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# NITROALKANES AND NITROALKENES

## CARCINOGENICITY AND STRUCTURE-ACTIVITY RELATIONSHIPS. OTHER BIOLOGICAL PROPERTIES. METABOLISM. ENVIRONMENTAL SIGNIFICANCE.

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### 5.2.2.6.1 Introduction.

Nitroalkanes (nitroparaffins) and nitroalkenes (nitro-olefins) have the general formulas $C_nH_{2n+1}NO_2$ and $C_nH_{2n}NO_2$, respectively. Several nitroalkanes, including nitromethane (NM), nitroethane (NE), 1-nitropropane (1-NP), and 2-nitropropane (2-NP) have been commercially available since 1940. By virtue of their unusual spectrum of industrially desirable properties, the demand for them has rapidly increased for many diversified applications (see Section 5.2.2.6.5). These compounds are now produced in multi-million lbs. quantities annually in the United States (1). A brief discussion of potential occupational exposure and genotoxic effects of nitroalkanes has been included in a recent review by Fishbein (2).

Studies in the 1950's suggested that both NM and 2-NP were noncarcinogenic in several animal species (3, 4). More recent investigations by Lewis et al. (5) also failed to show tumor induction in rats and rabbits exposed to NM vapor; however, under very similar experimental conditions, 2-NP was found by them to be a potent liver carcinogen in the rat.

Recently emerging evidence on the carcinogenicity in experimental animals, along with various other toxic effects observed in workers exposed to nitroalkanes, have attracted the attention of U.S. regulatory agencies to the potential hazards of these chemicals to human health. The U.S. National Institute for Occupational Safety and Health (NIOSH) issued guidelines for handling 2-NP in the workplace as if it were a human carcinogen (1).

Interest in nitroalkenes stems largely from studies on air pollution in metropolitan areas. It had been suspected for some time that conjugated nitroalkenes may be components of "smog," since this type of chemicals could

be formed by the reaction of unsaturated hydrocarbons with nitrogen oxides originating from automobile exhausts. Subsequent analysis provided unequivocal evidence that nitroalkenes were indeed present in the atmosphere (cited in refs. 6, 7). Although several earlier attempts to demonstrate the presence of nitroalkenes in automobile exhausts were unsuccessful due to the complexity of the combustion mixture formed from commercial gasoline, Deichmann and his associates (7, 8) identified several nitroalkenes in the exhaust of an experimental internal combustion engine (one-cylinder, four cycle) using isobutylene and 3-hexene (normal constituents of gasoline) as fuels. One of these nitroalkenes, 3-nitro-3-hexene, was found to induce primary carcinoma in the lungs of mice and rats in a chronic inhalation study (7, 9). Based on the histological similarity between the tumors observed in animals and lung tumors in man, the authors suggested that 3-nitro-3-hexene may be a potential human carcinogen (7).

## 5.2.2.6.2 Physical and Chemical Properties. Biological Effects.

### 5.2.2.6.2.1 PHYSICAL AND CHEMICAL PROPERTIES.

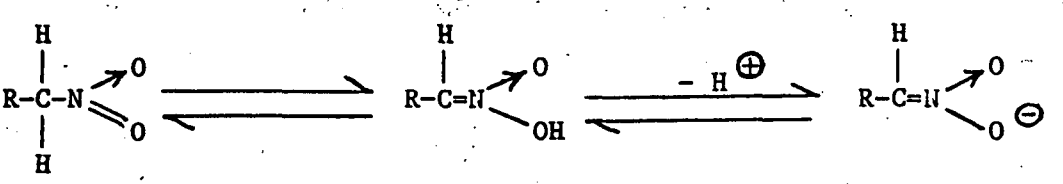
Nitroalkanes. The physical constants of nitroalkanes that have been tested for carcinogenicity are listed in Table I. These compounds are colorless, oily liquids with somewhat pleasant odors. Their boiling points are higher than those of the corresponding hydrocarbons. They have limited water solubility, but are miscible with aromatic hydrocarbons, alcohols, esters, ketones, ethers, and higher aliphatic carboxylic acids. Nitromethane is classified as an explosive since, under appropriate conditions of temperature, confinement, chemical reaction, and shock, explosion can occur. Other nitroalkanes are also explosive, although they are less hazardous than nitromethane.

Table I. Chemical Structures and Physical Properties of Nitroalkanes and 3-Nitro-3-hexene[a]

| Compound | Formula | Mol. Wt. | B.P. (°C) | Density at 25°C (g/ml) | Vapor Pressure at 20°C, torr | Solubility in $H_2O$ at 25°C (% by wt.) |
|---|---|---|---|---|---|---|
| Nitromethane | $CH_3NO_2$ | 61.04 | 101 | 1.131 | 27.3 | 11.1 |
| Nitroethane | $CH_3CH_2NO_2$ | 75.07 | 114 | 1.045 | 15.8 | 4.7 |
| 1-Nitropropane | $CH_3CH_2CH_2NO_2$ | 89.10 | 131 | 0.996 | 7.6 | 1.5 |
| 2-Nitropropane | $CH_3CH(NO_2)CH_3$ | 89.10 | 120 | 0.983 | 13.0 | 1.7 |
| 3-Nitro-3-hexene | $CH_3CH_2-C(NO_2)=CHCH_2CH_3$ | 129.18 | 71 | 0.978 | -- | -- |

[a] Data summarized from Kirk-Othmer: Encyclopedia of Chemical Technology [2nd Ed., Vol. 13, John Wiley, New York, 1976, p. 864-883] and from Lampe, K.F., Mende, T.J., and Mills, A.P. [J. Chem. Eng. Data 7, 85-90, 1962].

The chemistry of nitroalkanes has been extensively reviewed in a number of publications (10-14) and was the subject of two symposia (15, 16a). Nitroalkanes $C_1$ to $C_3$ are synthesized industrially by reaction in the vapor-phase between propane and nitric acid at elevated temperature and pressure. The nitromethane, nitroethane, and nitropropane formed are then separated by fractional distillation. Nitroalkanes exist in tautomeric equilibria with their nitronic acid isomers (aci forms), which are much more acidic than their nitro forms:



Nitro form Aci form

The ratio of the two forms in equilibrium is governed by the stability of the anion which depends in part on the nature of the R group. The aci form is amphoterically reactive, with the protonated aci form being electrophilic and the anionic aci form being nucleophilic (16b). It has been found that the proportion of the aci form present in water at 25°C increases with the size of the R group in the order: $C_3H_7 > C_2H_5 > CH_3$ (17).

Nitroalkanes are oxidized only slowly by strong oxidizing agents but are reduced quite readily by a number of reducing agents to yield oximes, hydroxylamines, or alkylamines. In the presence of strong alkali, NM reacts rapidly to form methazonic acid, whereas higher primary nitroalkanes decompose to give nitrites. Under alkaline conditions, chlorination of nitroalkanes may also occur, resulting in substitution by chlorine of one or more hydrogen atoms on the carbon linked to the nitro group. Chloronitroalkanes in which the chloro and nitro groups are linked to different carbons can be formed by

chlorinating the nitroalkanes under anhydrous conditions and irradiating with visible light. Interaction of nitroalkanes with aldehydes in the presence of alkali yields nitrohydroxy compounds, which can be further reduced to produce aminohydroxy derivatives. When molar equivalents of nitroalkanes, formaldehyde, and amines are reacted, Mannich bases are formed.

Nitroalkenes. Because of their importance as air pollutants, 21 nitroalkenes from $C_4$ to $C_9$ were synthesized by Deichmann's group for toxicological evaluation (6). The physical properties of these nitroalkenes have been described (18 ). They range from colorless to pale yellow liquids with boiling points in the same order of magnitude as those of nitroalkanes. Some physical constants of 3-nitro-3-hexene, the nitroalkene found to be carcinogenic in mice and rats (7, 9), are shown in Table I. The chemical properties of nitroalkenes, including reduction, hydration, halogenation, and reaction with alcohol, thiols, amines, and ammonia by double bond addition have been extensively described by Levy and Rose (10).

5.2.2.6.2.2 BIOLOGICAL EFFECTS OTHER THAN CARCINOGENIC

Toxic Effects. In marked contrast to the highly toxic aromatic nitro compounds, nitroalkanes have generally low toxicity (3, 4, 19-22). There appears to be no evidence for skin irritation or absorption through the skin sufficient to cause systemic injury. High concentrations of nitroalkanes are, however, lethal to animals either by oral administration or by inhalation. The toxicity of nitroalkanes generally increases with an increase in molecular weight. The oral $LD_{50}$ (expressed in g/kg) of NM, NE, 2-NP, and 1-NP in the rat was 1.21, 1.1, 0.725, and 0.455, respectively (cited in refs. 14, 21). Studies of the structure-toxicity relationships (20) indicate that introduction of additional nitro groups to carbon-1 in methane, ethane, and propane

derivatives leads to an increase in toxicity; replacement of one nitro group by a methyl group in the methane and ethane derivatives lowers the toxicity. Unsaturation of the hydrocarbon chain as in nitroalkenes results in great augmentation of toxicity (6, 7). Bromine-substituted nitroalkanes are generally more toxic than their chlorinated analogs (20.)

Acute inhalation studies using cats, rats, rabbits, and guinea pigs showed considerable species differences in their tolerance to 2-NP, with cats being the most sensitive to 2-NP and guinea pigs the least sensitive (3). Inhalation of lethal doses of nitroalkanes brings about in the animals restlessness, irritation of the eyes and the respiratory tract, salivation, and central nervous system symptoms, (convulsions, anesthesia, and coma) (19). Similar symptoms, as well as gastrointestinal tract irritation, are produced by oral administration. Animals that inhaled high doses of 2-NP showed general vascular endothelial damage, in addition to specific damage to the liver and brain, and pulmonary edema and hemorrhage (3). Methemoglobinemia and decrease in prothrombin content of the blood were also observed in animals exposed to 2-NP vapors (3, 23). There is evidence that low levels of both saturated and unsaturated aliphatic nitro compounds inhibit the oxygen consumption of polymorphonuclear leucocytes (24).

The acute toxic effects of nitroalkenes in several species have been extensively studied by Deichmann et al. (6). The nitroalkenes are highly toxic agents which produce, in addition to severe local irritation, many signs of systemic intoxication (hyperexcitability, tremor, clonic convulsions, tachycardia, increase in the rate and magnitude of respiration, etc.). All rats exposed to atmosphere containing 557 ppm 3-nitro-3-hexene died within 30-70 minutes. Regardless of the mode of administration, the damage was most severe to the lung; lethality was caused by respiratory failure and asphyxial convulsion.

Although epidemiological surveys on the consequences of exposure to nitroalkanes and nitroalkenes are scanty, a number of cases of occupation-related human intoxication by 2-NP have been recorded. In 1947, Skinner (25) reported that workers exposed to 20 to 45 ppm of 2-NP during an industrial coating-dipping process complained of anorexia, nausea, severe occipital headache, vomiting, and diarrhea. Similar symptoms were experienced by workers exposed to mixtures of 1- and 2-NP (cited in ref. 1). More recently, Gaultier et al. (26) described the development of fatal toxic hepatitis in workers exposed to high concentrations of 2-NP. Hine et al. (27) suspected that the fatalities of four men working with solvent mixtures containing 11-28% 2-NP might be attributed to chronic intoxication by 2-NP. In 1979, a retrospective mortality study of 1,481 workers employed between 1955 and 1977 at a 2-NP producing plant in the United States was reported (cited in ref. 28). The authors concluded that "analysis of these data does not suggest any unusual cancer or other disease mortality pattern among this group of workers." However, they added that "both because the cohort is small and because the period of latency is, for most, relatively short, one cannot conclude from these data that 2-NP is non-carcinogenic in humans."

No specific health effects of nitroalkenes have been documented. However, they are believed to be one of the classes of atmospheric pollutants responsible for eye and respiratory tract irritation commonly experienced by individuals residing in smoggy cities (29).

Mutagenicity. Limited information is available on the mutagenicity of nitroaliphatic compounds. Chiu et al. (30) tested the mutagenic activity of 53 commercially available nitro compounds (mostly aromatic) in Salmonella typhimurium. The majority of these compounds displayed mutagenic activity. However, nitromethane, the only aliphatic compound tested, was found to be

non-mutagenic to both TA100 and TA98 strains. 1-Nitropropane (1-NP), 1-nitrobutane, and 1-nitrohexane were selected for mutagenicity testing by the U.S. National Toxicology Program. Preliminary results indicate that neither of the three chemicals are mutagenic (31). Studies by Hite and Skeggs (32) also indicate that 1-NP and NE are inactive in several Salmonella tester-strains, with or without microsomal activation. 2-Nitropropane, however, was shown to produce a significant increase in revertants in all of the tester strains (particularly in strain TA100 in the presence of S-9 mix). The mutagenic effects of NE and 2-NP were also studied in the micronucleus test; the results were negative for both compounds (32, 33a). From these studies, the authors (32) concluded that 2-NP has the potential for causing point mutations but probably will not cause a chromosome mutation of the clastogenic type. Recent results from Speck et al. (33b) lend further support to the mutagenicity of 2-NP in strains TA100 and TA98 of S. typhimurium. Again, S-9 mix was not required, but it did enhance the mutagenic action of 2-NP. Moreover, mutagenicity was fully expressed in tester strains (TA100NR3 and TA98NR101), which are deficient in nitroreductase. These findings led the authors to suggest that 2-NP was an ultimate mutagen which did not require metabolic activation or enzymic reduction of the nitro group to the corresponding hydroxylamine; however, further biotransformation of 2-NP by microsomal enzymes probably produces additional mutagenic species.

Löfroth et al. (34a) conducted mutagenicity tests on several primary (C1 to C5) and secondary (C3 to C5) mono-nitroalkanes in strains TA100, TA98 and TA1535 of Salmonella typhimurium. They found that none of the primary nitroalkanes, except nitroethane (NE), exhibited detectable mutagenicity. The secondary nitroalkanes, on the other hand, are all mutagenic and their activity decreases in order: nitroporpane > nitrobutane > nitropentane. The

mutagenicity response is the highest in strain TA100 and is not significantly affected by S-9 mix.

Teratogenicity. The teratogenic effects of 2-NP on the fetal development of the rat have been studied by Harris et al. (34b). Adult female Sprague-Dawley rats were injected intraperitoneally with 170 mg/kg body weight of 2-NP on day 1 to 15 of gestation. Retarded heart development was observed in pups from 9 out of 10 litters from mothers treated with 2-NP. Thirty to 86% of the pups examined within a litter were affected.

There are no direct studies on the teratogenicity of other nitroaliphatic compounds. A teratogenesis study (35) and a three-generation reproduction study (36) in mice exposed to a mixture of NE, diethylhydroxylamine and diethylamine hydrogen sulfite has been reported. The data indicate no evidence of compound-induced terata, embryotoxicity, or inhibition of fetal growth and development.

5.2.2.6.3 Carcinogenicity.

While several nitroaromatic compounds have been shown to be potent carcinogens (see Section 5.1.2.4.1.3 in Vol. II B), there is a scarcity of information on the carcinogenic potential of nitroalkanes and nitroalkenes. Because of the increasing interest in nitroalkanes for industrial applications, several carcinogenicity bioassays have been conducted to supplement the information on the potential health hazard of these chemicals. A synoptic tabulation of the data on nitroalkanes up to $C_3$, as well as the results of the carcinogenicity studies on 3-nitro-3-hexene, are given in Table II.

Weatherby (4) reported first in 1955 the results of a chronic study on NM in the rat. Although definite pathological changes were observed in the liver, there was no evidence of carcinogenic activity of NM when it was

Table II. Carcinogenicity of Nitroalkanes and 3-Nitro-3-hexene

| Compound | Species and Strain | Route | Principal Organs Affected | References |
|---|---|---|---|---|
| Nitromethane | rat, albino | p.o. | None | (4) |
| | rat, Sprague-Dawley | inhalation | None | (5) |
| | rabbit, white | inhalation | None | (5) |
| Nitroethane[a] | rat, Long-Evans | inhalation | Testes | (37) |
| 1-Nitropropane | rat, Fischer | i.g. | Esophagus | (38) |
| 2-Nitropropane | rat, rabbit, cat, monkey and guinea pig | inhalation | None | (3) |
| | rabbit, white | inhalation | None | (5) |
| | rat, Sprague-Dawley | inhalation | None[b] | (39, 40) |
| | rat, Sprague-Dawley | inhalation | Liver | (5) |
| | rat, -- | inhalation | Liver | (Cited in 28) |
| 3-Nitro-3-hexene | mouse, Swiss | inhalation | Lung | (7, 9) |
| | rat, CFN | inhalation | Lung | (7) |
| | dog, beagle | inhalation | None | (7) |
| | goat, -- | inhalation | None | (7) |

[a]In a mixture also containing diethylhydroxylamine and diethylamine hydrogen sulfite.

[b]Preneoplastic liver nodules were observed.

administered to young male rats at dose levels of 0.1% and 0.25% in the drinking water for a period of 15 weeks. However, since the test was conducted for notably less than the lifetime of the animals, it is difficult to assess the carcinogenic potential of the compound. An early study of Treon and Dutra (3) found also 2-NP to be noncarcinogenic in rats, rabbits, cats, guinea pigs and monkeys which survived 130 7-hour periods of exposure (5 days/week) to 83 or 328 ppm 2-NP vapor. Again, the negative results of this study are difficult to interpret since only 1 or 2 animals of each species were used and the experiment was not carried out for the lifetime of the animals. More recently, NIOSH sponsored a comprehensive inhalation study of NM and 2-NP to appraise the adequacy of exposure standards in the workplace (5). Fifty male rats and 15 male rabbits were exposed to either 98 or 745 ppm of NM, or 27 or 207 ppm of 2-NP over a period of 6 months. To simulate conditions likely to be experienced by workers, the exposures were for 7 hours/day, 5 days/week. No exposure-related gross or microscopic alterations were observed in tissues of rats and rabbits exposed to the low dose of 2-NP and both doses of NM, nor in tissues of rabbits exposed to 207 ppm of 2-NP. However, hepatocellular carcinomas and neoplastic nodules were found in all 10 rats killed 6 months after exposure to 207 ppm of 2-NP. Control animals exposed to filtered air did not develop neoplasms. Although certain shortcomings existed in the conduct of this study, it was concluded that 2-NP was a potent carcinogen in the rat. In accord with the results of the above study, Griffin et al. (39) found preneoplastic liver nodules in rats exposed to 200 ppm for 6 months, but no malignancies or significant pathological lesions in the livers of male or female rats exposed to a low dose of 2-NP (25 ppm, 7 hours/day, 5 days/week) over a period of 22 months (40). Preliminary results of a report also indicate that rats exposed to 2-NP at 100 ppm 7 hours/day, 5 days/week for 9 months also developed liver tumors (cited in ref. 28).

In 1968, Hadidian et al. (38) mass screened the carcinogenic potential of 38 structurally diverse compounds, including 1-NP, by feeding the compounds at various doses to male and female rats, 5 times/week for 52 weeks. At the termination of the experiments, they found that 1 of the 15 male rats which received 1-NP at the dose of 3 mg/day by gavage developed an esophageal papilloma not seen in the controls. There has been no follow-up studies on the carcinogenicity of 1-NP; confirmation of the marginal activity of 1-NP is needed.

Heicklen et al. (37) have conducted a series of long-term toxicological tests on a mixture of diethylhydroxylamine, NE, and diethylamine hydrogen sulfite in rats to ascertain the safety of these compounds. This mixture was tested because diethylhydroxylamine is used as an inhibitor of the photochemical formation of smog from NE and diethylamine hydrogen sulfite. Of the 27 male rats exposed 7 hours/day, 5 days/week to the mixture of the compounds containing about 10 ppm NE, two developed interstitial cell tumors in the testes after about 2 years. One male rat also developed a hemangioendothelioma 3 months after the exposure. None of the 25 control males showed any tumor. However, whether this low incidence of carcinogenicity was actually due to NE or to the other two compounds in the mixture remains to be investigated.

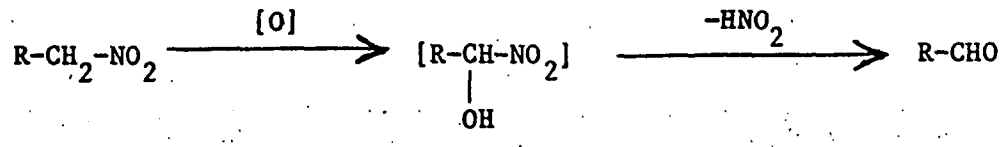
Two studies of the carcinogenicity of 3-nitro-3-hexene, identified in automobile exhausts, were carried out by Deichmann and his associates (7, 9). In the first study (9), 20 Swiss mice of each sex were exposed to 0.2 ppm 3-nitro-3-hexene vapor 6 hours/day, 5 days/week. Forty mice served as untreated controls. Among the 27 animals which survived 128-302 exposures (over 439 days), 5 developed adenocarcinomas of the lung. Of the 23 controls which survived the same length of time, one developed a pulmonary adenoma.

The low survival rate of the animals in both the test and control groups was attributed to bacterial infection which may have played some role in the promotion of tumorigenesis. In the second bioassay (7), goats, dogs, and rats were used. After 18 months of inhalatory exposure, there was no evidence of carcinogenic activity in 2 goats at 0.2 ppm level of exposure, nor in 4 dogs at either 0.2, 1, or 2 ppm level of exposure. However, 6 of 100 rats exposed to 1 ppm and 11 of 100 rats exposed to 2 ppm 3-nitro-3-hexene developed primary malignant lung tumors with histopathological characteristics similar to lung cancers in man. No primary malignant lesions were seen in the lung of 100 control rats. Based on these data, it was concluded that 3-nitro-3-hexene might be a potential human carcinogen.

5.2.2.6.4 Metabolism and Mechanism of Action.

Studies with rats and rabbits have demonstrated that nitroalkanes are rapidly absorbed and metabolized after inhalation or oral administration (41-43). Nitrite is the major metabolite found in the blood, urine, and various organs after administration of NE, 1-NP, or 2-NP but not NM. A portion of the unchanged compounds is excreted in the expired air. There is also evidence suggesting the formation of small amounts of mercapturic acid derivatives from NE and 1-NP (44). In in vitro studies in which NM was incubated aerobically with rat liver microsomes and NADPH, the compound was found to undergo denitrification, although to a lesser extent than 2-NP (45). Rat liver microsomes also catalyze the formation -- besides nitrite -- of formaldehyde, acetaldehyde and acetone, from NM, NE, and 2-NP, respectively (45, 46). Denitrification is decreased by inhibitors of microsomal mixed-function oxidases and increased in microsomes originating from animals treated with the enzyme inducers, phenobarbital and 3-methylcholanthrene, suggesting the involvement of cytochrome P-450 type mixed-function oxidases (46).

The oxidative metabolic degradation of nitroalkanes is assumed to proceed following the reaction:



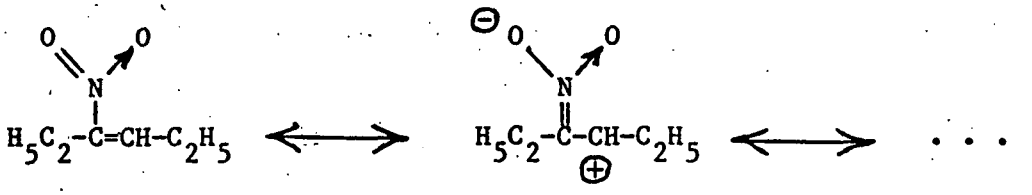

The metabolism of nitroalkenes does not appear to have been studied.

The mechanism(s) of the biological action of nitroaliphatic compounds is not known. It is possible that denitrification may be a molecular mechanism involved in carcinogenesis by nitroalkanes. This appears to be supported by the observation that 2-NP is a more potent carcinogen than the lower nitroalkanes; this is consistent with the relative rates of "oxidative denitrification" of nitroalkanes, since their affinity toward the microsomal mixed-function oxidase system decreases with decrease of the chain length (46). Thus, the absence of carcinogenicity and mutagenicity of NM may be attributed to the low rate of denitrification of this compound.

Speck et al. (33b) hypothesized, however, that 2-NP exerts its mutagenic, and probably, carcinogenic action via a direct, non-enzymic reaction between the compound and DNA. This was based on two findings. Firstly, that the mutagenicity of 2-NP does not require metabolic activation and is fully expressed in tester strains of S. typhimurium deficient in nitroreductase. Secondly, that the sedimentation of purified single-stranded DNA on sucrose gradient was altered after in vitro reaction with 2-NP, suggesting the alkylation of purine moieties of DNA by 2-NP (33b). As indicated in Section 5.2.2.6.2.1, the protonated aci form of nitroalkanes can act as an electrophile.

The reactivity of nitroalkenes towards simple nucleophiles (see Section 5.2.2.6.2.1 on Physical and Chemical Properties) is likely to be the basis of

their toxic effects. Also, nitroalkenes may be represented by the ionic resonant limit structures exemplified below:



further suggesting that they may act as alkylating agents under biological conditions. The reaction of nitroalkenes with cellular nucleophiles does not appear to have been studied.

5.2.2.6.5 Environmental Significance.

Nitroaliphatic compounds are not known to occur naturally, but arise during the combustion of organic materials. Several nitroalkanes have been detected in tobacco smoke (47, 48). A filterless 85 mm U.S. blend cigarette was found to contain 0.53 ug NM, 1.1 ug NE, 0.13 ug 1-NP, 1.1 ug 2-NP, and 0.71 ug nitrobutane in the smoke (47). Moreover, in the exhaust from various combustion systems, nitroalkenes and low levels of NM and NE have been detected (49).

Nitroalkanes are widely used as specialty solvents in industry. Their unique properties make them excellent solvents for a wide variety of organic compounds, resins, cellulose esters, fats, oils, gums, waxes, and dyes. Solvent blends containing nitroalkanes offer vast improvements over conventional solvent systems, especially for polyvinyl films in coating and paintings. Nitroalkanes also find important uses in industry as intermediates in the synthesis of a wide variety of products ranging from dyes and textile chemicals to pharmaceuticals and insecticides. In addition, the combustion properties of many nitroalkanes render them useful as gasoline and diesel fuel

additives, and as rocket propellants. Accordingly, occupational exposure to nitroalkanes occurs in various industries. It is estimated that about 30 million lbs. of 2-NP are produced annually, and approximately 185,000 workers are exposed to 2-NP during its production and use in the United States (28). The National Institute of Occupational Safety and Health has suggested that "it would be prudent to handle 2-NP in the workplace as if it were a human carcinogen" (1). The current Occupational Safety and Health Administration (OSHA) standards for occupational exposure to 1-NP and 2-NP are 25 ppm and the threshold limit values for NM and NE are 100 ppm (50). However, OSHA recommends that worker exposure to 2-NP be reduced to the lowest feasible levels (28).

The persistence of nitroalkanes in the environment is low and they are not considered to pose serious environmental hazards, except in the workplace. In both terrestrial and aquatic environments nitroalkanes are degraded rapidly under most conditions. In aerobic environments biodegradation of various nitroalkanes by bacteria in the soil and activated sludge has been described (51-53). Under anaerobic conditions nitroalkanes are easily reduced to products, which presumably serve as nitrogen source for many bacterial species (54). In aquatic environments, nitroalkanes evaporate at roughly the same rate as water. Nitroalkanes released from water or generated from cigarette smoke and combustion systems are degraded rapidly by direct photolysis.

During the chlorination of water, as during sanitary water treatment, there is the possibility that nitroalkanes may form trichloronitromethane (chloropicrin), a compound much more toxic than the original nitroalkanes (21) and used as a chemical warfare agent during World War I. Chloropicrin, formed by the reaction of NM (50 ug/l) and chlorine (1.12 mg/l) has actually been

detected in the finished drinking water in Seattle, Washington (55). Recent epidemiological studies have strengthened the evidence for a link between chlorinated organic contaminants in drinking water and increased incidence of human cancer (cited in ref. 56).

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