# Environmental Guidelines and Regulations for Nitramines: A Policy Summary

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# Table of Contents

## Executive Summary

This report summarizes environmental guidelines and regulatory context for nitramines, including: a summary of health-related scientific information; background information on nitramine formation; potential policy concerns and historical regulation; information on environmental concentrations and sources; and a summary of emerging issues.

Nitramines have been shown to be carcinogenic in laboratory animals, though information on these compounds is limited and regulatory authorities have taken few actions to date to address these substances. Most regulations and policies addressing nitramines have focused on nitramine explosive compounds; however, emerging interest in nitrosamines as drinking water contaminants may lead to more action on nitramines which often occur together in the environment.

Nitramine carcinogenicity has been measured in laboratory animals such as rats; however, carcinogenic potency for nitramines is lower than that of nitrosamines. With respect to nitrosamine explosives, health concerns focus on neurotoxicity. The explosive RDX may be carcinogenic; however, a recent re-evaluation of carcinogenicity data indicated it may be less potent than previously thought. In general, based on structure-activity relationships, aliphatic N-nitro groups and nitroaromatic compounds are associated with carcinogenic activity.

Nitramines are formed through nitrosation of amines. They co-exist in redox equilibrium with nitrosamines in the environment. Pathways of formation have been recently investigated, particularly in environmental and biological systems.

Aliphatic nitramines are currently unregulated in major regulatory systems in Europe and the United States. RDX is a potential candidate for regulation in the United States in drinking water systems, and the U.S. EPA has calculated a health advisory level for RDX. Nitramines are persistent in the environment, but not likely to bioaccumulate. They have been measured in environmental systems together with nitrosamines.

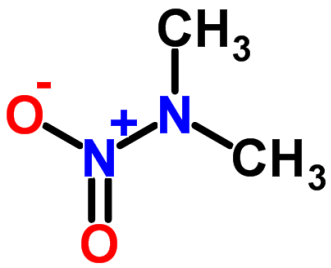
Emerging policy concerns about nitramines may emerge through regulation of nitramine explosives, drinking water concerns about nitrosamines, and concern due to their carcinogenic potential.

# 1. Introduction

This report summarizes the environmental guidelines and regulatory context for nitramines. It includes: a summary of the health-related scientific information available (Section 2); background information on pathways of formation of nitramines (Section 3); areas of potential policy concern and historical actions (Section 4); a comparative analysis of levels of nitramine environmental concentrations and a survey of environmental sources (Section 5). A brief summary of emerging issues is presented in section 6, and references to peer-reviewed literature and internet links to regulatory documentation are provided in Section 7.

Nitramines (also known as nitroamines) are compounds of the chemical form $R_2N$-$NO_2$. They are oxidation products of the nitrosamines ($R_1NNOR_2$) (Lijinksy, 1992). The category of nitramines encompasses a wide range of substances depending on the characteristics of $R_2$. Here, the discussion below focuses on N-nitrodimethylamine and related compounds, but where appropriate, discusses other nitramines. A structural diagram of N-nitrodimethylamine (DMN) is presented as Figure 1.

**Figure 1. Structure of N-nitrodimethylamine.**
(source: ChemSpider Database, http://www.chemspider.com/RecordView.aspx?rid=c5b40666-8e89-443d-bac4-3d9ef1fc68c6 )




Nitramines have been shown to be carcinogenic and mutagenic in laboratory animals. However, the amount of information available on these compounds is limited, and regulatory authorities have taken little action to date to address environmental concentrations and exposure to nitramines. This is in contrast to nitrosamines, which have garnered increasing regulatory attention in the last decade.

An area of increasing policy interest relative to nitramines regards nitramine explosives. Environmental releases of explosive compounds such as RDX (1,3,5-

Trinitroperhydro-1,3,5-triazine) and HMX (Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine) have been recently targeted as emerging contaminants, for example in drinking water. DMN has been used as a model compound in studies of nitramine explosives due to the similar properties of the nitramine group (Borges, 2008). In addition, recent growing policy activity around nitrosamines may translate into increased interest in nitramines, which are often found in the environment along with nitrosamines.

## 2. Health risks of Nitramines

A number of animal studies have found associations between aliphatic nitramines and carcinogenicity. Tumorigenic activity has been measured in rats, specifically tumors in the nasal cavities and liver. The Carcinogenic Potency Database (http://potency.berkeley.edu), a metaanalysis of carcinogenicity experiments, notes a mean $TD_{50}$ value for dimethylnitramine of 0.547 mg $kg^{-1}$ $d^{-1}$, with substantial (>10-fold) variation within different experiments. (The corresponding value for N-nitrosodimethylamine is 0.0959 mg $kg^{-1}$ $d^{-1}$for rats, which is indicative of much stronger carcinogenic potency). Table 1 presents $TD_{50}$ values from the Carcinogenic Potency Database for available nitramines and nitrosamines; a larger dose is indicative of a smaller carcinogenic effect.

**Table 1. $TD_{50}$ values from the Carcinogenic Potency Database for available nitramines and nitrosamines**

| Substance | $TD_{50}$ (rat), mg $kg^{-1}$ $d^{-1}$ |
|---|---|
| Dimethylnitramine | 0.547 |
| Methylnitramine | 17.4 |
| N-nitrosodimethylamine | 0.0959 |
| N-nitrosodiethylamine | 0.0536 |
| N-nitrosodiphenylamine | 167 |

Pliss et al. (1982) measured carcinogenic action of dimethylnitramine, diethylnitramine, and dibutylnitramine in various species (rats, amphibians, fish and mollusks). They found that dimethylnitramine induced tumors in frogs and amphibians, and both diethyl- and dibutylnitramine induced tumors in rats. They note, however, that the carcinogenic effect of nitramines appeared much lower than related nitrosamines.

Much of the toxicity and health effects information on nitramine exposure focuses on nitramine explosives. RDX has been classified as a possible human carcinogen (Category C) by the U.S. Environmental Protection Agency. HMX has been deemed not classifiable (Category D) by the U.S. EPA with regard to carcinogenicity. However, the health risk assessments of RDX and related nitramines may not be relevant with respect to assessment of aliphatic nitramines in the environment. In

July 2010, the U.S. Agency for Toxic Substances and Disease Registry released an updated Toxicological Profile for RDX (U.S. Department of Health and Human Services, 2010). Health effects most commonly reported from RDX in humans were neurologic effects such as seizures and convulsions. Laboratory animals also exhibited neurological impacts, as well as potential toxicity to the hematological system and liver and potential reproductive impacts. With respect to carcinogenicity, a link between RDX and hepatocellular adenomas and carcinomas was found in female mice; however, a reevaluation of that study found that carcinogenicity was not as potent as previously thought (U.S. Department of Health and Human Services, 2010). The U.S. EPA had classified RDX as possibly carcinogenic to humans prior to this re-evaluation; the International Agency for Research on Cancer (IARC) has not classified its carcinogenicity.

It has been noted in development of structure-activity relationships that both aliphatic N-nitro groups and nitroaromatic compounds are associated with carcinogenic activity. The European Chemicals Bureau has developed a hazard estimation software called Toxtree, which includes a module to address carcinogenicity and mutagenicity; in this software, the functional groups in nitramines are flagged for structural alerts for further analysis (Begnigni et al., 2008). Substances that are flagged are to undergo Quantitative Structure Activity Relationships (QSAR) analysis.

## 3. Pathways of Nitramine Formation

Nitramines can be formed through the nitration of amines. They are related to nitrosamines in that yields of nitrosamine and nitramine formation through nitration/nitrosation can vary depending on the starting amine and characteristics of the reactive solution (Anikin et al., 2009). Nitramines can also be oxidation products of nitrosamines. Photolysis can also be a pathway of nitramine formation from nitrosamine: dimethylnitramine can be formed through photolysis of dimethylnitrosamine (Pitts et al., 1978). In the atmosphere, dimethylnitramine and dimethylnitrosamine exist in redox equilibrium:

**Equation 1. Redox equilibrium between dimethylnitramine and dimethylnitrosamine. From Mezyk et al., 2006.**

$$(CH_3)_2N-NO \overset{\text{redox}}{\rightleftharpoons} (CH_3)_2N-NO_2$$

One area of some scientific discussion is the chemical reactions that produce nitrosamines and nitramines in both environmental and human systems. Westin et al. (1987) tested nitrosation of the amines dibutylamine, diethylamine, and diethylamine from children's pacifiers and baby-bottle nipples in artificial saliva, and found high levels of nitramines co-occurring with nitrosamines. More recently, the pathways of nitrosamine vs. nitramine formation have been of research interest

both in environmental (Walse and Mitch, 2008) and biological systems (Lv et al., 2008).

## 4. Potential Policy Concern and Historical Action

Aliphatic nitramines are currently unregulated substances by major regulatory authorities in the United States and European Union. The largest present-day policy activity surrounding nitramines in general relates to the presence and management of nitramine explosives in the environment. In addition, in developing general principles for regulation, policy authorities have expressed intent to regulate substances with carcinogenic, mutagenic or reproductive toxicity properties, and those that are persistent in the environment.

In the U.S., RDX has been listed in the EPA's Unregulated Contaminants Monitoring Rule. This means that data were required to be collected between 2008-2010 on their presence in drinking water systems nationwide (Unregulated Contaminant Monitoring Regulation (UCMR) for Public Water Systems Revisions, 2007). In October 2009, RDX was listed on the U.S. EPA's contaminant candidate list, a list of priority drinking water contaminants for which EPA will research whether regulations are needed. Though several nitrosamines are on this list as well, no other nitramines are included. In 2006, EPA also calculated a "health advisory" (non-enforceable guideline value) reference dose of RDX in drinking water of 0.003 mg $kg^{-1}$ $day^{-1}$, and a concentration associated with $10^{-4}$ cancer risk of 0.03 mg/L. A reference dose is an estimate of a daily exposure that is likely to be without appreciable risk of deleterious effects to populations (including sensitive groups). The EPA number was based on a no-observed adverse effect level (NOAEL) of 0.3 mg $kg^{-1}$ $day^{-1}$ based on inflammation of prostate in rates exposed to dietary RDX for two years, applying an uncertainty factor of 100 (factor of 10 for animal-human extrapolation and factor of 10 to protect susceptible individuals) (U.S. Department of Health and Human Services, 2010). The U.S. State of New Jersey used this level to set a standard of 0.5 μg $L^{-1}$ for RDX in drinking water (New Jersey, 2008).

With respect to drinking water regulation in the United States, an important factor in the ability of domestic authorities to regulate drinking water concentrations is the availability of test methods for analysis. EPA Method 8330B (2006) covers the analysis of 17 nitroaromatics, nitramines, and nitrate esters by High-Performance Liquid Chromatography (LC). These compounds are either used in the manufacture of explosives or propellants, are impurities in these manufacturing processes, or are degradation products of these substances (Richardson, 2007). As test methods are used by implementing authorities in the U.S. to monitor compliance, they are an indication of present and upcoming regulatory priorities.

**Table 2. Analytes covered by U.S. EPA Method 8330B.**

| Analyte | Abbreviation | CAS number |
|---|---|---|
| Octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine | HMX | 2691-41-0 |
| Hexahydro-1,3,5-trinitro-1,3,5-triazine | RDX | 121-82-4 |
| 1,3,5-Trinitrobenzene | 1,3,5-TNB | 99-35-4 |
| 1,3-Dinitrobenzene | 1,3-DNB | 99-65-0 |
| Methyl-2,4,6-trinitrophenylnitramine | Tetryl | 479-45-8 |
| Nitrobenzene | NB | 98-95-3 |
| 2,4,6-Trinitrotoluene | 2,4,6-TNT | 118-96-7 |
| 4-Amino-2,6-dinitrotoluene | 4-Am-DNT | 19406-51-0 |
| 2-Amino-4,6-dinitrotoluene | 2-Am-DNT | 35572-78-2 |
| 2,4-Dinitrotoluene | 2,4-DNT | 121-14-2 |
| 2,6-Dinitrotoluene | 2,6-DNT | 606-20-2 |
| 2-Nitrotoluene | 2-NT | 88-72-2 |
| 4-Nitrotoluene | 4-NT | 99-99-0 |
| Nitroglycerin | NG | 55-63-0 |
| Pentaerythritol tetranitrate | PETN | 78-11-5 |
| 3,5-Dinitroaniline | 3,5-DNA | 618-87-1 |

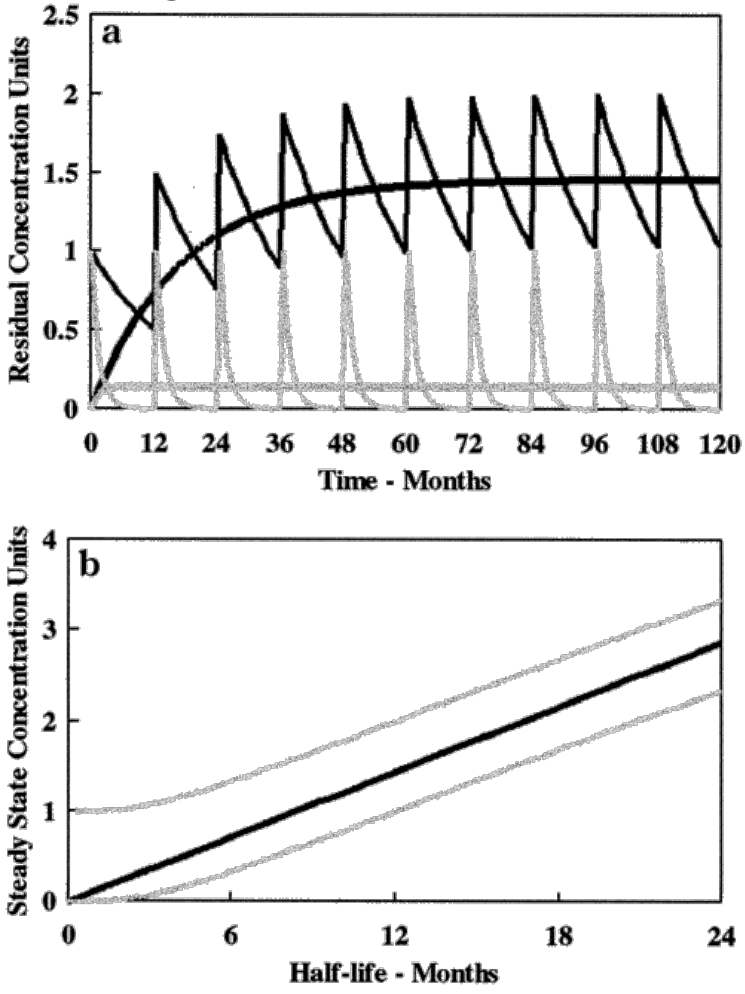
Under the European Union's regulation on safe use of chemical substances (Registration, Evaluation, Authorisation and Restriction of Chemical substances, EC 1907/2006), substances that are of very high concern are those that are carcinogenic, mutagenic or reproductive toxins, or those that are very persistent and very bioaccumulative. Nitramines are potential carcinogens. In addition, they may fulfill criteria for persistence. According to a model estimate based on physical properties, overall persistence in water was estimated at ≈40 days, half-life in soil ≈75 days and sediment ≈300 days.[1] This puts these substances near the "very persistent" criteria used by REACH, which is >60 days in water, >180 days in soil, or >180 days in sediment. It should be noted that a chemical under REACH is deemed very persistent if it meets even one of these criteria. The same persistence criteria in water, soil, or sediment are used under the Convention on Long-Range Transboundary Air Pollution and the Stockholm Convention on Persistent Organic Pollutants.

[1] Based on calculations with the U.S. EPA's EPI Suite, see http://www.epa.gov/opptintr/exposure/pubs/episuite.htm for information and http://www.chemspider.com/Chemical-Structure.18955.html for reported data on persistence using EPISuite.

It is not expected that nitramines would bioaccumulate. An indication of bioaccumulation potential for chemical substances is given by the octanol-water partition coefficient (Kow), usually expressed as a logarithmic value. This parameter represents a ratio of solubility in octanol (a surrogate for lipid) relative to solubility in water. Water-soluble compounds have low Kow values, while lipid soluble compounds have high Kow values. A Log Kow > 5 is a threshold value used by the Stockholm Convention on Persistent Organic Pollutants as indicative of a high level of bioaccumulation. The predicted value of Log Kow for dimethylnitramine is -2.89 (calculated in ChemSpider Database). For comparison, the Log Kow for NDMA is -0.57 (U.S. Department of Health and Human Services, 1989). For RDX, the Log Kow is estimated at 0.87 (U.S. Department of Health and Human Services, 2010). For all of these compounds, the relatively low values indicate water solubility and thus a low propensity to bioaccumulate.

It should be noted that there are no "bright lines" or clear scientifically determined thresholds for determining when environmental persistence becomes a policy concern (Rodan et al., 1999). Figure 2 (from Rodan et al., 1999) shows the accumulation over time of two hypothetical chemicals with half-lives of 1 and 12 months in an environmental medium (top panel), assuming either a single release each year or a continuous release. The bottom panel shows the relationship between chemical half-life and steady-state concentration. This figure illustrates that there is no clear universal threshold level for persistence, where a pollutant behavior would modify over time. Thus, the selection of persistence criteria for environmental media such as water, soil or sediment reflect policy judgments.

**Figure 2. Relationship between persistence (half-life) and environmental concentration.**
**Top panel shows the accumulation of two chemicals with half-life of one month (gray) and 12 months (black), under two release scenarios: continuous (smooth line) and annual (peak-trough). Bottom panel shows theoretical relationship between half-life and steady-state concentration (black); gray lines show maximum and minimum concentration given annual release scenario. Figure from Rodan et al., 1999.**




## 5. Environmental Concentrations and Sources

Nitramine explosives have been measured in groundwater at many military installations in both the United States and Europe (Levsen et al., 1993).
In a recent study, DMN was detected at median values of 64.5, 50, and 203 ng L-1 in outdoor pools, indoor pools, and hot tubs, respectively (Walse and Mitch, 2008). These levels were comparable to measured levels of the nitrosamine N-Nitrosodimethylamine (NDMA).

DMN has a half-life of approximately 2 days in the atmosphere, relative to oxidation by OH radicals (Tuazon et al., 1984). This suggests that DMN may be subject to transport beyond a local to regional area. A 2-day half-life is used as a screening criterion for long-range transport under international agreements on toxic chemicals, such as the Convention on Long-Range Transboundary Air Pollution and the Stockholm Convention on Persistent Organic Pollutants (Rodan et al., 1999; Selin and Eckley, 2003). Persistence in a transport medium such as air has different policy ramifications compared with persistence in water, soil or sediment, as this may determine the political scope (local, national, regional, global) under which the substance may be of concern due to its long-range transport. Given their lack of bioaccumulation, however, it is unlikely that nitramines would be subject to regulation as a persistent, bioaccumulative toxic substance.

## 6. Emerging Issues

Given the existing landscape of regulations on nitramines and similar substances, emerging regulations could take a number of different forms.

Assessment of potential regulation of nitramine explosives as a drinking water contaminant is well under way in the United States. Nitramine explosives are likely to continue to be subject to regulation at contaminated sites. With respect to aliphatic nitramines, drinking water regulations could emerge as a result of either concern about contamination or degradation products from sites where explosive residue is present; or from additional concern about nitration as a potential pathway to produce drinking water disinfection byproducts.

Concern about the carcinogenic properties of nitramines seem to be most likely to emerge in policy debates as additional scientific information links pathways of transformation between nitrosamines and nitramines, both in the environment and in biological systems. Given that nitrosamines are generally regarded as more potent carcinogens, any mechanisms of transformation that project an increasing pathway of nitrosamine formation could garner potential regulatory interest faster than nitramines alone. Likely future regulation of nitrosamines would most likely focus on their carcinogenicity and/or toxicity.

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