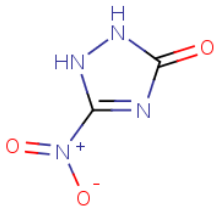
WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

OARS WEEL

3-Nitro-1,2,4-Triazol-5-One (2014)

I. IDENTIFICATION [1, 2]

Chemical Name: 3-NITRO-1,2,4-TRIAZOL-5-ONE
Synonyms: (NTO)
CAS Number: 932-64-9
Molecular Formula: $C_2H_2N_4O_3$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES [1,2,3]

Physical State: White to pale yellow crystalline powder
Odor Description: None
Molecular Weight: 130 g/mol
Conversion Factors: 1 ppm = 5.31 mg/m^3;
1 mg/m^3 = 0.188 ppm
Melting Point: 268–271°C (514.4–519.8 °F)
Boiling Point: Undergoes thermal degradation at temperatures above its melting point
Vapor Pressure: No data available
Saturated Vapor Concentration: No data available
Flammability Limits: No data available
Flash Point: 181°C (357.8 °F)
Autoignition Temperature: 347° C (656.6 °F)
Specific Gravity: 1.93 at 25°C (77 °F)
Log $K_{ow:}$ 0.858 at 25°C (77 °F)
Vapor Density: No data available
Solubility: 2000 mg/L in water.
Stability: No data available
Reactivities and Incompatibilities: No data available

III. USES

NTO was developed as a potential replacement for RDX and other energetics in military munitions. It is a component of IMX-101, an insensitive munition designed to prevent unplanned explosions. IMX-101 and other insensitive formulations exhibit a reduced potential for detonation resulting from impact and fires in military combat vehicles and aircraft. NTO is synthesized by nitration of a keto-triazine derivative in an enclosed system. The NTO is mixed with the other IMX compounds and melted in a large heated kettle; the molten IMX-101 is dispensed onto a moving belt where it is cooled and solidified. The solid IMX-101 is then broken into flakes and shipped to a load and pack (LAP) facility where it is re-melted and poured into various warheads and projectiles. Potential worker exposures include particulates from the initial mixing process with dry components and NTO vapors associated with the molten NTO and the IMX-101 mixture.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. Lethality Data

Mouse and rat LD_{50} > 5000 mg/kg[4]

2. Eye Irritation

Eye irritation was tested in white rabbits using the Draize protocol. NTO (100 mg) was placed into the conjunctival envelop of 6 rabbits; the compound was not rinsed out in 2 animals, but was rinsed out of the eyes at 30 seconds for 2 animals and 5 minutes for the other 2 animals. Ocular irritation was graded at 24, 48 and 72 hours. All rabbits showed erythema at 1 and 4 hours and by 72 hours the response had resolved in all but 1 rabbit.[4]

3. Skin Absorption

The dermal absorption of NTO was evaluated in an *in vitro* test. The test system used frozen human cadaver skin membranes in a static Franz cell system based on OECD 428 testing guidelines. NTO was applied to the skin as a powder and liquid samples were withdrawn from the receptor fluid at 1, 2, 4, 6, or 8 hours and analyzed for NTO. The authors estimated a steady state flux of 332 µg/cm^2/hr for NTO.[5] In contrast, McDougal[6] used a similar diffusion cell apparatus but with rat skin as the test membrane and estimated a dermal flux for RDX, another common munition, to be approximately 0.086 µg/cm^2/hr; for TNT, which is known to readily penetrate human skin the flux was approximately 1.14 µg/cm^2/hr. The reason is unclear for the difference in steady state flux estimates from similar compounds. Based on the contrasting data, the dermal penetration of NTO should be confirmed using *in vivo* uptake studies before definitive conclusions can be made regarding potential systemic toxicity following dermal exposures.

4. Skin Irritation

Rabbit skin irritation was evaluated using the Draize procedure. A paste of NTO in corn oil was applied to the backs of six New

Zealand white rabbits. The sites were occluded for 24 hours then scored for erythema and edema. The primary irritation score averaged for the 24 hour and 72 hour readings was 0.34, indicative of mild irritation.[4]

5. Skin Sensitization

Skin sensitization was evaluated in 10 female guinea pigs that received a series of 10 sensitizing injections with NTO dissolved in corn oil. Two weeks following the last injection the animals received a challenge injection of NTO and the injection site was graded after 24 hours. NTO did not induce sensitization in this test.[4]

6. Inhalation Toxicity

O'Neill & Crouse performed an acute inhalation study with NTO in order to estimate a 4-hour LC_{50} value in rats. [7] Since NTO is an explosive material the authors could not generate atmospheres of vapor or dry dust. They were able to solubilize NTO in water and aerosolize this solution in order to expose rats in a nose only system. At the highest air concentration tested (0.184 mg/L) there were no compound related animal deaths.

B. Subacute Toxicity

1. Inhalation

No Information available.

2. Oral Toxicity

The Army performed a 14-day repeated dose oral gavage study in male and female rats.[8] Rats were dosed daily with 0 (PEG 200 control), 250, 500, 1000, 1500, or 2000 mg/kg-day of NTO for 14-days. No compound-related lethality was observed throughout the 14-day dosing period and the majority of the changes were found in the male reproductive organ weights and weight ratios. Results from the 14-day subacute oral toxicity study in rats showed significantly smaller testes weights in the high dose groups (≥500 mg/kg).

C. Subchronic Toxicity

1. Inhalation

No Information available.

2. Oral Toxicity

A 90-day oral (gavage) subchronic study (7 days a week/13 weeks) was conducted in male and female rats. Doses were selected based on the results from the 14-day repeated dose study and were set at 0 (PEG 200 control), 30, 100, 315, or 1000 mg/kg-day for both sexes. No compound-related mortality was observed in any of the dose groups throughout the 90-day dosing period. All surviving animals were euthanized on day 91 at which time a complete necropsy was performed, organs were removed and weighed, and blood was collected for clinical and hematological analysis. Statistical significance versus controls was observed at doses of 315 mg/kg-day and above mainly limited to the male reproductive organs and organ weight ratios. Sporadic significant changes both between dose groups and compared to controls were observed in the following parameters: body weight, body weight gain, various organ weights and weight ratios, hematology, and clinical chemistry.[8]

Preliminary histopathology results indicated testicular hypoplasia in all dose groups with the incidence and severity increasing with dose. The histopathology was initially performed by a contract laboratory; however based on inconsistencies in the report, the testes slides were re-evaluated by a board certified veterinary pathologist and this evaluation was subsequently peer reviewed by a second board certified veterinary pathologist.[9] Based on this re-evaluation the groups treated with 315 mg/kg-day and 1000 mg/kg-day had moderate to severe degeneration and atrophy of the seminiferous tubules and these changes were statistically significant when compared to the control group. The incidence of changes in the testes of the rats dosed with 30 and 100 mg/kg-day was not different when compared to controls. The testicular effects were considered to be the critical effect for deriving various exposure criteria and a benchmark dose analysis of the re-evaluated incidence data (0/10, 1/10, 1/9, 9/9 and 10/10 at 0, 30, 100, 315 and 1000 mg/kg-day, respectively) from this study was performed. Three models (Logistic, Probit and Multistage) were selected based on goodness-of-fit and statistical parameters. Based on this analysis the $BMDL_{10}$ for testicular hypoplasia was estimated to range from 22 to 47 mg/kg-day depending on the subset of acceptable models used.[10]

D. Chronic Toxicity

No data available.

E. Reproductive/Developmental Toxicity

Only limited developmental and reproductive toxicity information is available for NTO. In a 90-day subchronic study, rats were exposed to doses of 0, 30, 100, 315, or 1000 mg/kg-day by oral gavage.[11] These data are discussed below in detail but there were marked effects on the male reproductive system.

The observation of male reproductive organ effects in the 90-day study was confirmed in a screening study for reproductive and developmental effects using the OECD 422 test guidelines. Groups of 10 male and 10 female rats were administered NTO at 0, 31, 125 or 500 mg/kg-day. An additional 20 males were included to serve as a satellite group in order to evaluate recovery and/or delayed effects from NTO. Male rats were dosed for 28 days including 2 weeks prior to and following mating. A complete necropsy was performed at the end of the dosing period. Female rats were dosed for 2 weeks prior to mating, during pregnancy and through day 4 post-partum. Treatment with NTO resulted in significant reductions in testes and epididymides mass and mass ratios in male rats given 500 mg/kg-day. Microscopic evaluation of these tissues revealed severe degeneration and atrophy of the testicular seminiferous tubules along with moderate to severe hypospermia and cribriform change of the epididymides. Sperm counts were significantly reduced in the high dose group (500 mg/kg-day) with no motile sperm observed. Despite the testicular atrophy

and reduced sperm counts there were no changes in reproductive success. This result probably reflects the actual duration of the pre-mating dosing since the male rats were dosed for only 2 weeks prior to mating and for additional 2 weeks during the mating period. If conception occurred early in the mating period the NTO effects were likely not completely manifest on the testes and developing sperm. Rats from the satellite group exhibited a partial recovery following the 4-week recovery period. In this group all spermatogonia and spermatocytes were present through all stages but maturing spermatids were only variably present. Cauda epididymal sperm counts in this group recovered slightly to 28.6% of recovery control animals, compared to 6.8% for the 500 mg/kg-day main study males, but no motile sperm were detected. It is likely that the duration of the recovery period was insufficient for a more complete recovery. There were no statistically significant dose related changes in male rats exposed to 125 mg/kg-day and lower and female rats at any dose tested. Based on gross external examinations of the offspring NTO did not cause any developmental effects. The NOAEL from this study was 125 mg/kg-day.[11]

F. Genotoxicity/Mutagenicity

NTO was evaluated for mutagenicity in *Salmonella typhimurium* and *Escherichia coli* plate incorporation assays both with and without S-9 activation. The results were negative in *Salmonella* at concentrations up to 500 µg/plate without activation, and up to 5000 µg/plate with activation. In *E. coli*, results were also negative at maximum concentrations up to 2500 µg/plate without activation and 5000 µg/plate with activation. Under the test conditions, NTO was negative with and without activation.[12]

NTO was tested for its potential to induce mutations in the L5178Y $TK^{+/-}$ mouse lymphoma mutation assay. Cells were treated with NTO at concentrations up to 5000 µg/mL, both with and without activation. Results of the assay were negative in all cases.[13]

NTO was tested in Chinese Hamster Ovary (CHO) cells for clastogenicity. The test was conducted both with and without exogenous metabolic activation at concentrations up to 5000 µg/mL with negative results.[14]
A rat micronucleus assay was conducted in conjunction a 14-day oral subacute study described below. The frequency of micronucleated reticulocytes ranged from 0.20 to 0.23% in female rats and 0.21 to 0.27% in male rats treated with 1000, 1500, and 2000 mg/kg-day of NTO in PEG. Treatment with NTO did not produce a statistically significant increase in the frequency of micronucleated reticulocytes in the peripheral blood of female or male rats. These results indicate that NTO is not genotoxic in rat peripheral blood at these doses.[8]

G. Metabolism/Pharmacokinetics

1. Absorption

O'Neill & Crouse[7] included an investigation into the time course of NTO absorption and clearance from both oral and inhalation exposure. NTO blood concentrations for male and female rats exposed via inhalation peaked at the 4-hr sampling time (immediately upon removal from the chamber) and averaged 41.5 µg/ml. Blood concentrations gradually increased during the exposure from 13.08 µg/ml at 1-hr to 23.0 µg/ml at 2-hr. Upon removal from the chamber (4-hr), blood concentrations rapidly decreased to 4.75, 1.42, and 0.68 µg/ml at 8, 12, and 24 hours post-exposure. In the oral gavage dosing component of the study, a calculated dose equivalent to the 4-hour inhaled dose was given in a single bolus. NTO blood concentrations peaked at 1-hr post-dosing (first sample time) and averaged 6.38 µg/ml. Average blood concentrations dropped to 3.52 µg/ml at 2-hr post-dosing and remained below the limit of detection at 5, 8, and 24 hours post-dosing. In a study with orally dosed primates, similar doses of NTO were also eliminated by 8 hours.[15] Together these data suggest rapid uptake and elimination following inhalation and oral dosing. In terms of absorption and elimination rates, the profile of NTO in rodents and primates was reported to be similar; male Rhesus monkeys given doses of 21 or 24 mg/kg showed peak profiles at around 2 hours in blood with elimination by 8 hours, while male rats given oral doses 25 mg/kg showed peak NTO in blood at approximately one hour with elimination from blood by 4 hours.[15]

Hoyt et al.[15] studied NTO absorption in primates, including a brief screen for ATO and urazole in urine samples with high NTO exposure levels, and found no indication of urazole and only slight traces of ATO. It is therefore unlikely that in primates hepatic metabolism of NTO takes place and more probably that it is excreted unchanged. Metabolism of NTO in primates was also examined in adult male rhesus monkeys that received oral doses of NTO of 5, 25, or 50 mg/kg followed by serial blood and urine sampling up to 48 hours post exposure. Doses were orally administered under sedation; at 5 hours, animals were recovered and returned to their cages with follow up samples at 8, 24, and 48 hours. At all three doses, NTO was absorbed quickly, peaked at 4 hours and was eliminated by 8 hours, with urinary concentrations at least 100-fold higher than that of blood or serum. Overall, these results show that there is little metabolism of NTO in primates and that for monitoring of exposure, urine samples are optimal.[15] Together these data suggest significant potential species differences in the metabolism of NTO. However, there is no clear evidence whether the toxicity of NTO observed in rodents is due to NTO or a metabolite, and thus, the implications of species differences in the metabolic profiles is uncertain.

2. Metabolism

A study using ^{14}C-NTO found that metabolic degradation of this compound using rat liver microsomes *in vitro* appeared to involve two separate enzymatic pathways. In the presence of oxygen, NTO was metabolized to two separate products: 5-amino-1,2,4-triazol-3-one (ATO) and 5-hydroxy-1,2,4-triazol-3-one (urazole). The presence of oxygen did not affect the overall conversion of NTO, but did alter the proportion of the metabolites. Under anaerobic conditions, the ATO was the primary product while urazole comprised only 5 percent of the product. Under aerobic conditions, urazole represented 40

percent of the product with a decrease in nitroreduction. Two separate pathways were represented here, since incubation of ATO with activated microsomes did not result in production of urazole, indicating that ATO did not represent an intermediate in this pathway and that urazole was formed directly from NTO in mammalian systems in the body.[16] Other explosives such as RDX, have been shown to display aerobic and anaerobic pathways in P450 metabolism.[17] It is therefore important, for mode of action, to fully describe the metabolic pathways of NTO given that LeCampion et al demonstrated oxygen sensitive metabolism *in vitro* using rat tissues.

H. Other

1. Endocrine Disruption Studies

NTO was tested in a battery of *in vitro* and *in vivo* tests for endocrine disruption.

NTO was tested in a battery of 5 *in vitro* tests, including assays for estrogen receptor binding, androgen receptor binding, estrogen transactivation, aromatase and steroidogenisis. All of these *in vitro* tests were negative with NTO.[18]

In vivo endocrine disruption assays included a pubertal assay, Hershberger assay and uterotropic assay. The pubertal test evaluated the potential for NTO to interact with the endocrine system to affect pubertal development and thyroid function in male and female rats. NTO did not affect pubertal development in either sex and the measured hormone levels were also not affected. Male rats exhibited reduced testis mass, tubular degeneration and these changes were associated with less pronounced reductions in the mass of androgen dependent accessory reproductive tissues.[19] The Hershberger and uterotrophic assays involved short term *in vivo* exposure screens that assessed NTO's potential to act as an estrogen agonist or an androgen antagonist through changes in sex steroid sensitive organ weights in ovariectomized or castrated Sprague-Dawley rats. The results of these two screens do not provide evidence for endocrine disrupting activity at the dose levels tested.[20]

2. Biomarker Studies

Rhesus monkeys were used to identify potential biomarkers of exposure. NTO was dissolved in deionized water and administered through a gastric tube to anesthetized animals. Serial blood and urine samples were taken for 5 hours. Based on this limited data set it appears that NTO is readily detectable in blood and urine even at the lowest (5 mg/kg) dose tested in this study.[15]

3. IMX-101 Mixture Studies

IMX-101 is one of the first of the insensitive munitions to contain NTO. It is a mixture of NTO, 2,4-dinitroanisole and nitroguanidine. Acute and 14-day repeated dose studies were conducted to determine if the toxicity of the mixture was based on the additive toxicity of the individual components. IMX-101 had an LD_{50} in male rats of 1237 mg/kg and in female rats of 924 mg/kg, with a combined (male-female average) value of 1100 mg/kg.[21] In the 14-day IMX-101 repeated oral dose study the notable adverse events were: 1) lethality in the 500 mg/kg-day and 1000 mg/kg-day dose groups; 2) splenomegaly (increased spleen weight) primarily in females; and 3) testicular atrophy and decreased sperm density and motility. The LOAEL for IMX-101 from this study was 100 mg/kg-day based on changes in testicular mass with a calculated $BMDL_{10}$ of 30.6 mg/kg-day.[22] The IMX-101 mixture data provided some indication of dose-relationships that were more than additive. For example, the testicular effects from IMX-101 exposure occurred at much lower doses (based on the NTO equivalent dose after reducing the LOAEL for concentrations in the IMX-101 mixture) than seen in tests with NTO alone. Toxic interactions are dependent on the doses present, and the IMX-101 dosing may not reflect actual ratios of workplace exposures to IMX-101 components. In addition, doses in both tests were much higher than those likely to occur in an occupational setting. Thus, the results from the IMX-101 study are not considered adequate for derivation of the WEEL.

V. HUMAN USE AND EXPERIENCE

NTO is a component of the IMX-101 mixture. There is very little information related to humans exposed to IMX-101 or its components. The Army published an Industrial Health survey, which investigated a number of jobs in a melt-pour operation at the Iowa Army Ammunition Plant (IAAP). Processes included emptying large boxes of IMX-101 onto a table, sifting the IMX 101 and dumping the powder into a kettle hopper where it was melted. Once the IMX-101 reached the correct temperature it was poured into projectiles. Air samples were taken at a number of workstations throughout the plant and analyzed for the IMX-101 components. NTO concentrations in all of the air samples were below the current recommended Army OEL of 1.6 mg/m^3.[23]

VI. RATIONALE

NTO is a crystalline powder with no odor and decomposes before melting. It was developed as a potential replacement for RDX and other military munitions as a component of IMX-101, which is an insensitive munition designed to prevent unplanned explosions. NTO is not acutely toxic: the oral the LD_{50} (mouse and rat) is > 5000 mg/kg and inhalation studies using an NTO:water mixture resulted in no deaths at a concentration of 0.184 mg/L. No dermal acute lethality studies are available and data on dermal penetration is inconclusive. NTO is mildly irritating to the eyes and skin. It is not a sensitizer and is negative is a variety of assays for genotoxicity and mutagenicity. Based on a subchronic oral toxicity study and a reproductive and developmental toxicity screening study in rats, the primary effect of concern is male reproductive toxicity. These studies revealed severe degeneration and atrophy of the testicular seminiferous tubules and moderate to severe hypospermia. No effects on male fertility were noted, but the absence of such effects likely reflects the duration of dosing prior to mating in the reproductive study protocol. No developmental effects were seen on gross external examinations.

The testicular effects serve as the point of departure (POD) for deriving the WEEL for NTO. A benchmark dose analysis modeled the lower 95% confidence interval on the 10% response rate for the testicular histopathology in the oral subchronic study in rats. The resulting $BMDL_{10}$ for WEEL derivation is 40 mg/kg-day (reflecting an average of several acceptable models).

The derivation of the WEEL considers several key uncertainties. Although there is evidence for interspecies differences in metabolism overall clearance rates of NTO from the blood are similar between rodents and primates. The absence of information on mode of action for reproductive effects precludes direct use of the toxicokinetic data to modify the POD to account for species differences. Adjustments based on toxicokinetic data are also limited by the absence of data on human variability in susceptibly. The POD is based on testicular effects observed in a subchronic study in male rats. Although the toxicokinetic data suggest limited potential for dose accumulation with chronic exposure, the possibility of effects occurring at a lower dose is not known in the absence of data on tissue repair rates or the availability of a longer-duration study.

VII. RECOMMENDED WEEL GUIDE

8-hour Time-Weighted Average: 2 mg/m^3. No additional hazard notations are assigned.

VIII. REFERENCES

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