Wildlife Toxicity Assessment for Hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) Breakdown Products:
Hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine (MNX)
Hexahydro-1,3-dinitroso-5-nitro-1,3,5-triazine (DNX)
Hexahydro-1,3,5-trinitroso-1,3,5-triazine (TNX)
4-Nitro-2,4-diazabutanal (NDAB)
Methylenedinitramine (MEDINA)

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14. ABSTRACT
This WTA is based on a thorough review of the scientific literature regarding the toxicological characteristics of the breakdown products of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) of relevance to the health of wildlife (mammals, birds, amphibians, and reptiles) exposed to these substances. While the parent compound RDX is mostly likely to be found in highest concentrations where contaminated sites exist, consideration should also be given to potential breakdown products and their toxicity when information is available. Evaluating the toxicity of RDX will contribute to the derivation of toxicity reference values (TRVs) for use as screening-level benchmarks for wildlife near contaminated sites. The protocol for the performance of this WTA is available in detail in Technical Guide No. 254 (Standard Practice for Wildlife Toxicity Reference Values).

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WILDLIFE TOXICITY ASSESSMENT FOR RDX BREAKDOWN PRODUCTS

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Department of the Army
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Wildlife Toxicity Assessment for RDX Breakdown Products

CAS No. 13980-04-6, 5755-27-1, 80251-29-2 **April 2020**

1. INTRODUCTION

This Wildlife Toxicity Assessment (WTA) is based on a thorough review of the scientific literature regarding the toxicological characteristics of the breakdown products of hexahydro-1,3,5-trinitro-1,3,5-triazine (RDX) that may pertain to the health of wildlife (mammals, birds, amphibians, and reptiles) exposed to these substances. While the parent compound RDX is mostly likely to be found in highest concentrations where contaminated sites exist, consideration should also be given to potential breakdown products and their toxicity when information is available. RDX is a cyclic nitramine with three nitro side groups (-NO_2) at nitrogen atoms 1,3, and 5 (Figure 1). Sequential reduction of one or more of the nitro-substituents to nitroso groups yields three closed-ring breakdown products of RDX; hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine (MNX: CAS No. 80251-29-2), hexahydro-1,3-dinitroso-5-nitro-1,3,5-triazine (DNX: CAS No. 5755-27-1), and hexahydro-1,3,5-trinitroso-1,3,5-triazine (TNX: CAS No. 13980-04-6). In addition, two ring cleavage products termed methylenedinitramine (MEDINA, CAS No. 14168-44-6) and 4-nitro-2,4-diazabutanal (NDAB, CAS No. 479422-92-9) have been identified (Figure 2). This report assesses the current knowledge on the potential effects of these degradation products on terrestrial vertebrate wildlife, notwithstanding the effects of the parent compound RDX for which the wildlife toxicity has been reviewed in a previously published companion document (Williams et al. 2015). The technical guidance for the performance of this assessment is documented in the U.S. Army Public Health Center Technical Guide 254, the *Standard Practice for Wildlife Toxicity Reference Values* (USACHPPM 2000).

2. TOXICITY PROFILE

2.1 Literature Review

Literature reviews were carried out for each of the three metabolites as described in Appendix B, including sources searched, dates of searches, search terms, and so forth. Since the major body of work has been carried out on the parent compound RDX, the literature was sparse with publications related to any of the three metabolites and even sparser with respect to wildlife. There is a relatively good understanding of metabolite formation and some measures of metabolites in the environment, but toxicity studies using only the metabolites number a few. The relevant studies are reviewed below.

RDX can be released into the environment during munition conversions from load, assembly, and pack (LAP) process; it also has been known to have released into the environment from waste streams during manufacturing at Army Ammunition plants (Talmage et al. 1999,

Abadin et al. 2012. Initially, it was thought that RDX biodegradation occurred in the natural environment under anaerobic conditions, yielding the reductive products mono-, di-, and tri-nitroso products TNX, MNX, and DNX (McCormick et al. 1981a). These three breakdown products are formed by sequential removal of a single oxygen from each nitro group (see Figure 1) to form a nitroso group; it was assumed that these would likely be present wherever RDX was found in the environment. However, two other breakdown products, MEDINA (methylenedinitramine) and NDAB (4-nitro-2,4-diazabutanal) (Figure 2) were also shown to be formed (Fournier, et al. 2004, Jackson, et al. 2007) from breakdown of RDX exposed to *Rhodoccus* and other species of bacteria or fungi. Both NDAB and MEDINA, a butenal and an amine, are open ring breakdown products formed under aerobic and anaerobic conditions respectively. MEDINA, NDAB, TNX, MNX, and DNX have no known commercial, industrial, or natural sources; so the presence of these compounds in the environment are distinctive indicators of RDX transformation (Beller and Tiemeier 2002).

MEDINA and NDAB, along with the three nitroso breakdown products, have been identified in groundwater samples where RDX was found (Zhao et al. 2011). Zhao et al. showed that while NDAB and nitroso derivatives were stable in aquifer samples under typical ambient environmental conditions, MEDINA was highly unstable and would most likely not be found without additional efforts to preserve samples (Zhao et al. 2011) and, therefore, would unlikely to be identified with regular sampling of groundwater. RDX is also naturally attenuated by soils (Ronen et al. 2008) but not when the soil has been irradiated to eliminate microbes and fungi (Sheremata et al. 2001). Even microbes found in RDX-contaminated marine sediment have been shown to biodegrade RDX to the three reductive metabolites and MEDINA (Bhatt et al. 2006). Abiotic breakdown of RDX can also occur using (zerovalent) elemental iron (Balakrishnan et al. 2004) and even hydrogen as electron donors (Beller 2002); the iron pathway suggests that RDX breakdown might occur in a cast iron water system (Oh et al. 2005, Larese-Casanova and Scherer 2008). However, the major breakdown pathway is thought to be biotic. Since breakdown products undergo further decomposition to end products of formaldehyde and carbon dioxide, they are unlikely to be persistent and may only be measurable where high concentrations of the parent compound, RDX, persist.

It is worth noting that biotransformation of RDX can occur also after mammalian exposure wherever reduction can take place; with *in-vitro* rabbit P450s (Bhushan et al. 2003), *in vitro* ovine rumen fluid (Eaton et al. 2013), as well as in the intestine of outbred (Pan et al. 2007a) and inbred mice (Pan, et al. 2013). Nonetheless, findings suggest that biotransformation by gut microbes to MNX, DNX, and TNX does take place in the mouse gastrointestinal (GI) tract (Pan et al. 2007a; Pan et al. 2013) and is, therefore, a potential secondary source of exposure to biotransformed products where there are high initial oral exposures to RDX. Since these types of studies can be considered co-exposures, it is difficult to assess the impact of each individual breakdown product. It should be noted that studies of RDX-exposed mammals often neglect or underreport neurological effects (convulsions or seizures), which can have a significant impact on the outcome.

While studies on the metabolism and biodegradation of RDX are available, toxicological studies on TNX, MNX, and DNX are rare and are non-existent for NDAB and MEDINA. While little or nothing is known about the potential toxicity of MEDINA and NDAB, the three nitroso breakdown products belong to a chemical class known as nitrosoamines, which have been positively

associated with cancer in oral exposure to rats (Mirvish et al. 1993) and humans (Magee 1996, Larsson et al. 2006). In addition, there are several toxicity studies available, which have examined the effects of these three breakdown products, primarily studies of acute toxicity with one examination of potential carcinogenicity of TNX. Most of the carcinogenicity tests of TNX were located by cross-referencing other toxicity papers and from using Science Citation Index™. No toxicity information on MNX and DNX were found after an extensive literature search.

2.2 Environmental Fate and Transport

RDX metabolites do not occur naturally and are only present where RDX has been or is being broken down in the environment. RDX may occur in many commercial and military activities including manufacturing of munitions, waste discharge during manufacture (up to 12 micrograms per milliliter (µg/mL) in process wastewater during the manufacture of RDX (McCormick et al. 1981b), testing and training at military facilities, demilitarization programs, and open burning/open detonation (Sheremata et al. 2001). These activities represent the primary release mechanisms of RDX in the environment and have resulted in RDX contamination of soil, surface water, and groundwater at military installations (Sheremata et al. 2001, Beller and Tiemeier 2002).

There are no known commercial, industrial, or natural sources of MNX, DNX, and TNX (Beller and Tiemeier 2002). Rather, these compounds are environmental breakdown products of RDX, which can occur though both geochemical and microbiological processes (Annamaria et al. 2010; Kwon et al. 2011) and even by photo degradation (Hawari et al. 2002) though the reactants are not typical in the latter case. The three nitroso products are formed by the stepwise reduction of the three nitro side groups (–NO2) in RDX (McCormick 1981a, McCormick et al. 1981b, Sheremata et al. 2001) (Figure 1). This was originally shown to occur anaerobically in activated sludge (McCormick et al. 1981a) while subsequent work showed that activated sludge treatment further resulted in a second route of biodegradation that produced the open ring products NDAB and MEDINA (Hawari et al. 2000). It was noted that none of the five reported breakdown products accumulated in the experimental system and that the final breakdown products were methane and carbon dioxide (McCormick et al. 1981a, Hawari et al. 2000) showing complete breakdown of RDX. Formaldehyde was identified as an intermediate product (Hawari et al. 2000).

Initially, MDX, DNX, and TNX were primarily thought to be formed under anaerobic conditions, with little to no formation under aerobic conditions (McCormick et al.1981a, Beller 2002). However, field studies have shown the co-existence of breakdown products from putative aerobic and anaerobic processes in aquifers (Zhao et al. 2011). Therefore, all potential breakdown products can be present in soil and groundwater contaminated with RDX though their presence in surface water is less likely due to the anaerobic conditions. It should also be noted that breakdown products are generally thought to be transient reactants of RDX biotransformation based on laboratory studies (Beller and Tiemeier 2002), specific information on the persistence of these compounds are not available nor is information on degradation rates (half-lives) for MNX, DNX, or TNX available.

WILDLIFE TOXICITY ASSESSMENT FOR RDX BREAKDOWN PRODUCTS

At the Iowa Army Ammunition Plant, MNX, DNX, and TNX were found in all groundwater samples that had concentrations of RDX greater than 1 µg/L, with concentrations of each ranging from 0.03 to 430 micrograms per liter (µg/L). Average concentrations were 65, 25, and 39 µg/L for MNX, DNX, and TNX, respectively (Beller and Tiemeier 2002); products seldom exceeded 4% of RDX concentrations. The authors suggested that the detection of these transient compounds in groundwater likely indicated that RDX biotransformation at the site was an ongoing process.

A list of key physico-chemical properties of TNX that pertain to the environmental fate and transport of the compound is provided in Table 1. Most of these properties were estimated using EPI 2000® Software (https://www.epa.gov/tsca-screening-tools/epi-suitetm-estimation-program-interface) [developed by the U.S. Environmental Protection Agency (USEPA)]. No measured or estimated values were available for MNX and DNX.

TNX has a low-estimated vapor pressure (7.75 X 10^{-7} millimeter Mercury (mm Hg) at 25 °C, USEPA EPI 2000 Software), indicating that TNX is unlikely to partition into air. TNX is highly soluble in water (1 x 10^{-6} milligrams per liter (mg/L) at 25 °C), and has been identified in groundwater (Beller and Tiemeier 2002). Although water solubility data are lacking for MNX and DNX, field and experimental evidence suggests that these compounds are also water soluble. Like TNX, MNX and DNX have been measured in groundwater (Beller and Tiemeier 2002). In the laboratory, microbial degradation of RDX resulted in detectable concentrations of MNX, DNX, and TNX in the aqueous phase and not in the solid sorbed phase (Sheremata et al. 2001). The authors suggested that MNX, DNX, and TNX are formed in the aqueous phase and do not subsequently sorb to topsoil. This is supported by the estimated log K_{ow} [octanol-water partition coefficient] (-1.78) for TNX. However, the estimated log K_{oc} [organic carbon partition coefficient] (2.96) indicates that TNX would be expected to adsorb to suspended sediments and would have moderate to high mobility in soil.

MNX, DNX, and TNX have been found to biodegrade in liquid cultures of municipal anaerobic sludge; however, TNX disappeared at a rate 10 times lower than the parent compound—RDX (Hawari al. 2000). Similar results were observed in the biodegradation of RDX by an anaerobic bacterium isolated from municipal sludge. In this study, TNX degraded at a much lower rate than either RDX or MNX (Zhoa et al. 2002). It was also found that MNX degraded in the control containing killed cells of the bacterium, suggesting that MNX undergoes hydrolysis in water. Conversely, TNX was not degraded in controls with killed cells. These microbial tests suggested that TNX degrades at a slower rate and is more likely to persist and accumulate than MNX. Information for DNX is lacking.

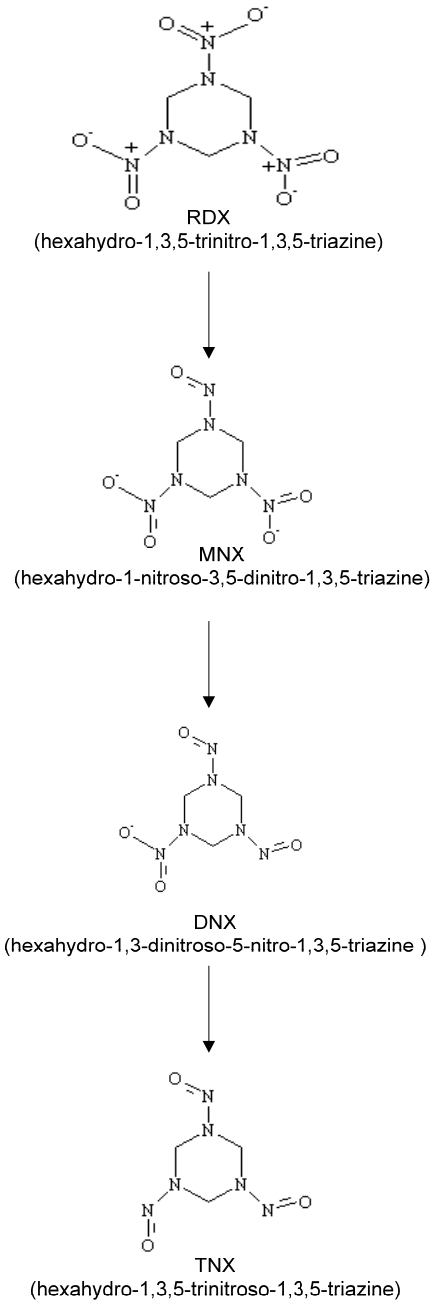

Figure 1. Metabolic Pathway for the RDX Metabolites

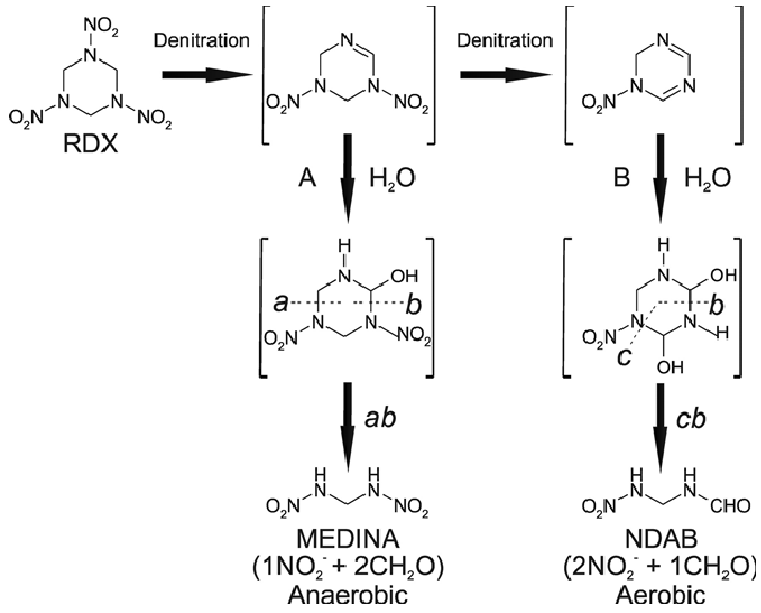

Figure 2. **Proposed Pathway for Aerobic (NDAB) and Anaerobic (MEDINA) Formation *in vivo*** (Source: Jackson et al., 2007)

Phytoremediation of RDX and other explosives has also been studied (Larsson et al. 1999) including the possibility of using transgenic plants (Rylott et al. 2011). Uptake and bio-transformation of RDX takes place in wetland plants (Best et al. 1999) though breakdown products were not identified. Although accumulation of RDX in certain tissues of plants (e.g., leaves and tassels of corn) have been observed, MNX or other products were rarely seen in plant tissue. When it was found, MNX was at low levels compared to RDX. DNX and TNX were not detected in the plant tissue. This suggests that MNX, and most likely DNX and TNX as well, do not readily accumulate in plant tissue (Larson 1997).

Secondary exposure to RDX products could occur after ingestion of parent compound. The production of breakdown products in the gastro-intestinal (GI) tracts of 45d old female deer mice (*Peromyscus maniculatus*) was investigated following exposure to either 10 or 100 mg/kg RDX for 9d (Pan et al. 2007a). TNX was not detected in either the stomach or intestinal tract. MNX was found at 85 and 1318 µg/kg for both respective treatment levels in the stomach, and at 14 and 43 µg/kg in the intestine. DNX was found at 217 µg/kg in the stomach and 40 ug/kg in the intestine for the 10 mg/kg dosed animals, and at 498 and 53 µg/kg respectively in the stomach and intestines for the 100 mg/kg dosed mice. Decreased activity, as measured by stereotyped behaviors (jumping, backward somersaulting), was decreased, and absolute and relative kidney and liver weights were significantly increased in the dose groups having the highest concentrations of MNX and DNX.

The results of this study suggest that reductive biotransformation of RDX occurs mainly in the stomach, but since the ratio of *N*-nitroso breakdown products to RDX were higher in the

intestine than the stomach, it is also believed that this transformation is progressively more efficient as the compounds move through the GI tract (Pan et al. 2007a).

Table 1. Summary of Physical-Chemical Properties of TNX [a]

CAS No.	13980-04-6
Molecular weight	174.12
Color	No data
Physical state	No data
Melting point	145.55°C (MPBPWIN™ v1.40 - mean or weighted melting point estimate)
Boiling point	407.93°C (MPBPWIN v1.40 - adapted Stein and Brown method estimate)
Odor	No data
Solubility in water	1×10^{-6} mg/L at 25 °C (WSKOW™ v1.4, estimated from Log K_{ow})
Partition coefficients:	
Log K_{ow}	-1.78 (KOWWIN™ v1.66 estimate)
Log K_{oc}	2.96 (PCKOCWIN™ v1.66 estimate)
Vapor pressure at 25°C	7.75×10^{-7} mm Hg (MPBPWIN v1.40 - modified grain method estimate)
Henry's Law constant at 25°C	1.69×10^{-8} atm-m^3/mole (HENRYWIN™ v3.10 – bond method estimate) 1.776×10^{-13} atm-m^3/mole (VP/WSol estimate using EPI values)
Conversion factors	1 ppm = 7.12 mg/m^3 1 mg/m^3 = 0.141 ppm 174.12

Note: [a] Physical-chemical properties were not available, even as estimates, for MNX and DNX.
Legend:
atm-m^3/mole: air to moles per cubic meter for water
ppm: parts per million
Source: USEPA EPI Software (2000)

2.3 Summary of Mammalian Toxicity

An extensive literature search was conducted on the toxicity of the RDX breakdown products: TNX, MNX, and DNX as detailed in Appendices A–C. Although numerous toxicity studies have been conducted for RDX, toxicity information on TNX, MNX, and DNX were exceedingly rare or absent in the case of DNX. Two acute studies were found for TNX, and only one for MNX. A chronic study of TNX also appeared to have been conducted in association with the acute test, but no survival information or other reproductive/developmental information was reported (Druckrey, Preussmann et al. 1966, Druckrey, Preussmann et al1967). Several papers discussed the carcinogenicity of TNX (Druckrey 1967, Danz et al. 1973, Amlacher and Rudolph 1981, Pan et al. 2007b). However, all carcinogenicity studies focused on the measurement endpoints commonly performed in carcinogenicity test such as histological examination and

hepatocarcinogenic effects. In one of the studies, mitosis count increased in the presence of dimethyl sulfoxide (DMSO) alone. DMSO is often used as a solvent carrier of TNX and such finding indicates that DMSO may have contributed to the positive carcinogenicity test result for TNX. Because of the possible confounding factor due to DMSO, it is probable that TNX is not a carcinogen, as other researchers have observed (Druckrey 1967, Danz et al. 1973, Amlacher and Rudolph 1981).

2.3.1 Mammalian Oral Toxicity

2.3.1.1 Mammalian Oral Toxicity–Acute

Druckrey et al. (1967) reported the oral gavage lethal dose at 50% (LD_{50}) for TNX to be 160 milligrams per kilograms body weight (mg/kg-bw) in rats, and stated that no liver damage was observed. Smith et al. (2009) reported an oral LD_{50} for TNX in deer mice at 12-, 50-, and 200-day old mice to be 338, 338, and 999 mg/kg, respectively indicating age-dependent acute toxicity. Smith et al. (2007) also determined the LD_{50} for MNX in deer mice at the same ages to be 181, 575, and 542 mg/kg, respectively. Meyer et al. (2005) found the LD_{50} for MNX, identified as the most potent metabolite, in female Sprague-Dawley rats to be 187 mg/kg, the same as their comparative estimate for RDX. Similar to RDX, central nervous system toxicity was observed at this exposure level prior to death as forelimb clonic seizures progressed to generalized clonic and tonic seizures. The highest nonlethal dose was determined to be 94 mg/kg. Meyer et al. also reported an ED_{50} for neurotoxicity to be 57 mg/kg, and showed splenic hemosiderosis and decreased blood hematocrit and hemoglobin concentration to occur at a threshold of 94 mg/kg in 14-day survivors (2005). Jaligama et al. (2013) observed that acute toxicity of MNX caused a modest decrease in hemoglobin and a 50% loss of granulocytes (NOAEL [no-observed adverse effect level] mg/kg); they concluded that delayed suppression of myelo- and erythropoiesis resulted in subsequent decrease of peripheral granulocytes and erythrocytes. No acute toxicity data were located for DNX.

2.3.1.2 Mammalian Oral Toxicity—Subchronic

Smith et al. (2006) exposed pairs of deer mice (*Peromyscus maniculatus*) to 1, 10, or 100 µg/L TNX ad libitum in drinking water through production of three litters. Mice from the first two litters were exposed to the TNX water until postnatal day (PND) 45, and individuals from the last litter were exposed until PND 21. Although reproductive success remained unaltered by TNX, postpartum mortality from day of birth through PND 4 were associated with TNX exposure. Unfortunately, the statistics used in this study do not allow the determination of a LOAEL for mortality. The lowest-observed adverse effect level (LOAEL) for significant decreases in body weight from birth until approximately weaning age, however, was determined to be 100 µg/L. TNX was also found to accumulate in liver tissue in levels approximately equal to dietary exposure level, and a decrease in kidney weights relative to brain weights in offspring exposed to 100 µg/L was also observed. No effects of TNX exposure in adults were described.

Ramasahayam et al. (2017) administered MNX in vehicle (5% DMSO in corn oil) to female Sprague-Dawley rats by oral gavage daily for 6 weeks at a dose of 47 mg/kg /day. MNX-induced convulsions and tremors, which ceased after 2 weeks of treatment. Hematological and clinical chemistry markers spleen weights, spleen and bone marrow histopathology, and

immunohistochemistry with DED1 and CD68 macrophage marker were evaluated. There was no decrease in blood erythroid parameters and no toxicological effects on bone marrow. Spleen weights were increased modestly with extramedullary hematopoiesis, but hemosiderin and relative red and white pulp areas were unaffected. Further analysis from this study showed that megakaryocyte expansion and macrophage infiltration in bone marrow was suggestive of an inflammatory component in MNX hematotoxicity (Ramasahayam et al. 2017a).

No subchronic toxicity data on DNX were located. According to Technical Guide (TG) 254 (USACHPPM 2000), chronic exposures are repetitive exposures greater than or equal to 10 percent of the lifespan of the organism. Subchronic exposures are considered to be studies less than 10 percent of the life span of the organism.

2.3.1.3 Mammalian Oral Toxicity—Chronic

No chronic toxicity data MNX and DNX were located. Druckrey (1967) examined the carcinogenicity of TNX as part of the investigation to determine the oral LD_{50}. The author noted that despite the relative high toxicity, TNX was not carcinogenic to the test species even after a chronic exposure of 546 days; no survivorship or other toxicity information was provided.

2.3.1.4 Mammalian Oral Toxicity—Other

No direct toxicity studies were located for DNX although studies on RDX metabolism to DNX were carried out (Smith et al. 2009). Many studies investigated the carcinogenic potential of TNX. Danz et al. (1973) exposed Wister rats by single oral gavage of 50 mg/kg of TNX in sunflower oil and measured the effect of TNX on the mitosis count/square meter (m^2) in the adrenal cortex as an indicator of potential carcinogenicity. An increased mitosis count is generally considered a promotion of cellular growth by the chemical stimulant and would, thus, be categorized as a carcinogen. Based on this result (i.e., no significant increase in mitosis count/m^2 in the adrenal cortex) TNX was categorized as being noncarcinogenic (Danz et al. 1973).

However, in other studies where DMSO was used as the carrier solvent, TNX was categorized as a carcinogen because high mitosis count and hepatocarcinogenicity were observed in both Wistar and Sprague-Dawley rats (Urban and Danz 1976, Danz et al. 1978). However, the authors noted that the carrier, DMSO, might have contributed to an increased mitotic count as well as a hepatocarcinogenic effect from chronic exposure. Using DMSO as the carrier solvent to compare with a sunflower oil solvent, it was revealed that with DMSO, mitosis count increased significantly by as much as 3.4 times via intraperitoneal (i.p.) injection, and 5.7 times from the control via oral gavage. In contrast, mitosis count was not statistically different from that of the control when sunflower oil alone was used as the carrier solvent (Urban et al. 1975). Danz et al. (1978) noted that it was unclear whether DMSO was a co-carcinogen with TNX, or whether DMSO served as a facilitator in the permeation of TNX through the cell membrane. Danz et al. (1978) acknowledged that DMSO may have contributed to the increase in mitotic count, as well as the long-term hepatocarcinogenic effect, but categorized TNX as carcinogen. Amlacher and Rudolph (1981) used a single i.p. injection in CBA mice at approximately 15 to 30% of the LD_{50} (24–48 mg/kg). The carcinogenicity of TNX was evaluated by using the autoradiograph of nuclei of the renal tubular epithelial and liver epithelium. Although one part of

DMSO was used against two parts of triethylenglycol, the result was not significantly different from the control. Therefore, TNX was considered a non-carcinogen by the authors. A summary of the mammalian oral toxicity values is summarized in Table 2.

To further assess the potential carcinogenicity of RDX's breakdown products, Pan et al. (2007b) used TNX and MNX in the *Salmonella tryphimurium* reverse mutation assay (Ames assay) with strains TA97a, TA98, TA100, and TA102. Although TNX and MNX were not found to be cytotoxic at doses up to 878.1 µg/plate and 1,118.9 µg/ plate respectively, both were observed to induce moderate mutagenesis in some of the strains. TNX induced mutagenesis in strains TA97a at 22.7 µg/plate and TA100 at 1200 µg/plate, and MNX induced mutagenesis in only strain TA97a at 21.7 µg/plate. This study used a higher S9 fraction (9%) than standard Ames assay procedures (4%) that previously showed no mutagenic effects of TNX and MNX (unpublished data reported in Pan et al. 2007b). The high S9, with an additional pre-incubation step that was necessary in facilitating the activation of TNX and MNX, caused the authors to suggest that these nitrosamines may require intensive metabolic activation to manifest carcinogenic effects.

2.3.1.4 Studies Relevant for Mammalian TRV Development for Ingestion Exposures

Although several studies relating to the toxicity of TNX were located, none of these studies are sufficient for TRV development for ingestion exposures. An LD_{50} of 160 mg/kg in rats (Druckrey 1967) suggests that TNX is not highly toxic, though it may be moderately toxic to mammals. In other studies, increased cell division/cell growth in the adrenal cortex was observed at low chronic dose levels (1.9 mg/kg/d). However, Urban et al. (Urban and Danz 1976) did not observe this effect in animals dosed with TNX in a sunflower oil carrier, suggesting that the effect was related to the DSMO carrier used in the other dose group.

2.3.2 Mammalian Inhalation Toxicity

No inhalation data for mammals were located for DNX, MNX, and TNX.

2.3.3 Mammalian Dermal Toxicity

No dermal data for mammals were located for DNX, MNX, and TNX.

2.4 Summary of Avian Toxicology

One study examining the neurotoxicogenomic mechanism of action of RDX on northern bobwhite quail (*Colinus virginianus*) was identified (Gust et al. 2009), but there was no information on breakdown products. Toxicological data for the effects of TNX, DNX, and MNX on avian species were not located.

2.5 Summary of Amphibian Toxicology

Toxicological data for the effects of TNX, DNX, and MNX on amphibian species were not located.

2.6 Summary of Reptilian Toxicology

Toxicological data for the effects of TNX, DNX, and MNX on reptilian species were not located.

3. RECOMMENDED TOXICITY REFERENCE VALUES

3.1 Toxicity Reference Values for Mammals

3.1.1 TRVs for Ingestion Exposures for the Class Mammalia

As indicated in Section 2.1.3.5, none of the studies located were sufficient for development of oral TRVs for mammals. There are five minimal requirements for a study to be considered including response, bioavailability, dose, repeatability, and corroboration with other studies. Although initial tests indicated that a dose of 1.9 mg/kg/d was carcinogenic to rats, it was subsequently determined that the carcinogenicity was due to the DSMO carrier and not TNX (Urban and Danz 1976). This suggests that the dose level 1.9 mg/kg/d may represent an unbounded NOAEL for carcinogenicity.

Although the exposure was chronic (459 days), only one dose level and one species was tested (Note: mice were tested with a single dose via i.p. injection (Amlacher and Rudolph 1981), which is not applicable to oral exposures). Additionally, Ramasahayam et al. (2017) conducted subchronic exposure via oral at single dose of 47 mg/kg/day in female rats showed spleen weight increase with extramedullary hematopoiesis erythroid effects. This is only single dose data, and no-dose response data was available. Given the lack of data and the uncertainties associated with the data (i.e., confounding factors related to DSMO), mammalian Toxicity Reference Values (TRVs) for ingestion exposures to TNX and MNX were not identified at this time.

3.1.2 TRVs for Ingestion Exposures for Mammalian Foraging Guilds

There is insufficient data for development of TRVs specific to particular guild associations.

3.1.3 TRVs for Inhalation Exposures for the Class Mammalia

Not available at this time.

3.1.4 TRVs for Dermal Exposures for the Class Mammalia

Not available at this time.

3.2 Toxicity Reference Values for Birds

Not available at this time.

3.3 Toxicity Reference Values for Amphibians

Not available at this time.

3.4 Toxicity Reference Values for Reptiles

Not available at this time.

4. IMPORTANT RESEARCH NEEDS

It is most likely that levels of RDX breakdown products will be a fraction of the parent compound; unless the breakdown products have specific toxic effects that are different from RDX, regulation of RDX to low levels would reduce or eliminate measurable levels of products. However, there may be cases where very high levels of RDX exist, and knowledge of the toxicity of the breakdown products to wildlife would be applicable. Although some mammalian toxicity data for TNX were available, these data were insufficient to develop TRVs. Additionally, no mammalian data were available for DNX.

For birds, amphibians, and reptiles, toxicity data were not available for any of the RDX breakdown products. Before reliable mammalian, avian, amphibian, and reptilian TRVs can be derived, TNX, MNX, and DNX toxicity to these classes of wildlife needs to be adequately characterized. Appropriate acute, subacute, subchronic, and especially chronic toxicity testing, by all exposure routes, is needed. The research studies should include experimental models of species genetically, biologically, and behaviorally close to wildlife most likely to be exposed; the experimental design should mimic both exposure type and duration and include assessments of long-term effects.

WILDLIFE TOXICITY ASSESSMENT FOR RDX BREAKDOWN PRODUCTS

APPENDIX A

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APPENDIX B

LITERATURE REVIEW

B-1. TNX (1,3,5-trinitroso-1,3,5-triazacyclohexane)

The following database were searched using the following keywords:

RTECS®

Conditions: one word or CAS number search; 1930 to present
1,3,5-trinitroso-1,3,5-triazacyclohexane OR hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine OR *CAS NO. 13980-04-6*

This database was considered irrelevant and was not searched again. Any citations in this database could be duplicated in other databases.

Number of hits: 2

All two citations were appropriate and were included.

TOXNET®/TOXLINE® and PUBMED®. /MEDLINE®

Conditions: one word or CAS number search; 1966 to present
1,3,5-trinitroso-1,3,5-triazacyclohexane OR hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine *CAS NO. 13980-04-6*

Date searched: April 4, 2019.

Number of hits: 20

Of the 20, 17 were in common with the BIOSYS search. Out of the remaining 3, 1 was not appropriate, while the final 2 were included. This made a total of 18 usable references from PubMed

Public STINET

Conditions: one word or CAS number; 1940 to present
1,3,5-trinitroso-1,3,5-triazacyclohexane OR hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine *OR* CAS NO. 13980-04-6
Date searched: April 4, 2019.
Number of hits: 0

BIOSYS

Conditions: one word or CAS number; 1969 to present
1,3,5-trinitroso-1,3,5-triazacyclohexane OR hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine *OR* CAS NO. 13980-04-6
Date searched: April 3, 2019.
Number of hits: 53.

Out of 53 hits, 11 were relevant and were usable. There were 17 hits in common with the PubMed search.

B-2. DNX (1,3-dinitroso-5-nitro-1,3,5-triazacyclohexane)

The following database were searched using the following keywords:

RTECS®

Conditions: Chemical Name or CAS number search; 1930 to present
1,3-dinitroso-5-nitro-1,3,5-triazacyclohexane OR
hexahydro-1-nitro-3,5-dinitroso-1,3,5-triazine OR
hexahydro-1,3-dinitroso-5-nitro-1,3,5-triazine OR
CAS NO. 5755-27-1.

This database was considered irrelevant and not searched again. Any citations will be duplicated in other databases.

Number of hits: 0

TOXNET/TOXLINE and PUBMED/MEDLINE

Conditions: one word or CAS number search; 1966 to present

1,3-dinitroso-5-nitro-1,3,5-triazacyclohexane OR
hexahydro-1-nitro-3,5-dinitroso-1,3,5-triazine OR
hexahydro-1,3-dinitroso-5-nitro-1,3,5-triazine OR
CAS NO. 5755-27-1.

Number of hits: 22

Out of 22 hits 7 were considered usable; all 7 were identified in searches for A1.

Public STINET

Conditions: one word or CAS number; 1940 to present
1,3-dinitroso-5-nitro-1,3,5-triazacyclohexane OR
hexahydro-1-nitro-3,5-dinitroso-1,3,5-triazine OR
hexahydro-1,3-dinitroso-5-nitro-1,3,5-triazine OR
CAS NO. 5755-27-1.

Number of hits: 0

BIOSIS

Conditions: one word or CAS number; 1969 to present
1,3-dinitroso-5-nitro-1,3,5-triazacyclohexane OR
hexahydro-1-nitro-3,5-dinitroso-1,3,5-triazine OR
hexahydro-1,3-dinitroso-5-nitro-1,3,5-triazine OR

CAS NO. 5755-27-1.
Number of hits: 22

Out of 22 hits, 8 were considered usable, 7 of which were identified in other searches.

B-3. MNX (1-nitroso-3,5-dinitro-1,3,5-triazacyclohexane)

The following database were searched using the following keywords:

RTECS

Conditions: Chemical Name or CAS number search; 1930 to present
1-nitroso-3,5-dinitro-1,3,5-triazacyclohexane OR
hexahydro-1,3-dinitro-5-nitroso-1,3,5-triazine OR
hexahydro-1,3-dinitro-5-nitroso-s-triazine OR
1,3-dinitro-5-nitrosohexahydro-1,3,5-triazine OR
hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine OR
CAS NO. 80251-29-2

Number of hits: 0

This database was considered irrelevant and not searched again. Any citations will be duplicated in other databases

TOXNET/TOXLINE and PUBMED/MEDLINE

Conditions: one word or CAS number search; 1966 to present
1-nitroso-3,5-dinitro-1,3,5-triazacyclohexane OR
hexahydro-1,3-dinitro-5-nitroso-1,3,5-triazine OR
hexahydro-1,3-dinitro-5-nitroso-s-triazine OR
1,3-dinitro-5-nitrosohexahydro-1,3,5-triazine OR
hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine OR
CAS NO. 80251-29-2

Number of hits: 20

Out of 22 hits, 8 were considered relevant, only 3 of which mentioned MNX. The 8 hits were also identified in other searches.

Public STINET

Conditions: one word or CAS number; 1940 to present
1-nitroso-3,5-dinitro-1,3,5-triazacyclohexane OR
hexahydro-1,3-dinitro-5-nitroso-1,3,5-triazine OR
hexahydro-1,3-dinitro-5-nitroso-s-triazine OR
1,3-dinitro-5-nitrosohexahydro-1,3,5-triazine OR
hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine OR
CAS NO. 80251-29-2

Number of hits: 0

BIOSIS

Conditions: one word or CAS number; 1969 to present
1-nitroso-3,5-dinitro-1,3,5-triazacyclohexane OR
hexahydro-1,3-dinitro-5-nitroso-1,3,5-triazine OR
hexahydro-1,3-dinitro-5-nitroso-s-triazine OR
1,3-dinitro-5-nitrosohexahydro-1,3,5-triazine OR
hexahydro-1-nitroso-3,5-dinitro-1,3,5-triazine OR
CAS NO. 80251-29-2

Number of hits: 48

Out of 48 hits, 19 were considered potentially useful, but only 8 were finalized for inclusion in the review. These 8 were also identified in other searches.