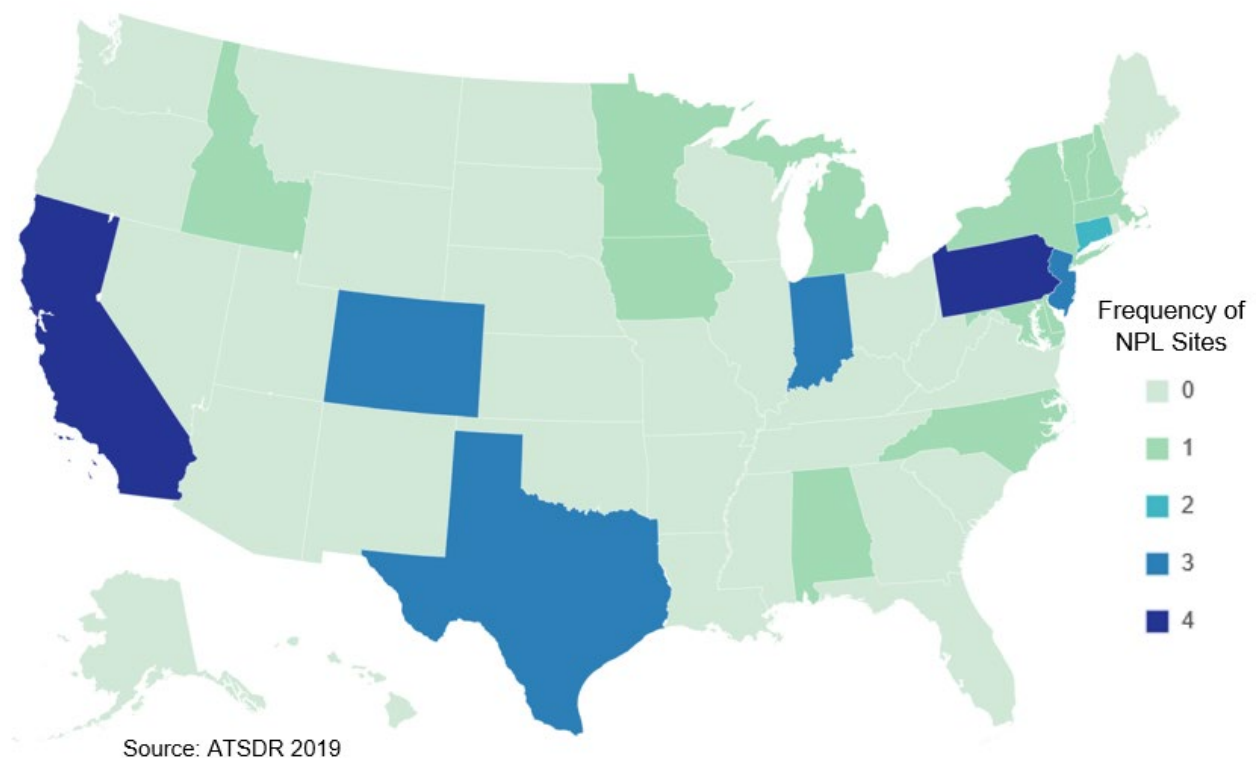


CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

NDMA has been identified in at least 34 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which NDMA has been evaluated is not known. The number of sites in each state is shown in Figure 5-1.

Figure 5-1. Number of NPL Sites with NDMA Contamination



- NDMA is naturally formed in the body from precursors that normally exist in the body and in foods. The general population may also be exposed to trace amounts of NDMA through ingesting foods containing nitrosamines such as cured or smoked meats and fish; ingesting foods containing alkylamines, which can form NDMA in the stomach; ingesting drinking water or malt beverages containing NDMA; and inhalation of tobacco smoke.
- NDMA has been detected in some prescription and over-the-counter pharmaceutical products (for example, valsartan, ranitidine, and metformin). Many of these substances have been recalled by the U.S. Food and Drug Administration (FDA) or the manufacturers, but exposure could have occurred prior to the recall or through continued use of purchased products.
- Potential occupational exposure to NDMA may occur in leather tanneries; rubber and tire industries; dye manufacturers; soap, detergent, and surfactant industries; foundries; fish-

5. POTENTIAL FOR HUMAN EXPOSURE

processing industries; pesticide manufacturers; warehouse and sales rooms (especially for rubber products); and research laboratories where NDMA is synthesized/studied.

- Very low levels of NDMA may form as an unintentional byproduct of the chlorination of drinking water at treatment plants that use chloramines and chlorine for disinfection. NDMA may also be formed in wastewater, but human exposure to wastewater is expected to be very limited.
- NDMA degrades rapidly by direct photolysis. In the absence of sunlight, NDMA will likely undergo biodegradation. NDMA is expected to have high mobility in soil and is unlikely to bioconcentrate in aquatic organisms.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

NDMA is not produced for commercial use in the United States (EPA 2014a) but can be prepared by reaction of nitrous acid with dimethylamine or by addition of acetic acid and sodium.

NDMA and other N-nitrosamines form as unintentional byproducts in water treatment plants using chloramines during the disinfection process. It has also been shown to form during chlorination and ozonation of treated drinking water if certain precursors are present (EPA 2016). NDMA in drinking water has become more prevalent because potable water utilities switched from predominantly free chlorine to chloramines for disinfection purposes in the early 2000s in response to EPA Maximum Contaminant Levels (MCLs) for regulated disinfection byproducts. The goal was to reduce the levels of four halomethanes (chloroform, bromodichloromethane, dibromochloromethane, and bromoform) as well as five haloacetic acids (mono-, di-, and trichloroacetic acid, bromoacetic acid, and dibromoacetic acid), which can form by reaction of chlorine or bromine with natural organic matter. Consequently, NDMA is observed as a disinfection byproduct in chloraminated drinking water systems more than free chlorine-based systems. The formation of NDMA from precursors and strategies for its removal are discussed in multiple reviews (Krasner et al. 2013, 2018; Sgroi et al. 2018; Tan et al. 2019). Leavey-Roback et al. (2016) studied the formation of NDMA at 20 water treatment facilities in Canada and the United States using chloramine disinfection and correlated water quality measurements and other treatment practices (e.g., pre-chlorination time, use of biofilters, etc.) to the level of NDMA that was formed during the treatment process. NDMA and other nitrosamines also occur unintentionally in certain foods, beverages, herbicides, and pharmaceutical products.

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-1 lists the facilities in each state that manufacture or process NDMA, the intended use, and the range of maximum amounts of nitrobenzene that are stored on site. The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥ 10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2005).

Table 5-1. Facilities that Produce, Process, or Use N-Nitrosodimethylamine

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AR	1	10,000	99,999	9, 12
IL	1	1,000	9,999	7, 12

^aPost office state abbreviations used.

^bAmounts on site reported by facilities in each state.

^cActivities/uses:

- | | | |
|----------------------|-----------------------------|--------------------------|
| 1. Produce | 6. Reactant | 11. Manufacture Aid |
| 2. Import | 7. Formulation Component | 12. Ancillary |
| 3. Used Processing | 8. Article Component | 13. Manufacture Impurity |
| 4. Sale/Distribution | 9. Repackaging | 14. Process Impurity |
| 5. Byproduct | 10. Chemical Processing Aid | |

Source: TRI21 2022 (Data are from 2021)

5.2.2 Import/Export

Data pertaining to the import of NDMA into the United States were not located in the available literature. It is unlikely that there are significant quantities of NDMA directly imported or exported to or from the United States.

5.2.3 Use

NDMA has been prepared in laboratory-scale quantities solely for use as a research chemical (EPA 2014a). NDMA was formerly used (prior to April 1, 1976) as an intermediate in the production of 1,1-dimethylhydrazine, a storable liquid rocket fuel, which was believed to have contained up to 0.1% NDMA as an impurity (IARC 1978). NDMA had also been used or proposed for use as an antioxidant,

5. POTENTIAL FOR HUMAN EXPOSURE

an additive for lubricants, and a softener for copolymers (Windholz 1983). NDMA had also been used as a solvent and rubber accelerator (Hawley 1981).

5.2.4 Disposal

Current information on recommended disposal method(s) for NDMA was not located. Combustion in an incinerator equipped with an afterburner and NO_x scrubber is the recommended method for disposing NDMA (Castegnaro et al. 1982). Liquid wastes should be neutralized, if necessary, filtered to remove solids, and then put into closed polyethylene containers for transport. All equipment should be thoroughly rinsed with solvent, which should be added to the liquid waste for incineration. Great care should be practiced to ensure that there is no contamination on the outside of the solvent container. If possible, solid waste should also be incinerated. If this is not possible, the nitrosamine should be extracted from the waste and the extract should be handled as a liquid waste. Any rags, papers, or other materials that are contaminated during the disposal process should be incinerated. Contaminated solid materials should be enclosed in sealed plastic bags that are labeled to indicate the presence of a carcinogen, with the name and amount of carcinogen. Bags should be stored in well-ventilated areas until they are incinerated (Castegnaro et al. 1982). Nitrosamine residues generated in laboratory research or accidental spills in research laboratories should be diluted to a concentration of <10 µg/L and then reduced to innocuous amines, ammonia, or alcohols by aluminum-nickel alloy powder and aqueous alkali (Castegnaro et al. 1982). This method of disposal is applicable to a variety of media (water, mineral oil, olive oil, dimethylsulfoxide, solutions of agar gel), but is not recommended for use in solutions of acetone or dichloromethane because reactions are slow and incomplete. After the reduced reaction mixture is filtered, the liquid can be disposed of by pouring it over a sufficient amount of absorbent material to convert it to a solid waste for incineration. The filtercake is discarded with non-burnable solid wastes (Castegnaro et al. 1982). Other methods of destruction of NDMA in laboratory wastes (e.g., using hydrobromic acid or potassium permanganate/sulfuric acid) are described by Castegnaro et al. (1982).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of

5. POTENTIAL FOR HUMAN EXPOSURE

generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes $\geq 25,000$ pounds of any TRI chemical or otherwise uses $>10,000$ pounds of a TRI chemical in a calendar year (EPA 2005).

NDMA can be unintentionally produced and then subsequently released from a number of industrial sources by chemical reactions involving alkylamines with nitrogen oxides, nitrous acid or nitrite salts (EPA 2014a). Some possible industrial sources are tanneries, pesticide manufacturing facilities, rubber and tire producers, alkylamine manufacture and use sites, fish processing facilities, foundries, and dye manufacturers (Tricker et al. 1989). NDMA is inadvertently formed in drinking water supplies during water disinfection (EPA 2016). Further, NDMA was found in municipal sewage sludge in the 1980s (Brewer et al. 1980; Mumma et al. 1984) and may thus be released from sewage treatment plants or the application of sludge for biosolids. Tobacco smoke has also been shown to be a source of NDMA release into the air (WHO 2008). NDMA may be released to the air during the grilling of meats such as beef, pork, and duck (Kim et al. 2019).

5.3.1 Air

Estimated releases of <1 pound of NDMA to the atmosphere from two domestic manufacturing and processing facilities in 2021, accounted for 100% of the estimated total environmental releases from facilities required to report to the TRI (TRI21 2022). These releases are summarized in Table 5-2.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use N-Nitrosodimethylamine^a

State ^c	RF ^d	Reported amounts released in pounds per year ^b						Total release		
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	On-site ^j	Off-site ^k	On- and off-site	
		AR	1	0.2	0	0	0	0	0.2	0
IL	1	0	0	0	0	0	0.2	0	0	

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use N-Nitrosodimethylamine^a

State ^c	RF ^d	Reported amounts released in pounds per year ^b							
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		
							On-site ^j	Off-site ^k	On- and off-site
Total	2	0.2	0	0	0	0	0	0	0.2

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI21 2022 (Data are from 2021)

The use of amine-containing solvents in post-combustion CO₂ capture plants to reduce greenhouse emissions from anthropogenic point sources such as fossil fuel fired power plants can result in atmospheric emissions of NDMA and other nitrosamines (SEPA 2015; Sørensen et al. 2015).

The EPA National Emissions Inventory is a comprehensive and detailed estimate of air emissions of criteria pollutants, criteria precursors, and hazardous air pollutants from air emissions and includes point and nonpoint sources, on- and off-road sources, and other events such as wildfires. Data from 2014 and 2017 for NDMA are shown in Table 5-3.

Table 5-3. Emissions of N-Nitrosodimethylamine (NDMA) to Air Reported to the National Emissions Inventory

Sector	2014 Emissions (pounds) ^a	2017 Emissions (pounds) ^b
Fuel combustion, electric generation, coal	54.41	622.10
Industrial processes, ferrous metals	35.60	57.60
Industrial processes, chemical manufacturing	0.00	32.25

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-3. Emissions of N-Nitrosodimethylamine (NDMA) to Air Reported to the National Emissions Inventory

Sector	2014 Emissions (pounds) ^a	2017 Emissions (pounds) ^b
Waste disposal	16.78	26.38
Fuel combustion, electric generation, oil	155.48	24.48
Industrial processes, petroleum refineries	17.00	15.38
Fuel combustion, industrial boilers, internal combustion engines, other	2.40	3.40
Fuel combustion, electric generation, natural gas	0.45	0.41
Industrial processes, not elsewhere classified	0.02	0.04
Solvent, degreasing	0.00	0.003
Solvent, industrial surface coating and solvent use	0.00	0.0001

^aEPA 2014b.^bEPA 2017.**5.3.2 Water**

There were no releases of NDMA to water from domestic manufacturing and processing facilities required to report to the TRI in 2021 (TRI21 2022).

5.3.3 Soil

There were no releases of NDMA to soil from domestic manufacturing and processing facilities required to report to the TRI in 2021 (TRI21 2022).

5.4 ENVIRONMENTAL FATE

NDMA is not released into environmental matrices via the same pathways by which industrial compounds or pesticides may be emitted; rather, it is unintentionally produced and released from industrial sources as a result of chemical reactions involving alkylamines with nitrogen oxides, nitrous acid, or nitrite salts (EPA 2014a). Based on its physical-chemical properties, NDMA is expected to volatilize from soil or water surfaces into the air where it is susceptible to photolysis. Environmental fate of NDMA produced in water treatment facilities would be subject to biodegradation and photolysis.

5. POTENTIAL FOR HUMAN EXPOSURE

5.4.1 Transport and Partitioning

Air. Organic compounds in the atmosphere having vapor pressures $>10^{-4}$ mm Hg are expected to exist almost entirely in the vapor phase (Eisenreich et al. 1981). The estimated vapor pressure of NDMA at 20°C [2.7 mm Hg (see Table 4-2)] indicates that this compound should not partition from the vapor phase to particulates in the atmosphere.

Water. Using linear regression equations based on log K_{ow} data (log K_{ow} of -0.57 [see Table 4-2]), a bioconcentration factor of 0.2, and a soil adsorption coefficient (K_{oc}) of 12 have been estimated for NDMA (Bysshe 1982; Hansch et al. 1995; Lyman 1982). These values, as well as the complete water solubility of NDMA, indicate that bioaccumulation in aquatic organisms and adsorption to suspended solids and sediments in water would not be important environmental fate processes. The low Henry's Law constant for NDMA (2.63×10^{-7} atm-m³/mol at 20°C [see Table 4-2]) suggests that volatilization is expected to occur slowly in water (Thomas 1982).

Sediment and Soil. NDMA is expected to be highly mobile in soil and it has the potential to leach into groundwater supplies (Dean-Raymond and Alexander 1976; Greene et al. 1981; Swann et al. 1983). If NDMA were released to soil surfaces, as might be the case during application of contaminated pesticides, a substantial proportion of the nitrosamine would volatilize. The volatilization half-life from soil surfaces under field conditions is estimated to be on the order of 1–2 hours (Oliver 1979). If NDMA were incorporated into subsurface soil, far less of the nitrosamine would enter the atmosphere by volatilization and the rate of volatilization would be greatly reduced. Under these circumstances, volatilization would be of minor importance (Oliver 1979).

5.4.2 Transformation and Degradation

Air. In the atmosphere, NDMA vapor would rapidly degrade by direct photolysis to form dimethylnitramine. Based on experimental data, the photolytic half-life of NDMA vapor exposed to sunlight has been determined to be about 5–30 minutes (Hanst et al. 1977; Tuazon et al. 1984). Reaction of NDMA with photochemically-generated hydroxyl radicals or ozone molecules in the atmosphere would be too slow to be environmentally significant (Atkinson and Carter 1984; Tuazon et al. 1984).

Water. Data suggest that NDMA would be subject to photolysis in natural waters exposed to sunlight (Abusallout and Hua 2016; EPA 1979; Lee et al. 2005; Polo and Chow 1976). In unlit waters, it appears

5. POTENTIAL FOR HUMAN EXPOSURE

that NDMA would be rather persistent, eventually degrading as the result of microbial transformation (Kaplan and Kaplan 1985; Kobayashi and Tchan 1978; Tate and Alexander 1975). There is evidence that suggests that formaldehyde and methylamine may form as biodegradation products of NDMA (Kaplan and Kaplan 1985). NDMA is not expected to undergo hydrolysis under the conditions found in natural waters (EPA 1979; Oliver et al. 1979). Because NDMA has strong absorbance at approximately 227 and 254 nm wavelengths and a large quantum yield at these absorption frequencies, photolysis by ultraviolet (UV) irradiation at water reuse and drinking water facilities, is a treatment technique to reduce NDMA levels (Szczuka et al. 2020; Sharpless and Linden 2003). UV-based advanced oxidation processes utilize irradiation of aqueous solution in conjunction with hydrogen peroxide or photocatalysts such as titanium dioxide, which produce powerful oxidizing agents (hydroxyl radicals), to assist in the degradation of NDMA at water treatment facilities (Fujioka et al. 2017; Szczuka et al. 2020). A field study conducted using a drinking water treatment plant in China suggested that photolysis and biodegradation are the primary removal mechanisms for NDMA in conventional drinking water treatment plants with less significant loss by off-gassing (Qiu et al. 2019). Sakai et al. (2012) studied the effects of UV wavelength on the degradation kinetics of NDMA in water. Three different light sources were studied: a 222-nm Kr Cl excimer UV lamp, a 254-nm mercury UV lamp, and a 230–270-nm filtered medium pressure (FMP) mercury UV lamp. It was concluded that a higher degradation efficiency of irradiated NDMA solutions was observed using the 222-nm lamp and FMP lamp as opposed to the 254-nm lamp but water quality parameters such as the amount of naturally occurring organic matter could affect the degradation efficiency. Nitrosamines such as NDMA have been shown to undergo direct photolysis under environmental conditions with the half-life on the order of several minutes (Sørensen et al. 2015). Direct photolysis of NDMA under simulated environmental conditions (wavelengths >290 nm) was investigated by Plumlee and Reinhard (2007). Using a light source that simulated Southern California midsummer, midday sun (intensity 765 W/m²), the direct photolysis half-life of NDMA was determined to be 16 minutes; however, increasing amounts of dissolved organic matter decreased the degradation rate of NDMA since these substances also absorb photons in the environmental UV spectrum. The direct photolysis half-life of NDMA in infiltration basins (advanced purified, recycled water) at initial levels up to 9.0 ng/L prior to sunrise declined to below the detection limit (<1.5 ng/L) by 10:00 A.M. due to natural photolysis, and the half-life ranged from 33 to 86 minutes depending upon the intensity of solar irradiation (Reny et al. 2021). Chen et al. (2010) used experimental photolysis data to derive a quantitative structure-activity relationship (QSAR) for the rate of photolysis of NDMA and several other disinfection byproducts produced in water treatment facilities.

5. POTENTIAL FOR HUMAN EXPOSURE

Sediment and Soil. It appears that microbial degradation would be an important removal process for NDMA in subsurface soil. Oliver et al. (1979) amended Metapeake loam with 10 ppm NDMA at 23°C and observed a half-life of 50 days (Oliver et al. 1979). Loss of NDMA was attributed to volatilization and biodegradation. Tate and Alexander (1975) amended silt loam with 22.5 ppm NDMA at 30°C and observed a lag of approximately 30 days before slow disappearance from soil commenced; 50% loss occurred after about 55 days incubation and 60% loss occurred after about 70 days incubation. As part of the same study, 40% loss was observed in 2 days in soil amended with 50 ppm NDMA and 44% loss was observed in 5 days in soil amended with 250 ppm NDMA. These initial losses were followed by very little or no loss over the next 3 weeks. Initial, rapid loss of NDMA was attributed to volatilization and slow, gradual loss of NDMA was attributed to biodegradation. Mallik and Tesfai (1981) incubated NDMA at 4, 25, and 37°C and found that at all three temperatures, about 20–30% of added NDMA disappeared in the first 20 days of incubation, but little loss was noted thereafter; even after 30 days of incubation, over 50% of the NDMA was retained. The rate of disappearance of NDMA was found to be slightly higher in sandy loam soil than in either clay or silt loam soil. The rate of loss was also found to be slightly higher in aerobic soil at field capacity compared to super saturated (anaerobic) soil. After a 30-day incubation period, 60% of added NDMA remained in soil at field capacity and 70% of added NDMA remained in super saturated soil. Available data on the degradation of NDMA in water and air indicate that photolysis may be an important removal process on soil surfaces as well.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to NDMA depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of NDMA in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on NDMA levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-4 shows the lowest limit of detections that are achieved by analytical analysis in environmental media.

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-4. Lowest Limit of Detection Based on Standards^a

Media	Detection limit	Reference
Air	0.5 parts per trillion ^b	Sawicki et al. 1977
Drinking water	0.28 ng/L	EPA 2004 (Method 521)
Surface water and groundwater	0.15 µg/L	EPA 1996 (Method 8070)
Soil	5.7 ng/g ^c	Venkatesan et al. 2014
Sediment	5.7 ng/g ^c	Venkatesan et al. 2014
Whole blood	0.1 µg/L	Lakritz et al. 1980

^aDetection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.

^bDetection limits in air are dependent upon the sampling time/volume; this value is for 150 L volume of air collected.

^cMeasured in biosolids.

Detections of NDMA in air, water, and soil at NPL sites are summarized in Table 5-5.

Table 5-5. N-Nitrosodimethylamine (NDMA) Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median ^a	Geometric mean ^a	Geometric standard deviation ^a	Number of quantitative measurements	NPL sites
Water (ppb)	29.5	366	607	4	4
Soil (ppb)				No data	
Air (ppbv)				No data	

^aConcentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Limited data on levels of NDMA in ambient air are available, and much of the available data was obtained many years ago in the vicinity of industrial sources. Because commercial uses of NDMA have been discontinued, and environmental control technologies have been instituted to reduce inadvertent NDMA formation and release, current levels in ambient air are expected to be lower. When it was used as a rocket fuel intermediate, NDMA was identified in ambient air on-site and in the vicinity of factories that were manufacturing rocket fuel (EPA 1978; Fine et al. 1977a). At a plant in Baltimore, Maryland, which was manufacturing unsymmetrical dimethylhydrazine rocket fuel, the average concentration on-site was 11.6 µg/m³, and in neighboring residential communities, it was 1.07 µg/m³, with levels ranging between 30 and 100 ng/m³ in the downtown area (Fine et al. 1977a). As a result of these findings, the use

5. POTENTIAL FOR HUMAN EXPOSURE

of NDMA was discontinued at this plant (Shapley 1976). During December 1975, NDMA was found in air samples collected in Belle, West Virginia near a factory that was manufacturing dimethylamine. The highest level found ($0.980 \mu\text{g}/\text{m}^3$) was collected during a temporary weather inversion (Fine et al. 1976). NDMA was measured in ambient air in urban areas with no known point sources of nitrosamines: Baltimore, Maryland several miles upwind of the rocket fuel plant ($0.02\text{--}0.1 \mu\text{g}/\text{m}^3$); the Cross Bronx Expressway in New York City ($0.8 \mu\text{g}/\text{m}^3$); and Philadelphia, Pennsylvania (0.025 ppb) (Fine et al. 1976; Shapley 1976). NDMA has been found in fogs and clouds at concentrations ranging from 7.5 to 397 ng/L (Hutchings et al. 2010; SEPA 2015).

Mean NDMA concentrations in fine particulate matter ($\text{PM}_{2.5}$) collected from ambient air in central London were 0.00136 and $0.0049 \mu\text{g}/\text{m}^3$ in winter and summer, respectively (Farren et al. 2015). In the 1990s, NDMA was found to be above the detection limits of $0.0029\text{--}0.0048 \mu\text{g}/\text{m}^3$ in 20 out of 41 samples obtained from a chemical production facility in Ontario, Canada (WHO 2008). The maximum level of NDMA in air samples within the perimeter of the production facility was reported as $0.230 \mu\text{g}/\text{m}^3$, while the maximum level collected in air samples nearby the facility was $0.079 \mu\text{g}/\text{m}^3$ (WHO 2008).

Occurrence of volatile nitrosamines in air has been associated with tire and rubber products, leather tanneries, and automotive upholstery, and, as a result, measurable levels of the nitrosamines have, in the past, been found in certain confined areas (e.g., automobile interiors). In studies conducted in the 1980s, levels of NDMA in interior air of new cars were found to range from <0.02 to $0.83 \mu\text{g}/\text{m}^3$ (EPA 1985; Rounbehler et al. 1980). Newer information was not located. As materials used in automobile interiors have changed since the 1980s, the relevance of these measurements to potential current exposures is unknown.

Tobacco smoke is an established source of airborne NDMA. The maximum NDMA level in indoor air for a residence with smokers was reported as $0.24 \mu\text{g}/\text{m}^3$ and the level in the air of a residence for a nonsmoker was below the detection level of $0.003 \mu\text{g}/\text{m}^3$ (WHO 2008). In their review of the chemical composition of tobacco smoke, IARC (2004) noted that NDMA concentrations in indoor spaces where people were smoking (restaurants, bars, conference rooms) ranged between <0.01 and $0.24 \mu\text{g}/\text{m}^3$.

5. POTENTIAL FOR HUMAN EXPOSURE

5.5.2 Water

NDMA is formed as an unintentional byproduct of the chlorination of wastewater and drinking water at treatment plants, especially where chloramines are used for disinfection (EPA 2016). Monitoring for NDMA was conducted under the Unregulated Contaminant Monitoring Rule (UCMR) Cycle 2 (EPA 2016). The EPA employs the UCMR program to obtain data for contaminants in PWSs that do not have health-based standards set under the Safe Drinking Water Act. In monitoring data collected from 2008 through 2010, 18,040 samples from 1,198 PWSs were analyzed for NDMA (EPA 2016). NDMA was detected in samples from 324 PWSs and at levels above the minimum reporting level of 0.002 µg/L in 1,841 samples (EPA 2016). The median and mean NDMA concentrations across all samples with detections were 0.0041 and 0.008 µg/L, respectively, well below the EPA's drinking water health advisory level of 0.07 µg/L. EPA (2016) estimated the size of the population served by PWSs with NDMA detections to be ~65 million people. As discussed in Section 5.6, exposures to NDMA in drinking water are very low compared to endogenous production and other exogenous sources.

Detections of NDMA in drinking water samples were most common from facilities using chloramines (34%) compared with chlorine or other disinfectants (4%) or no disinfection (1.8%) (EPA 2016). The maximum concentration detected in the positive samples from facilities using chloramines was 0.630 µg/L; in positive samples from facilities using chlorine or other disinfectants, the maximum was 0.0846 µg/L (EPA 2016). Other factors affecting the NDMA concentration included the source water type and the sample type. Systems using surface or mixed water sources had higher detection rates than systems using groundwater sources. In addition, samples collected at "maximum residence time locations" were higher than those collected at distribution entry points, suggesting ongoing formation of NDMA in the distribution system (EPA 2016).

In a review of published literature on NDMA exposure sources (publications dated between 2004 and 2011), Gushgari and Halden (2018) reported that the average NDMA concentration in U.S. potable waters was 0.0177 µg/L, and that its concentration was higher than those of other nitrosamines. It has been estimated that NDMA accounts for between 5 and 13% of total N-nitrosamines in potable waters (Dai and Mitch 2013; Gushgari and Halden 2018). NDMA formation can be enhanced depending upon algae concentrations during the disinfection process. Du et al. (2022) studied the effects of chlorination on nitrosamines formation from two algae (*Microcystis aeruginosa* and *Cyclotella meneghiniana*) and observed that NDMA was the dominant nitrosamine produced.

5. POTENTIAL FOR HUMAN EXPOSURE

NDMA was detected in treated water within the distribution system from 20 chloramine treatment plants located in Canada and the United States at maximum, mean, and median levels of 0.0586, 0.0094, and 0.0043 $\mu\text{g/L}$, respectively (Leavey-Roback et al. 2016). Repeated samples were collected over a 2-year period, but the specific dates were not provided. Liew et al. (2015) collected a total of 211 samples from 38 drinking water treatment plants across five states and one territory in Australia from 2007 to 2013. Nine out of 38 facilities reported NDMA levels above 0.005 $\mu\text{g/L}$. The highest concentration of NDMA was 0.074 $\mu\text{g/L}$ and was obtained from a facility using chloramine for disinfection.

The formation of NDMA in potable water supplies has been attributed to precursors contained in natural organic matter, tertiary and quaternary amines, anion exchange resins and cationic coagulant polymers (such as polydiallyldimethylammonium chloride), and/or in source waters impacted by wastewater contamination (which may include tertiary amine-based drugs, cosmetics, or toiletries) (Atkinson et al. 2020; Dai and Mitch 2013; EPA 2016; Tan et al. 2019; Zeng et al. 2016). It has been shown that the pharmaceutical agent, methadone, which is often used to treat heroin withdrawal symptoms, has a high potential to form NDMA in water treatment facilities (Hanigan et al. 2015; Hsieh et al. 2020). A review by Krasner et al. (2013) discusses the formation of NDMA and other nitrosamines from various precursors in water treatment facilities and the different methods to limit the formation of NDMA, such as physical removal of precursors by biologically activated carbon and granular activated carbon or the degradation of such compounds by ozonation or increased pre-chlorination time. The most important precursors are amine-containing coagulation polymers and effluent-impacted source waters (Krasner et al. 2013). In a separate study of 21 full-scale drinking water plants, ozonation of raw or settled water was shown to be an effective method of degrading NDMA precursors and increasing the free pre-chlorination time from <3 minutes of treatment to over 1 hour potential from 21 to 90% (Krasner et al. 2018). Hanigan et al. (2012) studied the ability of activated carbon to adsorb precursors and reduce the NDMA formation potential from river water and effluent from a wastewater treatment plant and found that the NDMA formation potential was in the range of 37–91%, depending upon the concentration of the activated charcoal used. While ozonation can facilitate the degradation of NDMA-forming precursors, it may also result in the formation of NDMA in the treatment of wastewater or highly contaminated surface water (Gao et al. 2022; Sgroi et al. 2014, 2016, 2018; Vaidya et al. 2021). Gao et al. (2022) demonstrated formation of NDMA from ozonation treatment of 3-(dimethylamino)-1-propylamine (DMAPA) with higher levels of NDMA formation observed with increasing pH (from 5 to 9) and ozone dosages. NDMA formation upon ozone treatment of the anti-yellowing agent, 4,4'-hexamethylenebis

5. POTENTIAL FOR HUMAN EXPOSURE

(1,1-dimethylsemicarbazide) (HDMS), has also been demonstrated with higher yields under slightly alkaline (pH 8) conditions (Shen et al. 2019).

EPA (2016) reported that several studies have demonstrated the presence of NDMA precursors in wastewaters. NDMA itself was detected in effluents from four wastewater plants in Connecticut at levels ranging between 0.0076 and 0.4 µg/L (Schreiber and Mitch 2006). Concentrations of NDMA in the receiving waterways were generally below the detection limit except in the river downstream of the Wallingford, Connecticut treatment plant, where concentrations of ~0.015 and 0.05 µg/L were detected (Schreiber and Mitch 2006). Sack et al. (2021) measured NDMA levels in the range of 20.7–56.7 ng/L in wastewaters from five large hospitals in Israel. Samples from 101 wastewater treatment plants (WWTPs) in Ontario, Canada were analyzed for the presence of NDMA from 1990 to 1998 (WHO 2002, 2008). NDMA was detected in raw surface water samples from 37 of the plants, with a maximum concentration of 0.008 µg/L. Wastewaters used for landscape irrigation may contain elevated concentrations of NDMA, but a field study (Gan et al. 2006) showed very little NDMA in leachate (detectable at 2 ng/L in only 9 of 400 samples) from turfgrass after 4 months of application of wastewater containing an average of 930 ng/L NDMA.

NDMA is infrequently found in groundwater samples, except in the vicinity of industrial activities such as rubber manufacturing and rocket engine testing (Gushgari and Halden 2018). However, it was the finding of very high NDMA concentrations in groundwater downgradient from rocket engine testing facilities in California that led to the discovery of NDMA associated with chloramine/chlorine disinfection (Mitch et al. 2003). Groundwater monitoring wells showed NDMA concentrations as high as 400 µg/L on site and as high as 20 µg/L in drinking water wells downgradient of the sites (Mitch et al. 2003). These findings led the California Department of Health Services to conduct a survey (in 2002) of NDMA in drinking waters in the state, which revealed the occurrence of NDMA in drinking waters influenced by chlorine-disinfected wastewaters, and in drinking water supplies where chloramine and chlorine disinfection were used (Mitch et al. 2003). NDMA was monitored for, and detected in, both groundwater and river water in Tokyo, Japan (Van Huy et al. 2011). Levels were <0.5–5.2 ng/L (median: 0.9 ng/L) in groundwater and <0.5–3.4 ng/L (median: 2.2 ng/L) in river water.

NDMA has been detected in pool water. Analysis of water in 23 indoor pools in South Carolina, Georgia, and North Carolina revealed that NDMA levels ranged from 2 to 83 ng/L (0.002–0.083 µg/L), with an average concentration of 26.5 ng/L (0.0265 µg/L) (Kanan 2010). UV treatment is often used as a disinfection technique in large pool maintenance. However, Soltermann et al. (2013) reported that UV

5. POTENTIAL FOR HUMAN EXPOSURE

treatment (at wavelengths of 254 nm) of swimming pool water containing chlorinated dimethylamine and monochloramine resulted in slightly increased NDMA formation instead of the expected decreases.

5.5.3 Sediment and Soil

Few data on NDMA in soil or sediment were located. Only one study of NDMA in soil was identified, and it was published in 1977. In that study, NDMA was found in soil at 1–8 µg/kg (dry basis) in Belle and Charleston, West Virginia, New Jersey, and New York City (Fine et al. 1977b). NDMA in soil may arise from absorption of NDMA in air, from absorption of dimethylamine from air and its subsequent N-nitrosation, or from pesticide application. NDMA was not detected in any sediment or soil samples from 2020 to 2022 in a search of the EPA Water Quality Portal (WQP 2022). Gushgari et al. (2017) analyzed 40 freshwater sediments in the vicinity of 13 WWTPs in the United States. Three nitrosamines (N-nitrosodibutylamine, N-nitrosodiphenylamine, and N-nitrosopyrrolidine) were detected in some of the sediment cores; however, NDMA was not detected (10.2 ng/g detection limit) in any of the sediments tested.

5.5.4 Other Media

NDMA has been detected in a variety of other media including foods and beverages, pharmaceutical products, toiletries and cosmetics, tobacco products, rubber products, pesticides, and sewage sludge. For media other than beverages and pharmaceutical products, however, the majority of published literature on NDMA levels in these media dates from before 1990, and more recent data were not located. In general, after NDMA was initially detected in foods, beverages, and rubber products (more than 40 years ago), producers and manufacturers modified their processes and techniques to reduce nitrosamine formation. However, due the ubiquitous nature of NDMA precursors and its facile formation, complete elimination of NDMA from these products has proved to be challenging. The discovery of NDMA contamination in prescription and over-the-counter drugs is a relatively recent phenomenon (2019 to present), and the FDA continues to update its information on affected medications (see <https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications>).

Foods and Beverages. Current food exposures to NDMA are uncertain because of changes in food processing techniques (Lee 2019). Food processing methods that foster the formation of NDMA or other nitrosamines include pickling, storage in humid conditions, smoking with saturated nitrogen, high temperature drying, and curing with nitrate or nitrite (Stuff et al. 2009). The use of nitrite and nitrate

5. POTENTIAL FOR HUMAN EXPOSURE

preservatives was thought to be a significant contributor to elevated NDMA levels in processed meats, and these uses have declined in the years since much of the data were collected (Lee 2019). However, Stuff et al. (2009) noted that many foods contain naturally occurring precursors that can yield NDMA or other nitrosamines under some conditions.

Based on food concentrations of N-nitrosamines in literature published between 1979 and 2015, Gushgari and Halden (2018) estimated the average concentration of NDMA across all food types to be 2.2 µg/kg; average concentrations for other N-nitrosamines ranged between 0.02 and 1.5 µg/kg (for N-nitrosodi-n-propylamine and N-nitrosodi-n-butylamine, respectively). In a study in Turkey, NDMA was detected in all samples (n=20) of salami tested, with levels ranging from 0.09 to 3.56 µg/kg (Özbay and Sireli 2021). Lee (2019) reviewed the available literature (publications dated 1985–2018) on N-nitrosamine levels in meats and poultry, identifying data from 14 countries. Table 5-6 shows the ranges of concentrations reported in the literature reviewed by Lee (2019). Weighting the published values by number of samples analyzed, Lee (2019) estimated the mean levels of N-nitrosamines in 40 different processed meats and poultry products. The estimated mean NDMA concentration ranged between 0.3 and 5.7 µg/kg; the highest means were estimated for fried-out bacon fat (5.7 µg/kg), fried pork fat, (4.1 µg/kg), ham and turkey (3.8 µg/kg), and blood sausage (3.5 µg/kg) (Lee 2019). For most other meats and poultry, estimated mean concentrations were ≤1 µg/kg. In foods other than meat and poultry, similar concentrations have been measured; however, these data are also older. In a review of literature published between 1988 and 2006, Stuff et al. (2009) reported NDMA concentrations for several other food types (see Table 5-6), with the highest concentrations (in foods other than meats and poultry) found in oysters (>11 µg/kg), sauerkraut (6.6 µg/kg), and fried fish (1.7 µg/kg). It is important to note that not all samples of a particular type of food contained detectable levels of NDMA; only the measurements above the detection limit are reported in the table.

Table 5-6. Detection of N-Nitrosodimethylamine in Foods and Beverages

Food item	Concentration
Foods other than meat and poultry ^a (µg/kg)	
Dairy (milk, butter, cottage cheese)	0.14–0.76
French fries	0.24
Margarine	0.26
Refried beans	0.33
Breads (rolls, bagels, muffins)	0.5
Fried fish	1.69
Sauerkraut	6.60

5. POTENTIAL FOR HUMAN EXPOSURE

Table 5-6. Detection of N-Nitrosodimethylamine in Foods and Beverages

Food item	Concentration
Oysters	11.39
Meat and poultry products ^b (µg/kg)	
Lamb products	1.0
Sausage products	0.1–3.6
Hot dogs	0.2–2.2
Ham products	0.1–4.9
Poultry products	0.5–5.0
Pork products	0.1–4.9
Bacon products	0.3–20.2
Chorizo	ND–109.4
Alcoholic beverages (µg/L)	
Alcoholic beverages (beer, wine) ^a	0.25–2.02
U.S. beer ^c	0.145
Beers produced other countries ^c	0.118–0.225
Lager ^d	0.105
Ale ^d	0.108
Dark beer ^d	0.055
Light beer ^d	0.05

^aAs reported in literature review published by Stuff et al. (2009) based on publications dated between 1988 and 2006; country of origin not limited.

^bAs reported in literature review published by Lee (2019) based on publications dated between 1986 and 2018 that reported levels in foods in the United States or in other countries with predominantly Western diets.

^cFan and Lin (2018).

^dBaxter et al. (2007).

Malt beverages, including domestic and foreign beers and whiskeys, may contain NDMA. In the 1970s, research suggested that NDMA in these beverages may result from formation during direct-fired kiln-drying of malt (from amines in the cereals and nitrogen oxides in the drying air), so malting processes were modified to reduce nitrosamine formation, leading to a sharp reduction in NDMA levels by the 1980s (Baxter et al. 2007). The FDA established an action level of 5 ppb (5 µg/L) for NDMA in malt beverages sold in the United States (FDA 2005a), and there are few publications reporting levels of NDMA in beverages produced since that time. NDMA concentrations ranging between 0.118 and 0.225 µg/L were measured in 10 beer samples from six different countries (dates of sample collection were not reported but assumed to be within a few years of publication); as shown in Table 5-6, the concentration in the one U.S. sample was 0.145 µg/L (Fan and Lin 2018). Baxter et al. (2007) analyzed 138 different beers from 42 different countries (obtained in 2003) for the presence of NDMA. A total of 21% of the beers sampled had detectable levels of NDMA (detection limit 0.1 µg/L) and three samples showed concentrations >0.5 µg/L. NDMA content in beer was not correlated with alcohol level, type, or

5. POTENTIAL FOR HUMAN EXPOSURE

geographical origin. Baxter et al. (2007) traced the source of elevated NDMA (1.9 µg/L) in one lager sample to an ion exchange resin used to treat water used in the brewery.

NDMA may occur in human breast milk; however, available data are limited to two studies published in 1996 and 1984. Uibu et al. (1996) reported NDMA levels ranging from <0.5 to 1.2 µg/L in milk from 10 of 54 nursing women (NDMA was not detectable in milk from the remaining women). In a 1984 study, 51 samples of breast milk were collected from 13 nursing women. NDMA concentrations >0.2 µg/L were found in 23.5% of the samples, and the maximum concentration detected was 1.1 µg/L (Lakritz and Pensabene 1984). While no measurements of NDMA in infant formula were located in the literature reviewed, Hrudey et al. (2013) calculated estimated NDMA levels in the range of 0.002–0.06 ng/g for prepared formula (made from cow's milk) using concentrations measured in milk proteins or nonfat dry milk. NDMA was detected in 100% of milk powder samples (n=64) at an average concentration of 2.6 µg/kg (Genualdi et al 2020).

Pharmaceuticals. In recent years, the FDA has detected NDMA (and other nitrosamines) in some prescription and over-the-counter medications, including angiotensin II receptor blockers (valsartan, losartan, irbesartan) (FDA 2019a); metformin extended-release (used to treat Type II diabetes) (FDA 2020a); and drugs used to block stomach acid such as ranitidine (also known by its brand name, Zantac) and nizatidine (FDA 2019b). NDMA was detected in about one-third of tested samples of metformin extended-release, one-half of the tested samples of valsartan, and in all samples of ranitidine and nizatidine tested. FDA testing showed that the amounts of NDMA in each tablet or other oral dose of drug were 0.33–20.19 µg in valsartan samples, 0.004–0.86 µg in ranitidine samples, 0.01–0.03 µg in nizatidine samples, and 0.005–0.19 µg in metformin extended-release samples (FDA 2019a, 2019b, 2020a). A number of these products have been the subject of voluntary or mandatory recalls (beginning in 2018 for valsartan products, 2019 for ranitidine and nizatidine products, and 2020 for metformin extended-release). In 2019, FDA established an interim limit of 96 ng/day (0.000096 mg/day) for NDMA intake from the use of angiotensin II receptor blockers such as valsartan; the limit is based on cancer risk. It is not clear whether the limit would also apply to other affected medications such as ranitidine. The FDA's investigation into nitrosamine impurities in medications is ongoing, and the reader is referred to the FDA website on this topic (<https://www.fda.gov/drugs/drug-safety-and-availability/information-about-nitrosamine-impurities-medications>) for up-to-date information pertaining to medications containing NDMA and recall of specific products. Other governments have also assessed levels of NDMA in pharmaceutical products. For example, the Ministry of Food and Drug Safety in South Korea suspended the manufacture and sale of 269 ranitidine products following a study that found levels as high

5. POTENTIAL FOR HUMAN EXPOSURE

as 53.50 ppm in some products; this is several hundred times greater than the provisional limit of 0.16 ppm set by the government (Kim et al. 2021a).

Recent *in vitro* studies using ranitidine tablets in simulated gastric fluid showed that NDMA was formed, but only at levels atypical of physiologic conditions (Gao et al. 2021). The authors of this study determined that the conversion of ranitidine to NDMA only began to occur under acidic conditions characteristic of human physiology when gastric nitrite concentrations were approximately 50 times greater than normal levels. Braunstein et al. (2021) also noted an increase in NDMA levels when ranitidine was in simulated gastric fluid at a constant pH of 2.5, but also at very high sodium nitrite levels (>2.5 mmol/L). A randomized study was conducted to assess the 24-hour urinary excretion levels of NDMA in a group of participants receiving oral ranitidine (300 mg) compared with a group given placebo. Each group was evaluated when the subjects were following a diet using noncured meats, and also when following a diet with cured meats containing high levels of nitrites (Florian et al. 2021). The study found that the group receiving ranitidine did not have a significantly increased 24-hour urinary excretion of NDMA as compared to the control group not receiving ranitidine. The study authors concluded that orally ingested ranitidine is not likely to be converted to NDMA in normal healthy human populations.

Accurate analytical testing methodologies are crucial for determining the concentrations of NDMA in pharmaceutical products. A comprehensive review of important analytical methods that may be used for the quantification NDMA in various active pharmaceutical ingredients has been published (Parr and Joseph 2019). A recent study by Yang et al. (2020) discussed the findings of NDMA levels in 38 metformin drug products. A private testing laboratory found that 16 of 38 of the metformin drug products they tested had NDMA levels greater than the allowable intake of 96 ng/day. However, FDA testing using orthogonal methods on the same set of 38 samples determined only 8 of the 38 products had levels over the allowable limit and generally observed much lower values than reported by the private testing firm. For example, a 500 mg tablet of metformin had a reported NDMA level of 0.364 ng/mg when analyzed by a private laboratory; however, a duplicate analysis using an FDA method found the level to be 0.021 ng/mg (Yang et al. 2020). Further investigation revealed that the cause of these discrepancies was a lack of specificity, because N,N-dimethylformamide (DMF) caused interference with NDMA measurements. Fritzsche et al. (2022) presented a review of analytical methodologies for measuring NDMA in metformin products (two metformin immediate release formulations and one extended-release formulation), in which they compared measurements of NDMA levels obtained from four laboratories using orthogonal mass spectrometric methods. They observed artefactual formation of

5. POTENTIAL FOR HUMAN EXPOSURE

NDMA when the solvent dichloromethane was used during the extraction step leading to inaccurate results that overestimate NDMA levels; however, artefactual NDMA was not formed *in-situ* when a mixture of water, methanol and acetonitrile were used in the extraction process.

A comprehensive review of NDMA levels in metformin for both the active pharmaceutical ingredient (API) and the finished dosage forms (FDF) was recently published (Keire et al. 2022). The results strongly suggest that NDMA is formed during the manufacture of the final product and that the active ingredient typically does not contain NDMA. These researchers tested 1,090 samples (875 FDF and 215 API samples) and found 213 out of 215 API lots tested had no measurable level of NDMA. For FDF samples tested, 156 out of 875 had levels above the acceptable intake (AI) of 96 ng per day. Other research seems to support these conclusions. Analyses of 105 samples of metformin tablets from 13 different manufacturers found that NDMA was not detected in the API; however, NDMA was detected in 64 (85.3%) and 22 (91.7%) of the finished product and prolonged finished product samples, respectively (Zmysłowski et al. 2020). Additional research showed that NDMA formation during the metformin manufacturing process can be reduced by limiting residual dimethylamine (DMA) and inorganic nitrites and nitrates of inactive ingredients used to create the marketed tablets (Schlingemann et al. 2022). They noted that NDMA content increased during wet granulation process and coating, which introduces heat and polyvinylpyrrolidone binder as a significant source of nitrite. Jireš et al. (2021) detected an increase in NDMA in coated metformin tablets following production and after 7 days of storage. They observed that samples of film-coated tablets produced from metformin containing high DMA content and polyvinylpyrrolidone with high peroxide content contained a significantly higher amount of NDMA than other batches. Nasr et al. (2021) also investigated the cause of NDMA formation in metformin pharmaceutical products and identified water, heat, and excipients with high nitrite content as key factors affecting NDMA formation. Their findings indicated that the polyvinylpyrrolidone (PVP K30) tested had lower nitrite and nitrate levels than other excipients such as sodium carboxymethyl cellulose and optimization of the granulation process and low nitrite/nitrate containing excipients can lead to the manufacture of NDMA-free product. Golob et al. (2022) detected NDMA in FDF of high blood pressure tablets, but not in the bulk drug product. They identified nitrocellulose primer in a lidding foil as the likely source of NDMA formation during blistering operations at elevated temperatures and recommended using nitrocellulose-free blister material as a replacement.

Tsutsumi et al. (2019) investigated methods for analyzing NDMA levels in valsartan with GC-MS/MS using selected ion monitoring (SIM) mode. They tested commercially available products in Japan which originated from a company in whose products NDMA had previously been detected; however, they

5. POTENTIAL FOR HUMAN EXPOSURE

observed that there were no NDMA levels in these samples above the detection limits of the analytical method they used to test the samples. Khorol'skii et al. (2019) also discussed analytical methods for accurately determining levels of NDMA in valsartan by using direct-introduction or vapor-phase analysis employing GC-MS/MS in SIM and multiple reaction monitoring (MRM). They determined direct-introduction SIM and MRM methods were comparable to SIM and MRM methods using vapor-phase analysis with similar detection and quantification limits.

The sources and levels of NDMA in pharmaceutical products are evolving areas of research. The reader is referred to the FDA website (<https://www.fda.gov>) for up-to-date information.

Tobacco Products. N-Nitrosamines, including NDMA, may be found in commercially available tobacco products in the United States, but little information on levels of NDMA in these products was identified in available literature. The literature on N-nitrosamine levels in tobacco products is largely focused on compounds other than NDMA (specifically, N-nitrosornicotine [NNN], 4-[N-nitrosomethylamino]-1-[3-pyridyl]-1-butanone [NNK] N-nitrosoanatabine, and N-nitrosoanabasine) (Gushgari and Halden 2018). In a review of international literature, Smith et al. (2000) reported NDMA concentrations up to 7.6 ng/cigarette in mainstream smoke. In an older study, Brunnemann et al. (1983) reported NDMA in mainstream cigarette smoke (4.2–15 ng/cigarette) and sidestream (secondhand or environmental) cigarette smoke (460–1,880 ng/cigarette). A study from 1973 reported a measurement of 160 ng NDMA in smoke condensate from a cigar (McCormick et al. 1973). In electronic cigarette fluid and nicotine cessation products, concentrations of N-nitrosamines are more than 97% lower than in traditional cigarettes (Gushgari and Halden 2018); however, data on concentrations of NDMA in such products were not located.

Toiletry and Cosmetic Products. N-Nitrosamines have been found to occur in a variety of toiletry and cosmetic products, including shampoos, hair conditioners, color toners, shower gels, bath cremes and oils, children's shampoos, children's bath and health care products, and face tonics, cleansers, and masks. Data on NDMA levels in these products were not located, but according to Hrudey et al. (2013), the levels and associated potential exposure are negligible. Consistent with this characterization, Gushgari and Halden (2018) reported that NDMA represents only a small fraction (0.01%) of the N-nitrosamine content in cosmetic products, which is dominated by N-nitrosodiethanolamine resulting from nitrosation of di- and tri-ethanolamine components.

5. POTENTIAL FOR HUMAN EXPOSURE

Rubber Products. Rubber products may contain N-nitrosoamines (including NDMA); these are postulated to derive from additives used in rubber vulcanization (Park et al. 2018). In 1985, the FDA established an action level of 10 ppb ($\mu\text{g}/\text{kg}$) for individual N-nitrosamines in rubber nipples (FDA 2005b). Data on NDMA levels in rubber nipples produced in the United States after the action level was established were not located. Using 30 samples from Korea, Park et al. (2018) reported a range of 1.02–3.67 $\mu\text{g}/\text{kg}$ NDMA (presumably reported as μg NDMA per kg rubber sample) when artificial saliva was exposed to silicone and natural rubber nipples for 24 hours. These authors also measured NDMA migrating from other rubber baby products (1.07–1.72 $\mu\text{g}/\text{kg}$ in 5 samples) and rubber bakeware (1.38–1.67 $\mu\text{g}/\text{kg}$ in 3 samples); NDMA migration was not detected in 16 samples of artificial saliva exposed to rubber cooking utensils (Park et al. 2018). Using a similar technique with a 1-hour exposure duration, RIVM measured the migration of NDMA from rubber balloons; as reported by the Scientific Committee on Consumer Products (SCCP 2007), the maximum estimate of NDMA release was 2.82 mg/kg rubber/hour. SCCP (2007) noted that between samples collected in 2002 and 2004, there was evidence for a reduction in nitrosamine release from balloon samples. Rubber gaskets may also be a source of NDMA in drinking water distribution systems (EPA 2016).

Pesticides. In studies conducted in the 1970s, NDMA was found to occur in various technical and commercial pesticides used in agriculture, hospitals, and homes (Bontoyan et al. 1979; Cohen and Zweig 1978; Hindle et al. 1987; Ross et al. 1977). WHO (2008) reported that concentrations of NDMA in pesticides are decreasing over time, but recent data in the United States were not located. Dimethylamine-based pesticides (e.g., bromacil, benzolin, 2,4-D, dicamba, 2-methyl-4-chlorophenoxyacetic acid, and mecoprop) may be contaminated with NDMA. In its Six-Year Review of nitrosamines, the EPA (2016) reported that NDMA was detected in 49 of 100 Canadian samples (collected since 1990) of dimethylamine phenoxy acid herbicides at an average level of 0.44 $\mu\text{g}/\text{g}$ (ppm) and a maximum concentration of 2.32 $\mu\text{g}/\text{g}$ (ppm).

Municipal Sewage Sludge. Data from the 1980s showed that NDMA was a common constituent of municipal sewage sludge (Brewer et al. 1980; Mumma et al. 1984). In the 1980s, NDMA was detected at levels ranging from 0.6 to 45 ppb in dried sludges from 14 out of 15 cities geographically located throughout the United States (Mumma et al. 1984). Occurrence of NDMA in sewage sludge was attributed to biological and chemical transformation of alkylamines in the presence of nitrite (Ayanaba and Alexander 1974; Mills and Alexander 1976; Pancholy 1978). Biosolids that are often applied to agricultural lands to supply nutrient-rich organic materials to the soils have been shown to contain nitrosamines, including NDMA (Venkatesan et al. 2014). Biosolid materials obtained from 74 WWTPs

5. POTENTIAL FOR HUMAN EXPOSURE

in the contiguous United States contained NDMA at a detection frequency of approximately 3% and at an average concentration of 504 ± 417 $\mu\text{g}/\text{kg}$ dry weight of biosolid.

5.6 GENERAL POPULATION EXPOSURE

For the general population, the primary route of exposure to NDMA is through endogenous production. Exogenous sources of NDMA to which the general population may be exposed include foods and malt beverages, water, cigarette smoke, and to a lesser extent rubber products, toiletry and cosmetic products, and pesticides. Exposure to NDMA and other nitrosamines from water can arise from direct ingestion of drinking water; through inhalation and dermal contact when showering or bathing; or from inhalation, dermal contact, and incidental ingestion while swimming in a chlorinated pool (Chowdhury 2014; Mustapha et al. 2021). Some people may have had exposures to NDMA through the use of contaminated medications prior to their recall.

Hrudey et al. (2013) prepared a detailed analysis of the endogenous production of NDMA, including estimates of the daily rate of production. NDMA is produced endogenously through acid-catalyzed nitrosation of amine precursors (primarily in the stomach) and through biologically catalyzed nitrosation in other tissues including the oral cavity, intestine, liver, blood, and bladder. The rate of acid-nitrosation is influenced by the pKa of amine precursors in the stomach, while biologically catalyzed nitrosation is influenced by levels of amino acids that compete for nitrite (Hrudey et al. 2013). It is believed that systemic (biologically catalyzed) nitrosation is the primary contributor to endogenous NDMA production (higher than acid-catalyzed) except when there are very high dietary intakes of amine and nitrate precursors (Hrudey et al. 2013). Using different methods based on measured human NDMA blood levels, O⁶-methylguanine DNA adducts, and urinary excretion levels, Hrudey et al. (2013) estimated the rate of endogenous production to be approximately 1 mg/day (equivalent to 0.014 mg/kg/day for a 70-kg adult). A study examined the mean urinary excretion of NDMA using 25 subjects who consumed a diet that was initially low in nitrate for 7 consecutive days followed by a diet that was high in nitrate levels in the second week. Mean urinary NDMA levels in the control week were 287 ng per 24-hour period but increased to 871 ng per 24-hour period in the second week when the subjects were consuming a diet high in nitrate concentration (Vermeer et al. 1998). Subjects consuming either a diet of processed red meat or unprocessed white meat (3.75 g/kg body weight) for 2 weeks showed significantly greater urinary excretion of apparent total N-nitroso compounds in the second week when they used drinking water high in nitrate levels as opposed to the first week when nitrate levels in drinking water were kept low (van Breda et al. 2019).

5. POTENTIAL FOR HUMAN EXPOSURE

Estimates of exogenous NDMA exposure (primarily food, beverages, and drinking water) among consumers of Western diets have been reported by a few investigators. The most recent estimates, which made use of the extensive drinking water data collected for the UCMR2, were published by Hrudey et al. (2013) and are shown in Table 5-7. White (2020) reported a comparable estimate of adult NDMA intake from food and water (110 ng/day or ~1.6 ng/kg/day for a 70-kg adult).

Table 5-7. Estimates of Daily Intake of N-Nitrosodimethylamine (NDMA) from Endogenous and Exogenous Sources for Selected Age Groups (ng/kg Body Weight/Day)

Source	Mean			95 th Percentile		
	0– 0.5 years	6– 12 years	20– 49 years	0– 0.5 years	6– 12 years	20– 49 years
Endogenous production	– ^a	–	1.4–35	–	–	4.1–62
Food ^b						
Without beer included	0.011	1.6–1.8	0.7–0.8	8.9	2.8	1.6
With beer included	NA	NA	1	NA	NA	2.1
Drinking water	0.05–0.37	0.008–0.07	0.007–0.06	0.12–1.6	0.02–0.26	0.02–0.23

^aNo data.

^bBased on a published study of NDMA concentrations in foods measured between 1987 and 1992 in France.

NA = not applicable

Source: Hrudey et al. 2013.

Hrudey et al. (2013) estimated the mean intake of NDMA in infants exclusively fed powdered infant formula to be 6.9 ng/kg/day (without the contribution of added water), but this estimate is uncertain, as the authors did not identify any measurements of NDMA in formula, but instead used concentrations in milk proteins and nonfat dry milk to calculate intake. Similarly, these authors estimated that exclusively breast-fed infants may take in 15 ng NDMA/kg/day on average, but this estimate is based on NDMA concentrations in breast milk from two older studies (Lakritz and Pensabene 1984; Uibu et al. 1996).

WHO (2002) estimated that “reasonable worst case” exposures to NDMA in ambient air ranged up to 11 ng/kg/day. These estimates were based on measurements of NDMA in short-term samples of ambient air near point sources (rubber production facilities) in Ontario in 1992. As a result, these estimates are of uncertain relevance to long-term exposures under current conditions and at locations further from point sources.

5. POTENTIAL FOR HUMAN EXPOSURE

NDMA has been detected in several prescription and over-the-counter medications, including angiotensin II receptor blockers like valsartan, heartburn medications like ranitidine and nizatidine, and the diabetes medication, metformin extended-release (FDA 2019a, 2019b, 2020a). Pottegard et al. (2018) estimated daily NDMA exposures of 0.14–0.31 $\mu\text{g}/\text{kg}/\text{day}$ from valsartan use based on measured concentrations of NDMA in valsartan tablets. Several of these substances have been recalled by the manufacturers or by the FDA; however, they were commonly used as prescription and over-the-counter treatments prior to this.

No estimates of plausible current general population exposure to NDMA from other sources (tobacco use; migration from rubber products such as bottle nipples, pacifiers, or cooking implements; handling or application of toiletries and cosmetics; or pesticide use) were located. As noted earlier, FDA (2005b) established an action level of 10 ppb ($\mu\text{g}/\text{kg}$) for NDMA in rubber baby bottle nipples in the United States more than 30 years ago, so it is expected that current NDMA levels are lower than 10 $\mu\text{g}/\text{kg}$.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Occupational settings in which there is potential for exposure to NDMA include, but are not limited to, leather tanneries; rubber and tire industries; rocket fuel industries; dye manufacturers; soap, detergent and surfactant industries; foundries (core-making); fish-processing industries (fish-meal production); pesticide manufacturers; warehouse and sale rooms (especially for rubber products); and laboratories using NDMA for experiments (Ducos et al. 1988; de Vocht et al. 2007; Oury et al. 1997; Reh and Fajen 1996; Rounbehler et al. 1979; Spiegelhalder and Preussman 1983; Tricker et al. 1989). Nitrosamines such as NDMA may form in the air of occupational settings when nitrogen oxides, which are ubiquitous in air, react with amines and moisture. Exposure may result from inhalation or dermal contact. N-nitrosamines, including NDMA, were monitored in the breathing zone of 96 workers employed at eight different companies in the rubber industry in Sweden (Jönsson et al. 2009). Total nitrosamine levels ranged from below the detection limits to 36 $\mu\text{g}/\text{m}^3$. For NDMA, the median levels ranged from below the detection limit of 0.19 $\mu\text{g}/\text{m}^3$ (3-hour sampling time) to 8.2 $\mu\text{g}/\text{m}^3$. A comprehensive study that examined levels of nitrosamines in air samples in the British rubber industry using the EU-EXASRUB database over the period of 1977–2002 reported that the arithmetic mean of measured NDMA levels over all job descriptions was 0.32 $\mu\text{g}/\text{m}^3$ (N=2,023), while the reported geometric mean was 0.16 $\mu\text{g}/\text{m}^3$; 88.7% of the samples were below the detection limits (Hidajat et al. 2019a).

5. POTENTIAL FOR HUMAN EXPOSURE

It appears that those segments of the general population with potentially high exposure to NDMA from exogenous sources would include tobacco smokers and nonsmokers who come in contact with tobacco smoke for extended periods of time (reviewed by Smith et al. 2000), people who consume large quantities of foods or beverages containing NDMA or its precursors (e.g., nitrites) (Baxter et al. 2007; Fan and Lin 2018; Lee 2019; Stuff et al. 2009), and individuals who have taken medications containing NDMA or its precursors (FDA 2019a, 2019b, 2020a) for prolonged periods of time.

In addition to dietary intake of precursors, other factors can affect the rate of endogenous NDMA production. One of the most important and well-studied appears to be inflammation, which increases endogenous NO production (Hrudey et al. 2013). A number of conditions associated with inflammation have been shown to increase NO synthesis and NDMA formation in animal studies; in humans, bladder infections, schistosomiasis, and liver fluke infections have been demonstrated to result in higher levels of endogenous NDMA (reviewed by Hrudey et al. 2013).