ) and adults ( $BW_c$ ) ( $\mu = 71.9$  kg  $\sigma = 13.7$ ) (EPA 1997a).

### NDMA concentrations in drinking water

NDMA concentrations in drinking water were estimated from a 2001-02 survey of 21 U.S. and Canadian drinking water treatment plants that reported a range of NDMA levels from below the MRL of  $6 \times 10^{-4}$   $\mu\text{g/L}$  to  $2.4 \times 10^{-2}$   $\mu\text{g/L}$  (Valentine *et al.* 2006). Although samples were collected at all stages in the treatment process, we restricted our analysis to those collected from distribution (finished) waters because NDMA concentrations in these waters were expected to be most similar to those found at the tap. These and other concentration estimates are shown in Table 2.

In order to test for the existence of measurements that are outside the expected range and may significantly influence the statistical inferences of the dataset (outliers), the first quartile ( $q1$ ), third quartile ( $q3$ ) and inter-quartile range ( $iqr$ ) were computed from natural logarithms of the Valentine *et al.* data (2006) using PROC UNIVARIATE in SAS v9.1.2<sup>®</sup>. Values that were  $(3 * iqr) > q3$  or  $(3 * iqr) < q1$  were identified as potential outliers. Based on our calculations, six out of 95 distribution water measurements, 0.01, 0.012, 0.015, 0.016, 0.022 and 0.024  $\mu\text{g/L}$ , were identified as extreme values and eliminated from the analysis dataset. Of the remaining 89 distribution-water samples, 34 (38%) had levels reported as ND. Of the 21 utilities, seven treated with chlorine and 14 with chloramine. Chlorine treated systems comprised 26 of the distribution water samples with 17 (65%) reported as ND. Chloramine treated systems comprised 63 of the distribution water samples with 17 samples (27%) reported as ND.

Due to difficulties in analytical procedures used in the beginning of the study, the authors switched MRLs from  $1 \times 10^{-3}$   $\mu\text{g/L}$  to  $6 \times 10^{-4}$   $\mu\text{g/L}$ , which was used for most samples (Barrett, 2005). Values above the MRL, which is three times the DL, are considered to differ significantly from zero and those below the MRL were censored and reported as non-detects (ND) (Barrett 2005). Commonly

**Table 1** | Ingestion rates for selected foods and drinking water used in developing parametric distributions

Parameter	Units	Infant		Child		Adult		Reference
		$\mu$	$\sigma$	$\mu$	$\sigma$	$\mu$	$\sigma$	
Body weight	Kg	6.6	0.12	33.7	6.6	71.9	13.7	(EPA 1997a)
Cereal	g/day			21.9	6.0	16.6	3.6	(EPA 1997b)
Dairy	g/day			43.6	17.3	33.6	12.5	
Fish	g/day			13.9	50.0	17.4	54.0	
Meat	g/day			96.8	5.1	126.6	1.9	
Vegetables	g/day			169.9	20.5	187.0	5.8	
Beer	L/day					0.24	0.54	(NESARC 2002)
Formula	L/day	0.82	0.15					(Köhler <i>et al.</i> 1984)
Nitrite/nitrate sources*	g/day			18.7	1.1	43.1	4.0	(EPA 2003)
Water	L/day	0.30	0.26	0.85	0.48	1.5	0.64	(Ershow & Cantor 1989; Jacobs <i>et al.</i> 2000)

$\mu$  = mean;  $\sigma$  = standard deviation about the mean.

\*Per capita intake rates for cured meats were used for nitrite sources. Per capita intake rates for beets, celery and spinach were used for nitrate sources. The values shown in the table reflects the sum of the mean values for each source for each age group.

**Table 2** | NDMA concentrations in foods and drinking water

Source	Units	$\mu$	$\sigma$	Reference
Beer	$\mu\text{g/L}$	$7.3 \times 10^{-2}$	+	(Scanlan <i>et al.</i> 1990)
Cereals	$\mu\text{g/g}$	$1.8 \times 10^{-4}$	+	(Tricker <i>et al.</i> 1991; Biaudet <i>et al.</i> 1994)
Dairy	$\mu\text{g/g}$	$7.9 \times 10^{-4}$	+	
Fish	$\mu\text{g/g}$	$8.2 \times 10^{-4}$	+	
Meat	$\mu\text{g/g}$	$3.7 \times 10^{-4}$	+	
Vegetables	$\mu\text{g/g}$	$7.5 \times 10^{-5}$	+	
Formula*	$\mu\text{g/L}$	$8.3 \times 10^{-2}$	+	(Libbey <i>et al.</i> 1980; Sen & Seaman 1981)
Nitrosation, <i>in vitro</i>	$\mu\text{g/g}$	0.53	0.30	(Krul <i>et al.</i> 2004)
Water	$\mu\text{g/L}$	$2.1 \times 10^{-3}$	$2.9 \times 10^{-4}$	(Valentine <i>et al.</i> 2006)

\*Reflects NDMA concentration in formula powder and in drinking water used to reconstitute.

*In vitro* refer to the type of study used for calculation of endogenous NDMA formation.

+Not reported.

used substitution methods, such as replacing censored values with half the MRL, are inappropriate for this study due to the high percentage of ND and multiple detection limits reported by Valentine *et al.* (2006). Replacement values are often arbitrary and do not necessarily represent the true value in a sample, resulting in estimates with a larger bias and mean square error than methods such as maximum likelihood estimation (MLE). For data sets of at least 50 observations, MLE provides a robust method for estimating descriptive statistics from a distribution of observed values (Helsel 2004). Under the assumption that the data below and above the MRL follow a lognormal distribution, the values above the MRL and the proportion of data below the MRL are used to solve a log-likelihood function  $L$ . For a distribution with mean  $\beta_1$  and standard deviation  $\beta_2$ ,  $L(\beta_1, \beta_2)$  defines the likelihood of matching the observed distribution of the data (Helsel 2004). MLE was computed with an expectation maximization algorithm (EM) method using PROC MI in SAS<sup>®</sup> v9.1.2. EM is a series of iterations of a simulation over a censored dataset consisting of an expectation (E) step followed by a maximization (M) step. In the E-step, the expected  $L$  for the data is computed where the expectation is taken with respect to observed data; in the M step, all the parameters are re-estimated by maximizing the  $L$  until it reaches a local maxima (Dempster *et al.* 1977).

#### NDMA concentrations in powdered infant formula reconstituted with drinking water

Estimating NDMA concentrations in powdered infant formula reconstituted with drinking water required several steps. The mean ratio of powdered formula to water (144.8 g/L) was calculated from information given in the preparation instructions of three powdered infant formula brands<sup>4</sup>. The NDMA concentration in infant formula powder ( $5.6 \times 10^{-4}$   $\mu\text{g/g}$ ) was calculated from two studies (Libbey *et al.* 1980; Sen & Seaman 1981). The product of the ratio of powdered formula to water and the formula powder NDMA concentration ( $8.1 \times 10^{-2}$   $\mu\text{g/L}$ ) was added to the

mean NDMA water concentration ( $2.1 \times 10^{-3}$   $\mu\text{g/L}$ ) from the Valentine *et al.* (2006) to obtain a point estimate for NDMA in reconstituted infant formula of  $8.3 \times 10^{-2}$   $\mu\text{g/L}$ .

#### NDMA concentrations in foods

Distributions of NDMA concentrations in meat, fish, dairy, cereal and vegetables were based on the results of a French study conducted from 1987 to 1992 (Biaudet *et al.* 1994) and a German study conducted from 1989 to 1990 (Tricker *et al.* 1991). Several studies identified dietary sources of nitrites and nitrates (Walker 1990; NRC 1995). Distributions of NDMA concentrations in beer were developed from values reported in two surveys of North American beers (Scanlan *et al.* 1990; Scanlan & Barbour 1991).

#### NDMA concentrations from endogenous formation

*In vivo* studies of endogenous NDMA formation provided estimates only for adults, necessitating the use of an *in vitro* study that reported estimated levels of NDMA formed from nitrosation of food and nitrites within a dynamic gastrointestinal model under simulated human physiological conditions (Krul *et al.* 2004). Krul *et al.* (2004) used 2X and 10X the acceptable daily intake (ADI) of nitrite level in combination with codfish as a source of nitrosatable precursors at an average pH of 3. We chose this study over other *in vitro* studies because it appeared to best simulate the conditions under which foods were digested. We normalized the data to the nitrite ADI and multiplied by a factor of three meals per day yielding an estimate of 0.37  $\mu\text{g}$  NDMA formed endogenously per gram of nitrate/nitrite-rich food ingested.

We also estimated endogenous formation for the adult ADD and the LADD using the results of an *in vivo* study by Vermeer *et al.* (1998). The study of 25 participants reported a significant correlation between NDMA levels in urine, and intake of nitrate (at the ADI level) with a meal of fish rich in amines (Vermeer *et al.* 1998). Assuming 0.5% of NDMA formed is excreted in urine (Spiegelhalter *et al.* 1982), 174  $\mu\text{g}$  of NDMA per day was estimated to form endogenously in adults (Vermeer *et al.* 1998) which is significantly higher than those calculated using the *in vitro* data.

<sup>4</sup> The three brands used were Good Start<sup>®</sup> manufactured by Nestle, Similac<sup>®</sup> manufactured by Mead Johnson, and Enfamil<sup>®</sup> manufactured by Abbott Laboratories. Mention of trade names or commercial products does not constitute endorsement or recommendation for use by the EPA.

### Identifying contributors to variability and uncertainty

To identify those parameters having the greatest impact on the variability in the model results, a sensitivity analysis was performed to measure the potential importance of the model inputs to the variance of the ADD estimates. A sensitivity analysis ranks model inputs with respect to their contribution to model output variability or uncertainty (Iman & Helton 1991). Spearman Rank correlation coefficients ( $\theta$ ) were calculated for the ADD and LADD models using SAS<sup>®</sup> v9.1.2, with all  $\theta$  corresponding to a p-value of  $<0.0001$  reported in this study. A nonparametric measure of association,  $\theta$  is based on the ranks of the data values and is sensitive to the strength of linear relationships and ranges of variation of a model relative to its inputs (Cullen & Frey 1999).

## RESULTS

Bottle-fed infants received their largest NDMA exposure dose from powdered infant formula reconstituted with drinking water, contributing  $0.07 \mu\text{g}/\text{day}$  ( $\sigma = 0.01$ ) or 98% of total intake. The largest source of NDMA intake for children [ $9.96 \mu\text{g}/\text{day}$  ( $\sigma = 5.7$ )] and adults [ $23.1 \mu\text{g}/\text{day}$  ( $\sigma = 13.5$ )] is predicted to be from endogenous formation, contributing 99% of total intake for both age groups. The next largest source of daily NDMA intake for children and adults, on average, is meat ( $0.04 \mu\text{g}/\text{day}$ ), contributing 0.30% of total intake. Daily intake for all sources is summarized in Table 3. Results from a preliminary sensitivity analysis indicated that endogenous nitrosation contributed over 99% to the variance, dominating the overall uncertainty and obscuring the contributions of other model parameters. Because of this dominance, endogenously formed NDMA was excluded from the final sensitivity analysis. The ADD, LADD and POI estimates and sensitivity analysis results are summarized below and in Table 4.

### Lifetime

Over a 75-year lifetime, the estimated LADD of NDMA in drinking water was  $7.3 \times 10^{-7} \mu\text{g}/\text{kg}\text{-day}$ . The LADD from all sources was estimated to be  $4.4 \times 10^{-5} \mu\text{g}/\text{kg}\text{-day}$

(POI = 0.02%) and  $0.03 \mu\text{g}/\text{kg}\text{-day}$  (POI = 0.003%) using *in vitro* and *in vivo* estimates of endogenous NDMA formation, respectively. Exogenous sources contributed  $2.6 \times 10^{-5} \mu\text{g}/\text{kg}\text{-day}$  (POI = 2.8%). Excluding endogenous sources, the results were well correlated with adult fish IR ( $\theta = 0.44$ ), child fish IR ( $\theta = 0.26$ ), adult dairy IR ( $\theta = 0.10$ ) and child dairy IR ( $\theta = 0.09$ ).

### Adults ( $\geq 18$ Years)

For adults, the estimated ADD of NDMA in drinking water was  $4.8 \times 10^{-5} \mu\text{g}/\text{kg}\text{-day}$ . The LADD from all ingestion sources was estimated to be  $0.33 \mu\text{g}/\text{kg}\text{-day}$  (POI = 0.01%).  $2.5 \mu\text{g}/\text{kg}\text{-day}$  (POI = 0.002%) using *in vitro* and *in vivo* estimates of endogenous NDMA formation, respectively. Exogenous sources contributed  $1.6 \times 10^{-3} \mu\text{g}/\text{kg}\text{-day}$  (POI = 3.1%). Excluding endogenous sources, the results were well correlated with fish IR ( $\theta = 0.75$ ) and dairy IR ( $\theta = 0.17$ ).

### Children ( $>6$ months $< 18$ years)

For children, the estimated ADD of NDMA in drinking water was  $7.1 \times 10^{-5} \mu\text{g}/\text{kg}\text{-day}$ . The ADD from all ingestion sources was estimated to be  $0.31 \mu\text{g}/\text{kg}\text{-day}$  (POI = 0.02%) with exogenous sources contributing  $3.1 \times 10^{-3} \mu\text{g}/\text{kg}\text{-day}$  (POI = 2.3%). Excluding endogenous sources, the results were well correlated with fish IR ( $\theta = 0.67$ ) and dairy IR ( $\theta = 0.21$ ).

### Bottle-fed infants ( $<6$ months)

Bottle-fed infants were assumed to be exposed only to preformed NDMA in formula and drinking water used to reconstitute the powdered formula; we assumed no endogenous formation of NDMA in this age group. The ADD for NDMA in drinking water was estimated to be  $2.0 \times 10^{-4} \mu\text{g}/\text{kg}\text{-day}$ . The ADD from formula and drinking water was estimated to be  $0.01 \mu\text{g}/\text{kg}\text{-day}$ , with a POI of 1.9%. This result was well correlated with formula IR ( $\theta = 0.90$ ) and drinking water IR ( $\theta = 0.08$ ).



**Table 3** | Daily NDMA intake ( $\mu\text{g}/\text{day}$ ) calculated from a randomly generated sample of 10,000

Category	$\mu$	$\sigma$	p50*	p95	% all
<i>Infant</i>					
Water	$1.3 \times 10^{-3}$	$2.2 \times 10^{-3}$	$6.2 \times 10^{-4}$	$4.5 \times 10^{-3}$	1.9
Formula	0.07	0.01	0.07	0.09	98.1
All	0.07	0.01	0.07	0.09	
<i>Child</i>					
Water	$2.3 \times 10^{-3}$	$2.0 \times 10^{-3}$	$1.8 \times 10^{-3}$	$5.9 \times 10^{-3}$	0.02
Cereals	$4.0 \times 10^{-3}$	$1.1 \times 10^{-3}$	$4.0 \times 10^{-3}$	$5.8 \times 10^{-3}$	0.04
Dairy	0.03	0.01	0.03	0.06	0.34
Fish	0.01	0.04	0.04	0.08	0.12
Meat	0.04	$1.8 \times 10^{-3}$	0.04	0.04	0.40
Vegetables	0.01	$1.5 \times 10^{-3}$	0.01	0.02	0.13
Endogenous	9.9	5.7	8.6	21.0	99.0
All	10.1	5.7	8.7	21.1	
Exogenous	0.10	0.04	0.10	0.17	0.01
<i>Adult</i>					
Water	$3.3 \times 10^{-3}$	$1.6 \times 10^{-3}$	$3.0 \times 10^{-3}$	$6.4 \times 10^{-3}$	0.01
Beer	0.02	0.04	0.02	0.08	0.08
Cereals	$3.0 \times 10^{-3}$	$6.5 \times 10^{-4}$	$3.0 \times 10^{-3}$	$4.0 \times 10^{-3}$	0.01
Dairy	0.03	0.01	0.03	0.04	0.11
Fish	0.02	0.04	0.02	0.09	0.07
Meat	0.05	$7.0 \times 10^{-4}$	0.05	0.05	0.20
Vegetables	0.01	$4.2 \times 10^{-4}$	0.01	0.01	0.06
Endogenous	22.9	13.5	19.7	48.7	99.5
All	23.1	13.5	19.8	48.8	
Exogenous	0.11	0.05	0.11	0.18	0.01

\*The pth percentile of a data set is a value such that at least p percent of the data or less is reported and at least (100-p) percent of the data or more is reported

**Table 4** | Average daily dose ( $\mu\text{g}/\text{kg}\cdot\text{day}$ ) and proportional oral intake (%) estimates for NDMA in foods and drinking water calculated from a randomly generated sample of 10,000

Category	ADD ( $\mu\text{g}/\text{kg}\cdot\text{day}$ )					POI (%)
	$\mu$	$\sigma$	p10	p50	p95	
<i>Infant</i>						
Water	$2.0 \times 10^{-4}$	$3.4 \times 10^{-4}$	$2.0 \times 10^{-5}$	$9.4 \times 10^{-5}$	$7.1 \times 10^{-4}$	
All sources	0.01	$1.9 \times 10^{-3}$	$8.1 \times 10^{-3}$	$1.1 \times 10^{-2}$	$1.4 \times 10^{-2}$	1.9
<i>Child</i>						
Water	$7.1 \times 10^{-5}$	$6.5 \times 10^{-5}$	$1.9 \times 10^{-5}$	$5.3 \times 10^{-5}$	$1.9 \times 10^{-4}$	
All sources	0.31	0.19	0.13	0.26	0.69	0.02
Exogenous	$3.1 \times 10^{-3}$	$1.6 \times 10^{-3}$	$1.3 \times 10^{-3}$	$3.0 \times 10^{-3}$	$5.8 \times 10^{-3}$	2.3
<i>Adult</i>						
Water	$4.8 \times 10^{-5}$	$2.7 \times 10^{-5}$	$2.2 \times 10^{-5}$	$4.2 \times 10^{-5}$	$9.9 \times 10^{-5}$	
All sources <sub>in vitro</sub>	0.33	0.21	0.14	0.28	0.74	0.01
All sources <sub>in vivo</sub>	2.5	0.57	1.9	2.4	3.5	0.002
Exogenous	$1.6 \times 10^{-3}$	$7.6 \times 10^{-4}$	$6.7 \times 10^{-4}$	$1.5 \times 10^{-3}$	$2.9 \times 10^{-3}$	3.1
<i>Lifetime</i>						
Water	$7.3 \times 10^{-7}$	$3.5 \times 10^{-7}$	$3.8 \times 10^{-7}$	$6.6 \times 10^{-7}$	$1.4 \times 10^{-6}$	
All sources <sub>in vitro</sub>	$4.4 \times 10^{-3}$	$2.7 \times 10^{-3}$	$1.8 \times 10^{-3}$	$3.7 \times 10^{-3}$	$9.5 \times 10^{-3}$	0.02
All sources <sub>in vivo</sub>	0.03	0.01	0.02	0.03	0.04	0.003
Exogenous	$2.6 \times 10^{-5}$	$9.1 \times 10^{-6}$	$1.6 \times 10^{-5}$	$2.6 \times 10^{-5}$	$4.2 \times 10^{-5}$	2.8

Note: POI values shown are calculated from non-rounded ADD and LADD estimates.

Exogenous and endogenous refer to the sources of NDMA; *in vitro* and *in vivo* refer to the type of study used for endogenous NDMA formation.

## Outlier influence

As discussed in the methods section, we excluded six values of NDMA in drinking water from the analysis because they were considered outliers. Had we included these values in our analysis, the mean NDMA water concentration would increase from  $2.1 \times 10^{-3}$  to  $3.7 \times 10^{-3}$   $\mu\text{g}/\text{L}$ . POI estimates would also increase, on average, 70% (e.g. relative to all sources the POI would increase from  $1.7 \times 10^{-3}$  to  $2.9 \times 10^{-3}$ %).

## DISCUSSION

The validity of our exposure models are contingent upon assumptions about age-related exposure, bioavailability, appropriateness of the data used, shapes of the distribution of data and the relationship of endogenous and exogenous sources. The ubiquitous nature of NDMA, combined with a lack of data on NDMA in U.S. foods and drinking waters, as well as our limited confidence in the estimates of the

quantities of NDMA formed endogenously, introduces a substantial level of uncertainty and variability into our exposure estimates.

The model data were obtained from peer-reviewed publications. We identified no recent, systematic evaluations on the occurrence of NDMA in U.S. foods. The preponderance of data on levels of NDMA in foods is available from studies conducted during the 1970s and 1980s. These studies used different analytical methods than those available for NDMA today. In addition, efforts undertaken in the 1990's reduced potential NDMA levels in foods worldwide (Sen & Baddoo 1997). We assumed that NDMA levels reported by Biaudet *et al.* (1994) and Tricker *et al.* (1991), were similar to those in U.S. foods and that these European data are a reasonable surrogate for calculating nationally representative U.S. estimates. The study used to estimate drinking water levels consisted of a statistically small number of drinking water treatment plants. Additional U.S. food and drinking water concentration data are needed to confirm our POI estimates.

Estimates of NDMA concentrations from endogenous formation are uncertain because little information on the levels normally produced during digestion is available. Based on distinct sources of data, two estimates of endogenously NDMA formed were developed because of this uncertainty. The differences among the LADD estimates, including and excluding endogenously formed NDMA, are predicted to be quite large. When endogenous sources are excluded from the LADD calculations, the POI estimates increase dramatically.

Our study results are consistent with those of a recently released WHO (2006) report, in which the ADD of NDMA from ingestion of drinking water for a 60 kg adult with a drinking water intake of 2 L/day was estimated to be  $3.0 \times 10^{-5}$  to  $1.0 \times 10^{-3}$   $\mu\text{g}/\text{kg}\cdot\text{day}$ , based on a mean NDMA concentration of 0.012  $\mu\text{g}/\text{L}$  and a maximum concentration of 0.04  $\mu\text{g}/\text{L}$  obtained from 20 samples from four water treatment plants in Canada (WHO 2006). By contrast, our study used a body weight of 72 kg and a drinking water intake of 1.5 L/day for adults and estimated the mean ADD to be  $4.8 \times 10^{-5}$   $\mu\text{g}/\text{kg}\cdot\text{day}$  based on a mean NDMA concentration of  $2.1 \times 10^{-3}$   $\mu\text{g}/\text{L}$  obtained from 89 samples from 21 water treatment plants in the U.S. and Canada. WHO stated that the relative contribution of drinking water is expected to be below

10% of total exposure, which is consistent with our estimates. Other differences between the studies include (1) our consideration of the potential contribution of endogenous sources of NDMA and (2) our use of probabilistic models.

Our assessment focuses on a single route of exposure. As noted previously, inhalation route exposures from ETS could increase total NDMA exposure. NDMA concentrations in soil are unavailable, so we could not estimate dermal or ingestion exposures of NDMA-contaminated soils. If these exposures are significant, the POI would be reduced. Ideally, exposures across multiple routes and additional pathways could be integrated with ingestion exposures through a physiologically based, pharmacokinetic model and POI estimates could be based on internal dose estimates. During the literature search, we did not identify data needed to develop such a model.

Other nitrosamines, such as N-Nitrosodiethylamine (NDEA), N-Nitrosodi-n-propylamine (NDPA), N-Nitrosodi-n-butylamine (NDBA), N-Nitrosomethylethylamine (NMEA) and N-Nitrosopyrrolidine (NYPR), have been reported in foods, beverages, drugs, and tobacco smoke (NTP 2005) and are classified as probable carcinogens (EPA 1987a, b, 1991a, b, c). The formation of these nitrosamines in treated drinking waters may depend on a particular treatment method employed creating the potential for one treatment approach to remove one targeted nitrosamine while inadvertently introducing another (Munch 2005). Analyses of the formation mechanisms and concentrations of these nitrosamines are needed to thoroughly assess nitrosamines in treated waters.

To place our POI estimates further into perspective, we recalculated the LADD using 90th percentile drinking water intake rates. On average, there was a 7-fold increase in the LADD for water ( $5.1 \times 10^{-6}$   $\mu\text{g}/\text{kg}\cdot\text{day}$ ) and a 17% increase in the LADD for exogenous sources ( $3.1 \times 10^{-5}$   $\mu\text{g}/\text{kg}\cdot\text{day}$ ). There was no significant difference in the LADD for all sources reflecting the strong contribution of endogenously formed NDMA. These results suggest that although there was an increase in the POI values observed using upper percentile drinking water intake values, NDMA exposure from consumption of drinking water is still predicted to be low relative to other ingestion route sources of NDMA. In a separate analysis, we determined that the mean concentration of NDMA in drinking water would need to increase from

$2.1 \times 10^{-3} \mu\text{g/L}$  to  $0.10 \mu\text{g/L}$ , a 47-fold increase, for the POI to reach 1%, relative to all sources of NDMA considered in our model.

## CONCLUSION

The results of our analysis suggest that the occurrence of NDMA in finished drinking water leads to U.S. population exposures that are low relative to other ingestion route NDMA sources. Although the concentrations of NDMA in food are often small and human exposure to NDMA in foods is quite low, the NDMA contribution from food is still predicted to be high relative to the NDMA in drinking water. The contribution of the NDMA formed endogenously through the nitrosation of ingested secondary and tertiary amines increases the total NDMA encountered and diminishes the contribution of contaminated drinking water ingestion to total NDMA exposure.

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## DISCLAIMER

Although this work was reviewed by the EPA and approved for publication, it may not necessarily reflect official Agency policy.

## REFERENCES

ATSDR 1989 *Toxicological Profile for N-Nitrosodimethylamine (Final Report)*. Agency for Toxic Substances and Disease

- Registry, Public Health Service, U.S. Department of Health and Human Services, Atlanta, GA.
- Barrett, S. 2005 Personal Communication 02/03.
- Biaudet, H., Mavelle, T. & Debry, G. 1994 Mean daily intake of N-Nitrosodimethylamine from foods and beverages in France in 1987-1992. *Food Chem. Toxicol.* **32**(5), 417-421.
- Burmaster, D. E. & Crouch, E. A. 1997 Lognormal distributions for body weight as a function of age for males and females in the United States, 1976-1980. *Risk Anal.* **17**(4), 499-505.
- CADHS 2002 *California's Experience With NDMA in Drinking Water: Studies on the Occurrence of NDMA in Drinking Water*. California Department of Health Services, URL: <http://www.dhs.ca.gov/ps/ddwem/chemicals/ndma/studies.htm>. Accessed: 12/22/04.
- CADHS 2005 *Drinking Water Notification Levels*. California Department of Health Services, URL: <http://www.dhs.ca.gov/ps/ddwem/chemicals/AL/notificationoverview.pdf>. Accessed: 9/15/05.
- Cantor, K. P., Lynch, C. F., Hildesheim, M. E., Dosemeci, M., Lubin, J., Alavanja, M. & Craun, G. 1998 Drinking water source and chlorination by products: risk of bladder cancer. *Epidemiology* **9**(1), 21-28.
- CDC 1997 *U.S. Decennial Life Tables for 1989-91*. National Center for Health Statistics, U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Bethesda, MD.
- Choi, J., Duirk, S. E. & Valentine, R. L. 2002 Mechanistic studies of N-Nitrosodimethylamine (NDMA) formation in chlorinated drinking water. *J Environ. Monit.* **4**(2), 249-252.
- Choi, J. & Valentine, R. L. 2002 Formation of N-Nitrosodimethylamine (NDMA) from reaction of monochloramine: a new disinfection by-product. *Water Res.* **36**(4), 817-824.
- Choi, J. & Valentine, R. L. 2003 N-Nitrosodimethylamine formation by free-chlorine-enhanced Nitrosation of Dimethylamine. *Environ. Sci. Technol.* **37**(21), 4871-4876.
- Chung, M. J., Lee, S. H. & Sung, N. J. 2002 Inhibitory effect of whole strawberries, garlic juice or kale juice on endogenous formation of N-Nitrosodimethylamine in humans. *Cancer Lett.* **182**(1), 1-10.
- Cullen, A. C. & Frey, H. C. 1999 *Probabilistic Techniques in Exposure Assessment: A Handbook for Dealing With Variability and Uncertainty in Models and Inputs*. Plenum Press, New York.
- Dempster, A. P., Laird, N. M. & Rubin, D. B. 1977 Maximum likelihood from incomplete data via the EM algorithm. *Journal of the Royal Statistical Society, Series B.* **39**, 1-38.
- EPA 1987a *Integrated Risk Information System (IRIS): N-Nitroso-N-Methylethylamine (CASRN 10595-95-6)*. US Environmental Protection Agency, Office of Research and Development, URL: [http://www.epa.gov/iris/substance\\_nmbr=0179](http://www.epa.gov/iris/substance_nmbr=0179). Accessed: 2/28/06.
- EPA 1987b *Integrated Risk Information System (IRIS): N-Nitrosodi-N-Propylamine (CASRN 621-64-7)*. US Environmental Protection Agency, Office of Research and

- Development, URL: [http://www.epa.gov/iris/substance\\_nmbr=0177](http://www.epa.gov/iris/substance_nmbr=0177). Accessed: 2/28/06.
- EPA 1991a *Integrated Risk Information System (IRIS): N-Nitrosodi-N-Butylamine (CASRN 924-16-3)*. US Environmental Protection Agency, Office of Research and Development, URL: [http://www.epa.gov/iris/substance\\_nmbr=0037](http://www.epa.gov/iris/substance_nmbr=0037). Accessed: 2/28/06.
- EPA 1991b *Integrated Risk Information System (IRIS): N-Nitrosodiethylamine (CASRN 55-18-5)*. US Environmental Protection Agency, Office of Research and Development, URL: [http://www.epa.gov/iris/substance\\_nmbr=0042](http://www.epa.gov/iris/substance_nmbr=0042). Accessed: 2/28/06.
- EPA 1991c *Integrated Risk Information System (IRIS): N-Nitrosopyrrolidine (CASRN 930-55-2)*. US Environmental Protection Agency, Office of Research and Development, URL: [http://www.epa.gov/iris/substance\\_nmbr=0081](http://www.epa.gov/iris/substance_nmbr=0081). Accessed: 2/28/06.
- EPA 1993 *Integrated Risk Information System (IRIS): N-Nitrosodimethylamine (CASRN 62-75-9)*. US Environmental Protection Agency, Office of Research and Development, URL: [http://www.epa.gov/iris/substance\\_nmbr=0045](http://www.epa.gov/iris/substance_nmbr=0045). Accessed: 9/26/04.
- EPA 1994 *Region 9'S Preliminary Remediation Goals (PRG) Table*. US Environmental Protection Agency, Region 9, San Francisco, CA, URL: <http://www.epa.gov/region09/waste/sfund/prg/index.htm>. Accessed: 01/04/05.
- EPA 1997a *Exposure Factors Handbook, Volume I: General Factors*. US Environmental Protection Agency, Office of Research and Development, Washington, DC, EPA/600/P-95/002Fa.
- EPA 1997b *Exposure Factors Handbook, Volume II: Food Ingestion Factors*. US Environmental Protection Agency, Office of Research and Development, Washington, DC, EPA/600/P-95/002Fb.
- EPA 2003 *CSFII Analysis of Food Intake Distributions*. National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, EPA/600/R-03/029.
- EPA 2005 *Unregulated Contaminant Monitoring Regulation (UCMR) for Public Water Systems Revisions*. US Environmental Protection Agency. 49093-138, Washington, DC, 40 CFR Part 141.
- EPA 2006 *National Primary Drinking Water Regulations: Stage 2 Disinfectants and Disinfection Byproducts Rule (Stage 2 DBPR): Final Rule*. US Environmental Protection Agency, Washington, DC, pp. 387–493, 40 CFR (9,141,142).
- Ershow, A. G. & Cantor, K. P. 1989 *Total Water and Tap Water Intake in the United States: Population-Based Estimates of Quantities and Sources*. National Cancer Institute, Bethesda, MD, 263-MD-810264.
- FDA 1995a *FDA Compliance Policy Guides Manual: Sec. 578.500 Dimethylnitrosamine in Barley Malt*. US Food and Drug Administration, Washington, DC.
- FDA 1995b *FDA Compliance Policy Guides Manual: Sec. 500.450 Volatile N-Nitrosamines in Rubber Baby Bottle Nipples*. US Food and Drug Administration, Washington, DC.
- FDA 1996 *FDA Compliance Policy Guides Manual: Sec. 510.600 Dimethylnitrosamine in Malt Beverages*. US Food and Drug Administration, Washington, DC.
- Fiddler, W., Pensabene, J. W., Kushnir, I. & Piotrowski, E. G. 1973 Effect of frankfurter cure ingredients on N-Nitrosodimethylamine formation in a model system. *J Food Sci.* **38**, 714–715.
- Fiddler, W., Feinberg, J. I., Pensabene, J. W., Williams, A. C. & Dooley, C. J. 1975 Dimethylnitrosamine in souse and similar jellied cured-meat products. *Food Cosmet. Toxicol.* **13**, 653–654.
- Fine, D. H., Ross, R., Rounbehler, D. P., Silvergleid, A. & Song, L. 1977 Formation *in vivo* of volatile N-Nitrosamines in man after ingestion of cooked bacon and spinach. *Nature* **265**(5596), 753–755.
- Fine, D. H., Challis, B. C., Hartman, P. & Van Ryzin, J. 1982 Endogenous synthesis of volatile Nitrosamines: model calculations and risk assessment. In *N-Nitroso Compounds: Occurrence and Biological Effects* (ed. H. Bartsch, I. K. O'Neill, M. Castegnaro & M. Okada), pp. 379–396. International Agency for Research on Cancer, Lyon, France.
- Groenen, P. J., de Cock-Bethbeder, M. W., Bouwman, J. & Dhont, J. H. 1980 Formation of N-Nitrosamine and N-Nitrosamino acids from food products and Nitrite under simulated gastric conditions. *IARC Sci. Publ.* **31**, 215–229.
- Groenen, P. J., Luten, J. B., Dhont, J. H., de Cock-Bethbeder, M. W., Prins, L. A. & Vreeken, J. W. 1982 Formation of volatile N-Nitrosamines from food products, especially fish, under simulated gastric conditions. *IARC Sci. Publ.* **41**, 99–112.
- Havery, D. C., Kline, D. A., Miletta, E. M., Joe, F. L., Jr & Fazio, T. 1976 Survey of food products for volatile N-Nitrosamines. *J. Assoc. Off. Anal. Chem.* **59**(3), 540–546.
- Helsel, D. R. 2004 *Nondetects and Data Analysis: Statistics for Censored Environmental Data*. Wiley-Interscience, New York.
- Hildesheim, M. E., Cantor, K. P., Lynch, C. F., Dosemeci, M., Lubin, J., Alavanja, M. & Craun, G. 1998 Drinking water source and chlorination byproducts: risk of colon and rectal cancers. *Epidemiology* **9**(1), 29–35.
- Hile, J. P. 1983 *Volatile N-Nitrosamines in Rubber Baby Bottle Nipples and Pacifiers*. US Food and Drug Administration, Washington, DC, CFR, 48: 57014-17.
- Hoffman, D., Adams, J. D., Paide, J. J. & Hecht, S. 1980 *Chemical Studies on Tobacco Smoke, LXVIII Analysis of Volatile and Tobacco Specific Nitrosamines in Tobacco Products*. IARC Scientific Publication (51). International Agency for Research on Cancer, Lyon, France, pp. 507–516.
- Hoffmann, D., Adams, J. D. & Brunemann, K. D. 1987 A critical look at N-Nitrosamines in environmental tobacco smoke. *Toxicol. Lett.* **35**(1), 1–8.
- Hotchkiss, J. H. 1989 Preformed N-Nitroso compounds in food and beverage. *Cancer Surv.* **8**, 295–321.
- IARC 1978 *Some N-Nitroso Compounds: IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans*. International Agency for Research on Cancer, Lyon, France.

- Iman, R. L. & Helton, J. C. 1991 The repeatability of uncertainty and sensitivity analyses for complex probabilistic risk assessments. *Risk Anal.* **11**(4), 591–606.
- Jacobs, H. L., Du, J. T., Kahn, H. D. & Stralka, K. A. 2000 *Estimated Per Capita Water Ingestion in the United States, Based on Data Collected By the Usda 1994-96 Continuing Survey of Food Intakes By Individuals*. U.S. Environmental Protection Agency, Office of Water, Washington, DC, EPA/822/00/008.
- Jobb, D. B., Hunsinger, R. B., Meresz, O. & Taguchi, V. Y. 1995 Removal of N-Nitrosodimethylamine from the Ohsweken (Six Nations) water supply. In *Disinfection Dilemma: Microbiological Control Versus By-products* (ed. W. Robertson, R. Tobin & K. Kjartanson) American Water Works Research Foundation, Denver, CO, pp. 241–252.
- Kirmeyer, A., Martel, K., Thompson, G., Radder, L., Klement, W., LeChevallier, M., Baribeau, H. & Flores, A. 2004 *Optimizing Chloramine Treatment*, Second Edition. AWWA Research Foundation, Denver, CO.
- Köhler, L., Meeuwisse, G. & Mortenson, W. 1984 Food intake and growth of infants between six and twenty-six weeks of age on breast milk, cow's milk formula, and soy formula. *Acta Paediatr. Scand.* **73**, 40–48.
- Krul, C. A., Zeilmaker, M. J., Schothorst, R. C. & Havenaar, R. 2004 Intra-gastric formation and modulation of N-Nitrosodimethylamine in a dynamic *in vitro* gastrointestinal model under human physiological conditions. *Food Chem. Toxicol.* **42**(1), 51–63.
- Leaf, C. D., Wishnok, J. S. & Tannenbaum, S. R. 1989 Mechanism of endogenous nitrosation. *Cancer Surv.* **8**, 323–334.
- Libbey, L. M., Scanlan, R. A. & Barbour, J. F. 1980 N-Nitrosodimethylamine in dried dairy products. *Food Cosmet. Toxicol.* **18**(5), 459–461.
- Licht, W. R. & Deen, W. M. 1988 Theoretical model for predicting rates of Nitrosamine and Nitrosamide formation in the human stomach. *Carcinogenesis* **9**, 2227–2237.
- MADEP 2005 *Standards and Guidelines for Contaminants in Massachusetts Drinking Waters*. Commonwealth of Massachusetts, Department of Environmental Protection, Office of Research and Standards, Boston, MA, URL: <http://www.mass.gov/dep/brp/dws/files/dwstand.pdf>.
- Milligan, J. R., Zucker, P. F., Swann, P. F. & Archer, M. C. 1987 Absence of urinary N-Nitrosodimethylamine in fasting humans following alcohol consumption. *IARC Sci. Publ.* **84**, 297–298.
- Mirvish, S. S. 1974 Formation of N-Nitroso compounds: chemistry, kinetics, and *in vivo* occurrence. *Toxicology and Applied Pharmacology* **31**, 325–351.
- Mirvish, S. S. 1992 *In vivo* formation of N-Nitroso compounds: formation from Nitrite and Nitrogen Dioxide, and relation to gastric cancer. In *Nitrosamines and Human Cancer, Banbury Report 12* (ed. P. N. Magee) Cold Spring Harbor Laboratory, New York, pp. 227–241.
- Mitch, W. A. & Sedlak, D. L. 2004 Characterization and fate of N-Nitrosodimethylamine precursors in municipal wastewater treatment plants. *Environ. Sci. Technol.* **38**(5), 1445–1454.
- Mitch, W. A., Sharp, J. O., Trussell, R. R., Valentine, R. L., Alvarez-Cohen, L. & Sedlak, D. L. 2003 N-Nitrosodimethylamine (NDMA) as a drinking water contaminant: a review. *Environmental Engineering Science* **20**(5), 389–404.
- Munch, J. 2005 Personal Communication, 5/15.
- Najm, I., Teeffy, S. & Barrett, S. E. 2004 NDMA formation from water treatment polymers. In *Proceedings of the American Water Works Association Annual Conference*. New Orleans, LA (June 2004). American Water Works Research Foundation, Denver, CO (CD-Rom).
- Najm, I. & Trussell, R. R. 2001 NDMA formation in water and wastewater. *J AWWA.* **93**(2), 92–99.
- NESARC 2002 *National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)*. National Institute on Alcohol Abuse and Alcoholism, URL: <http://niaaa.census.gov/data.html>. Accessed: 09/15/05.
- NIOSH 1984 *National Occupational Exposure Survey (1981-83)*. National Institute for Occupational Safety and Health, Cincinnati, OH.
- NRC 1995 *Nitrate and Nitrite in Drinking Water*. Subcommittee on Nitrate and Nitrite in Drinking Water, Committee on Toxicology Board on Environmental Studies and Toxicology, Commission on Life Sciences, National Research Council, Washington, DC, p. 1.
- NTP 2005 *Report on Carcinogens*. Eleventh Edition. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program, Research Triangle Park, NC.
- OMOE 2003 *Technical Support Document for Ontario Drinking Water Standards, Objectives and Guidelines*. Ontario Ministry of the Environment, Ottawa, Canada.
- Ralt, D. & Tannenbaum, S. R. 1981 The role of bacteria in Nitrosamine formation. In *N-Nitroso compounds* (ed. R. A. Scanlan & S. R. Tannenbaum) American Chemical Society, Washington, DC, pp. 157–164.
- Richardson, S. D. 2003 Disinfection by-products and other emerging contaminants in drinking water. *Trends in Analytical Chemistry* **22**(10), 666–684.
- Roseberry, A. M. & Burmaster, D. E. 1992 Lognormal distributions for water intake by children and adults. *Risk Anal.* **12**(1), 99–104.
- Scanlan, R. A. & Barbour, J. F. 1991 N-Nitrosodimethylamine content of US and Canadian beers. *IARC Sci Publ.* **105**, 242–243.
- Scanlan, R. A., Barbour, J. F. & Chappel, C. I. 1990 A survey of N-Nitrosodimethylamine in US and Canadian beers. *J. Agric. Food Chem.* **38**, 442–443.
- Schreiber, I. M. & Mitch, W. A. 2005 Influence of the order of reagent addition on NDMA formation during chloramination. *Environ. Sci. Technol.* **39**(3–4), 3811–3818.
- Sen, N. P. 1972 The evidence for the presence of Dimethylnitrosamine in meat products. *Food Cosmet. Toxicol.* **10**, 219–223.
- Sen, N. P., Donaldson, B., Iyengar, J. R. & Panalaks, T. 1973 Nitrosopyrrolidine and Dimethylnitrosamine in bacon. *Nature* **241**, 473–474.

- Sen, N. P. & Seaman, S. 1981 Volatile N-Nitrosamines in dried foods. *J. Assoc. Off. Anal. Chem.* **64**(5), 1238–1242.
- Sen, N. P. & Baddoo, P. A. 1997 Trends in the levels of residual nitrite in Canadian cured meat products over the past 25 years. *Journal of Agricultural and Food Chemistry* **45**, 4714–4718.
- Sen, N. P., Tessier, L., Seaman, S. W. & Baddoo, P. A. 1985 Volatile and non-volatile Nitrosamines in fish and the effect of deliberate nitrosation under simulated gastric conditions. *J. Agric. Food Chem.* **33**, 264–268.
- Shapiro, K. B., Hotchkiss, J. H. & Roe, D. A. 1991 Quantitative relationship between oral Nitrate-reducing activity and the endogenous formation of N-Nitrosoamino acids in humans. *Food Chem. Toxicol.* **29**(11), 751–755.
- Siddiqui, M. & Atasi, K. 2001 NDMA occurrence and formation - a review. In *Proceedings of the American Water Works Association Annual Conference in Washington, DC*. American Water Works Research Foundation, Denver, CO (CD-Rom), p. 1, (June 2001).
- Singh, A. K., Singh, A. & Engelhardt, M. 1997 *The Lognormal Distribution in Environmental Applications*. US-EPA, Office of Research and Development, Office of Solid Waste and Emergency Response, Washington, DC, EPA600R-94006.
- Spiegelhalder, B., Eisenbrand, G. & Preussmann, R. 1982 Urinary excretion of N-Nitrosamines in rats and humans. In *N-Nitroso Compounds: Occurrence and Biological Effects, IARC Scientific Publications No 41* (ed. H. Bartsch, M. Castegnaro, I. O'Neill & M. Okada) International Agency for Research on Cancer, Lyon, France, pp. 44–449.
- Tomkins, B. A. & Griest, W. H. 1996 Determinations of N-Nitrosodimethylamine at part-per-trillion concentrations in contaminated groundwaters and drinking waters featuring Carbon-based membrane extraction disks. *Anal. Chem.* **68**(15), 2533–2540.
- Tomkins, B. A., Griest, W. H. & Higgins, C. E. 1995 Determination of N-Nitrosodimethylamine at parts per trillion in drinking waters and contaminated groundwaters. *Analytical Chemistry* **67**(23), 4387–4395.
- Tricker, A. R. & Kubacki, S. J. 1992 Review of the occurrence and formation of non-volatile N-Nitroso compounds in foods. *Food Addit. Contam.* **9**(1), 39–69.
- Tricker, A. R., Pfundstein, B., Theobald, E., Preussmann, R. & Spiegelhalder, B. 1991 Mean daily intake of volatile N-Nitrosamines from foods and beverages in West Germany in 1989–1990. *Food Chem. Toxicol.* **29**(11), 729–732.
- Tricker, A. R. & Preussmann, R. 1992 Volatile N-Nitrosamines in mainstream cigarette smoke: occurrence and formation. *Clin. Investig.* **70**(3–4), 283–289.
- Tricker, A. R., Pfundstein, B. & Preussmann, R. 1994 Nitrosatable secondary amines: exogenous and endogenous exposure and nitrosation in-vivo. In *Nitrosamines and Related N-Nitroso Compounds: Chemistry and Biochemistry* (ed. R. N. Leppky & C. J. Michejda) American Chemical Society, Washington, DC, pp. 93–101.
- Valentine, R. L., Zho Chen, J. C., Barrett, S. E., Cordelia Hwang, C., Guo, Y., Wehner, M., Fitzsimmons, S., Andrews, S. A., Werker, A. G., Brubacher, C. & Kohut, K. 2006 *Factors affecting the formation of NDMA in water and occurrence*. American Water Works Research Foundation, Denver, CO, pp. 99–138.
- Vermeer, I. T., Pachen, D. M., Dallinga, J. W., Kleinjans, J. C. & van Maanen, J. M. 1998 Volatile N-Nitrosamine formation after intake of Nitrate at the ADI level in combination with an amine-rich diet. *Environ. Health Perspect.* **106**(8), 459–463.
- Walker, R. 1990 Nitrates, Nitrites and N-Nitroso Compounds: a review of the occurrence in food and diet and the toxicological implications. *Food Addit. Contam.* **7**(6), 717–768.
- Westin, J. B. 1990 Ingestion of carcinogenic N-Nitrosamines by infants and children. *Arch Environ. Health.* **45**(6), 359–363.
- Wilkes, C. R., Small, M. J., Davidson, C. I. & Andelman, J. B. 1996 Modeling the effects of water usage and co-behavior on inhalation exposures to contaminants volatilized from household water. *J. Expo. Anal. Environ. Epidemiol.* **6**, 395–412.
- WHO 2006 N-Nitrosodimethylamine in drinking-water. In *Background document for development of WHO Guidelines for Drinking-water Quality*. World Health Organization, Geneva, Switzerland, pp. 3–22.

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