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NITROSAMINES – CARCINOGENIC CHEMICAL “INTRUDERS” IN OCCUPATIONAL ENVIRONMENTS

Abstract: *Nitrosamines, or more precisely* N-*nitrosamines, along with* N-*nitrosamides, belongs to* N-*nitroso compounds, a class of organic compounds that have a nitroso (-N=O) group attached directly to a nitrogen atom. Only a few of them occur naturally while the majority is formed by nitrosation of secondary amines in a living and working environment, food, tobacco smoke, etc. These compounds have scarce application in the industry, but they can be formed* in situ*, so they can be considered as chemical intruders in working environments. Considering their toxicity, especially carcinogenicity, where there is a risk of exposure to* N-*nitroso compounds, appropriate protection measures should be taken, including process control, work practices, protective clothing, use of respirators, legal regulations.*

Key words: *N*-nitrosamines, *N*-nitroso compounds, occupational exposure, carcinogenicity, monitoring

INTRODUCTION

N-Nitroso compounds (NOCs) are a class of organic compounds that have a nitroso (-N=O) group attached directly to a nitrogen atom. They are divided into two groups: *N*-nitrosamines (NOAs), derived from secondary amines (dialkyl, alkyl-aryl, diaryl, or cyclic), and *N*-nitrosamides, derived from *N*-alkylated/arylated amides, ureas, or carbamates (Figure 1).

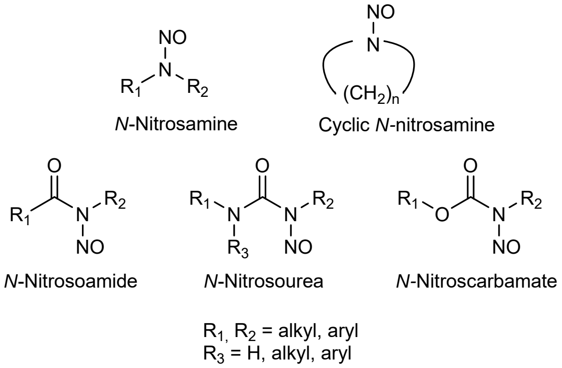


Figure 1. *Structures of* N-*nitroso compounds*

Only a few *N*-nitroso compounds occur naturally, while most of them can be readily synthesized by a reaction of nitrosable substance, secondary amine or *N*-substituted amide, and nitrosating agent, i.e. nitrosonium cation (NO^+) (Figure 2). The nitrosation can occur either *in vitro*, e.g. in a living and working environment, or *in vivo*, e.g. in the stomach, by simultaneous ingestion of nitrosable substance and nitrosating agent [1]. The sources of nitrosable substances are numerous, while there are two main sources of NO^+ [2]:

1. nitrogen oxides, N_2O_3 and NO_2, in equilibrium with N_2O_4, that are mostly generated by oxidation of nitrogen-containing organic matter (e.g. during the combustion of fossil fuels),
2. nitrates (NO_3^-) and nitrites (NO_2^-), which are used as industrial and consumer products, as well as food-preservatives, in an acidic medium.

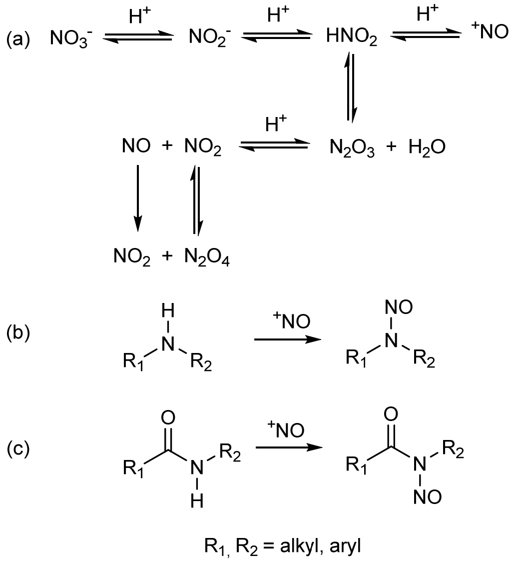


Figure 2. *General mechanism of (a) nitrosonium cation, (b)* N-*nitrosamines and (c)* N-*nitrosoamides formation*

Although the first report on NOAs dates back to the mid-19th century, this class of compounds remained in relative obscurity for almost a century, until their biological properties (especially the knowledge that they are carcinogenic) unveiled them to the scientific community [3]. In particular, over the last few decades, the occurrence of NOAs in the human diet has warranted much concern, since they are either generated from various food constituents containing amine groups and nitrites, used as food preservatives or are generated during the food preparing processes [1, 4].

The average daily human exposure to NOCs is estimated to be 1 μmol of these compounds (in total). Important sources of exposure, besides the dietary one (72% of the total exposure), are occupational exposure (25%), exposure *via* tobacco smoke (2%), and *via* consumer products (1%), such as cosmetics and personal care products, products that contain rubber, etc. [5]. The primary interest in human exposure to NOAs was centered around their occurrence in food-staffs and *in vivo* formation from precursor chemicals. The emphasis on human exposure to these compounds was shifted towards working environments with the finding of *N*-nitrosodimethylamine (NDMA) in the atmospheres near manufacturing facilities producing and/or using dimethylamine [6].

As occupational exposure comprises ¼ of the total human exposure to these carcinogenic compounds, herein we will discuss the potential sources of nitrosamines formation in working environments, their physical properties, reactivity, and toxicity, as well as potential preventive measures to reduce occupational exposure to this important carcinogens.

PHYSICAL AND CHEMICAL PROPERTIES OF NITROSAMINES

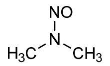
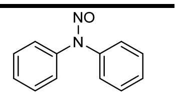
The physical properties of NOAs depend on the type of substituent (R_1, R_2, Figure 1). For example, NDMA is an oily liquid soluble in water and polar solvents, while *N*-nitrosodiphenylamine (NDPA) is a solid substance insoluble in water and soluble in non-polar organic solvents. Some of the physical properties of NDMA and NDPA, two nitrosamines with the most frequent occurrence in working environments, are given in Table 1.

Considering their chemical reactivity, nitrosamines are fairly labile compounds sensitive to prolonged thermal treatment, photochemical irradiation, as well as to excessive conditions of pH [6]. Moreover, they may undergo "transnitrosation", and this reaction is credited for their biological activity [9].

TOXCICITY OF NITROSAMINES

It has been proven that over 300 NOCs are carcinogenic in one or more animal species and that more than 40 animal species, including higher primates, are susceptible to NOCs-induced carcinogenesis. The International Agency for Research on Cancer (IARC) has classified NOAs as Group 2A or Group 2B carcinogens. Extensive experimental and some epidemiological data suggest that NOAs are carcinogenic for humans and that the intake of these compounds may be regarded as an aetiological risk factor for certain types of cancer, including cancers of the esophagus, stomach, nasopharynx, liver, kidneys, etc. [2].

Table 1. *Physical and chemical properties of NDMA [7] and NDPA [8]*

Physical/chemical property	NDMA	NDPA
Structure		
Molecular weight	74.08	198.23
Physical state	liquid	amorphous solid; plates
Color	yellow	orange-brown; yellow
Odor	no distinct odor	no data
Melting point (ºC)	-50	66.50
Boiling point (ºC)	151-154	no data
Density (g/cm^3, at 25 ºC)	1.01	1.23
Vapour pressure (Pa, at 25 ºC)	1080	13.33
Solubility in water (mg/l)	miscible	40
LogK_{ow}	-0.57	2.57-3.13
Henry's law constant (Pa m^3/mol, at 25 ºC)	3.34	66.87

Generally, nitrosamines, *per se*, are stable under physiological conditions and have to undergo metabolic activation before they express carcinogenic or mutagenic potential [10]. The activation occurs by the action of cytochrome P450-dependent mixed-function oxidase system at the carbon adjacent to the *N*-nitroso group to yield an intermediate radical (**1**, Figure 3). The radical further undergoes either hydroxylation or denitrosation [7]. Hydroxylation yield an α-hydroxynitrosamine (**2**) that breaks down to the corresponding carbonyl compound and monoalkyl/monoarylnitrosamine, in the case of NDMA, formaldehyde (HCHO) and methylnitrosamine. The latter is very unstable and undergoes rearrangement to the strongly methylating methyldiazonium ion (**4**). The diazonium ion (**4**) alkylates a variety of biological macromolecules, such as DNA, RNA, and proteins, releasing molecular nitrogen (N_2). The alkylation of DNA is generally considered to be the critical step in the initiation of cancer [7]. Another metabolic pathway is denitrosation of the formed intermediate radical (**1**) that may lead to the formation of alkyl-/aryl-amine and a corresponding carbonyl compound, in the case of NDMA, methylamine (CH_3NH_2) and formaldehyde (HCHO). The latter is also highly reactive and may react with macromolecules.

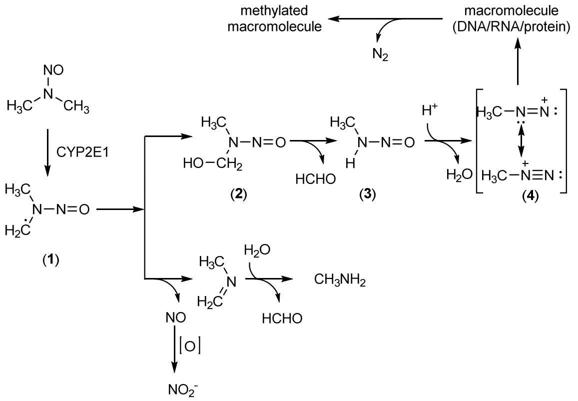


Figure 3. *Metabolism of MDMA*

NITROSAMINES IN WORKING ENVIRONMENTS

The first case on the *N*-nitroso compounds poisoning in the working environment was reported by Freund in 1937 who described the hepatotoxic effects of NDMA on two chemists that had been accidentally poisoned by this compound [6]. A decade later, Hamilton and Hardy reported the toxic effects of NDMA that was used in an automobile factory [11]. In 1954, Barnes and Magee noticed the appearance of cirrhosis of the liver among three men working in the research laboratory of an industrial facility, in which NDMA was used as a solvent [11]. They further evaluated the toxic effects of NDMA on laboratory animals and concluded that this compound was highly hepatotoxic.

NOAs, *per se*, have wide application neither in the industry nor in general. In chemistry, NOAs can be useful synthetic building blocks in organic synthesis [1, 12, 13]. In industry, they were used in the manufacture of dyestuffs, lubricating oils, explosives, insecticides, fungicides, organic accelerators, antioxidants in the production of rubber [9]. Although now used only as a research chemical, NDMA was previously used for many industrial applications [12], as an industrial solvent, nematocide, in the synthesis of the rocket fuel 1,1-dimethylhydrazine, a solvent in the plastics and fiber industry, an additive for lubricants, and to increase the dielectric constant in condensers [9]. More often, workers are exposed to NOAs as a result of their *in situ* formation in working environments, where the precursors of these compounds, amines and nitrosating agents, are either used directly or are formed as side products, as well as a result of intramolecular rearrangements.

US National Institute for Occupational Safety and Health (NIOSH), conducted a study [14] to examine workers exposure to five NOAs (*N*-nitrosodimethylamine (NDMA), *N*-nitrosodiethylamine (NDEA), *N*-nitrosomorpholine (NMOR), *N*-nitrosodiphenylamine (NDPA), and *N*-nitrosopyrrolidine (NPYR)) in different industries, including the dye industry, rubber industry, fish meal factory, leather industry, manufacturing of synthetic metalworking fluids, foundries, and the soap, detergent, and surfactant industry. These carcinogenic compounds were found in 25 of 40 surveyed plants. Alongside the 5 mentioned NOAs, *N*-nitrosodiisopropylamine (NDiPA) was found in the rubber industry, and *N*-nitrosodiethanolamine (NDE1A) is the industry of manufacturing metalworking fluids [6, 14]. The levels of NOAs in some industries are given in Table 2.

Table 2. *NOAs in some industries [6]*

Industry	NOA	Level range ($\mu g/m^3$)
Rubber	NDMA, NDEA, NMOR, NFPA, NDiPA	0.005 – 16
Leather (tanning)	NDMA, NMOR	0.3 – 10.8
Fish processing	NDMA	0.01 – 0.06
Soap, detergent, and surfactant	NDMA	up to 0.8
Iron and steel casting	NDMA, NDEA	n.r.
Manufacturing and users of synthetic metalworking fluids	NDE1A	n.r.
Dye	n.r.	n.r.

n.r. – not reported

Among surveyed industries, the highest level of NOAs, was detected in the rubber manufacturing facilities, as various amines, nitrosamines, and other nitroso or nitro compounds are used for the production of rubber [6]. Also, a high level of NOAs, in particular NDMA, was found in the leather industry, more precisely in tanneries, that used dimethylamine sulfate in the unhairing process [14]. NDMA in these tanneries is formed in a rection of dimethylamine and airborne nitrogen oxides, in either the gas phase or on surfaces [14]. Moreover, NDMA was found in the air and the total sample in the fish processing industry and it is assumed that this compound is formed from dimethylamine, which is naturally present in fish, and nitrites (which are often added as preservatives) or nitric oxide from the atmosphere [14]. The only *N*-nitroso compound detected in the soap, detergent, and surfactant industries was NDMA that is most likely formed by the reaction of dimethylamine, which is used in the synthesis of cationic surfactants, with ambient levels of nitrogen oxides [14]. In iron and steel casting plants NDMA and NDEA were detected. NDMA is formed from dimethylamine from an unknown source, while NDEA is most probably generated from triethylamine that is reported to be used in these plants, while the source of nitrozating agents in these industries is nitrogen oxides, which is generated by the many combustion sources within the foundry [14]. Furthermore, those who work with metalworking fluids may be exposed to NDE1A, which is a known contaminant in metalworking fluids formulated with nitrite and ethanolamines [14]. In the paint industry, NOAs can be formed as undesirable by-products since nitrites and amines are often used in the production of paints [14].

Possible ways of occupational exposure to NOAs are explosive manufactures, ore smelters, and amine manufactures, as well as *via* pesticides, where they can occur as impurities or as inadvertent contaminants [15]. Detectable levels of NOAs contaminants were found in the following classes of pesticides: substituted dinitroaniline derivatives, dimethylamine salts of phenoxyalkanoic acid herbicides, di- and triethanolamine salts of several pesticides, some quaternary ammonium compounds, and some morpholine derivatives. One of the most rigorous options of EPA to regulate the safe use of these pesticides was to forbid their use, but manufacturers overcame the problem of NOAs formation in pesticides by changing the chemical process of synthesis (the example of trifluralin), by the elimination of nitrite-salts in the formulation (chlorinated phenoxy- and benzoic acid herbicides), by the changing metallic container, to which nitrites were added as corrosion inhibitors, with the non-metallic ones [15].

ANALYSIS OF NITROSAMINES IN WORKING ENVIRONMENTS

As NOAs are present in working environments in very low amounts (ppm or ppb), the analytical technique used for their analysis has to be: sensitive, selective, free of false results, and capable of dealing with a wide variety of sample types. There are several steps in NOAs analysis in the workplace: sampling, concentration (extraction), chromatographic separation of the extract, and detection. Analytical methods for measuring NOAs concentrations in working environments include not only analysis of NOAs but also the analysis of their precursors (nitrosable substances and nitrosating agents) [6].

The sampling includes a collection of area and process air samples, as well as process water samples. The purpose of the analysis of the process-air samples is to determine if any specific process could be contributing to the airborne NOAs. For air sampling, wet-air traps and dry-solid sorbent traps are used [6]. Wet-air traps are impinger traps containing a sorbent such as KOH, KOH with piperidine, pyrrolidine, and morpholine, potassium biphthalate-hydrochloric acid buffer solution, phosphate-citrate buffer solution. Dry-solid sorbent traps are cartridges containing a dry sorbent and the most frequently used ones are ThermoSorb/N, ThermoSorb/A, and TrhermoSorb/A with morpholine coated onto the sorbent. ThermoSorb/N air sampling cartridge is used to sample air for NOAs, while ThermoSorb/A is an amine trap used to sample NOAs precursors (secondary amines). The role of piperidine, pyrrolidine, or morpholine in the sorbent trap, is to estimate the nitrosating capacity of the sampled air, i.e. to determine the level of airborne nitrosating agents, such as NO_2. The mentioned compounds can be directly nitrosated by NO_2 and the amount of *N*-nitrosated products is proportional to the square of concentrations of NO_2 [6].

The process-water samples are examined for both *N*-nitroso compounds and amine precursors. The amine precursors are determined by nitrosating a portion of the sample and examining it for NOAs. The step that precedes the analysis of NOAs in water samples is the extraction (concentration) of these compounds from water. The two most frequently used concentration techniques are: 1) liquid-liquid extraction with an organic solvent, such as dichloromethane, and 2) and solid-phase extraction, i.e. adsorption on a sorbent material such as a XAD resin [6].

For separation, gas chromatography (GC) and high-pressure liquid chromatography (HPLC) may be used. Gas and high-pressure liquid chromatographs that are used for NOAs analysis are usually coupled to the detector specifically designed for NOAs detection – thermal energy analyzer (TEA) [16]. The method of detection is based on one of the most significant physical properties of NOAs – the relative ease of the dissociation of the N-NO bond upon heating. NOAs are subjected to catalytical pyrolysis in the GC carrier gas or, in the case of HPLC, a liquid sample is swept through the catalytic pyrolyzer by argon carrier gas where all organic materials are being vaporized and/or pyrolyzed. Pyrolysis of NOAs leads to the homolytic cleavage of the N-NO bond and release of nitrosyl radical ($^{\bullet}$NO). In the detector, this radical is oxidized by ozone to generate electronically excited NO_2, which on decay to the ground state manifests chemiluminescence (Figure 4). The intensity of chemiluminescence is proportional to the concentration of NOA present in the sample.

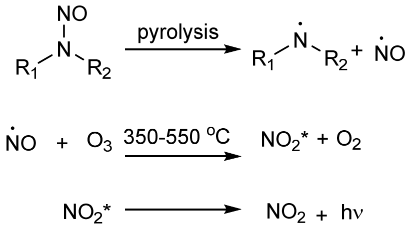


Figure 4. *The processes occurring in the thermal energy analyzer (TEA)*

Besides this, the detection of NOAs, for example, NDMA, has been accomplished by flame ionization detector, nitrogen–phosphorus detectors, the Hall electrolytic conductivity detector operated in the reductive mode, electron ionization low-resolution mass spectrometry, high-resolution mass spectrometry, chemical ionization tandem mass spectrometry on an ion trap mass spectrometer, and laser ionization time-of-flight mass spectrometry. Liquid chromatography has also been used in conjunction with a photolysis reactor and (electrospray ionization) mass spectrometry [17].

Currently, the recommendation of the Occupational Safety and Health Administration (OSHA) is to use Thermosorb/N media or a 15 ml isopropanol bubbler for air sampling, except for *N*-nitrosophenylamine which is unstable in isopropanol, and the samples are further analyzed by TEA or HPLC. Samples must be protected from light during and after sampling and either stored in a freezer or analyzed within six days after collection. The limit of the detection is 0.26 $\mu g/m^3$ [14].

PROTECTIVE MEASURES IN WORKING ENVIRONMENTS

In the occupational environment, where there is a risk of exposure to hazardous chemicals, it is necessary to perform a risk assessment [18]. Moreover, appropriate protection measures should be taken, which include process control, work practices, protective clothing, use of respirators [19]. The reducing risk from NOAs exposure at the workplace can be accomplished by [20]:

- Technological improvement,
- Use of “safe” amines,
- Avoidance of nitrosating chemicals,
- Reduction in nitrite use,
- Reduction of NO_x pollution,
- Proper ventilation at working places,
- Legal regulations.

Processes in which the formation of *N*-nitroso compounds can occur should be sealed, local and general ventilation should be provided and the reduction of the concentration of these compounds in the air should be accomplished by dilution [14, 21]. Operations and equipment should be isolated. The suggested technological changes, in general, are neither complicated nor unjustifiably expensive and they can be applied in many cases. Moreover, workers must observe special hygiene rules, and certain procedures must be followed for the movement of the material and in case of accidental spills or emergencies.

Currently, there are no OSHA Permissible Exposure Limits (PELs) for NOAs [14]. Mixtures containing more than 1% of NDMA must be maintained in isolated or closed systems The OSHA standard for working with NDMA requires workers to wear respirators that cover half of the face with filters for dust, fog, and smoke (approved by NIOSH / MSHA) in accordance with 29 CFR 1910.134 [14]. Occupational safety and health personnel should select personal protective equipment and other protection measures depending on the results of risk assessments based on expected exposure levels. When choosing personal protective equipment one should bear in mind that NOAs are uncharged, very soluble, and can readily diffuse through many media and “barriers”, including rubber gloves [22].

CONCLUSION

N-Nitrosamines are highly toxic, carcinogenic and mutagenic compounds that endanger human health. These compounds do not have wide application in industry, nor in general, but they can be formed *in situ* in those working environments where secondary amines and nitrosating agents (nitrites/nitrates or nitric oxides) occur. The industries where the highest levels of NOAs are found are the rubber and leather industry, dye industry, fish meal factory, manufacturing and users of synthetic metalworking fluids, foundries, and the soap, detergent, and surfactant industry. Considering their toxicity, especially carcinogenicity, where there is a risk of exposure to NOAs, appropriate protection measures should be taken, including process control, work practices, protective clothing, use of respirators, legal regulations, etc. The fact that these compounds can be formed from a wide range of precursors under different conditions, makes the prevention of nitrosamines a multifaceted problem with no single solution.

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NITROZAMINI – KARCINOGENI HEMIJSKI “ULJEZI” U RADNOJ SREDINI

Ana Miltojević, Tatjana Golubović, Marina Stojanović

Rezime: *Nitrozamini, ili tačnije* N*-nitrozamini, zajedno sa* N*-nitrozamidima, pripadaju* N*-nitrozo jedinjenjima, klasi organskih jedinjenja koja imaju nitrozo (-N=O) grupu vezanu direktno za atom azota. Samo nekoliko njih ima prirodno poreklo, dok se većina formira nitrozvanjem sekundarnih amina u životnoj i radnoj sredini, hrani, duvanskom dimu, itd. Ova jedinjenja nemaju široku primenu u industriji, ali se mogu formirati* in situ*, pa se mogu se smatrati hemijskim uljezima u radnom okruženju. S obzirom na toksičnost, posebno karcinogenost, u radnim sredinama u kojima postoji rizik od izloženosti* N*-nitrozaminima, treba preduzeti odgovarajuće mere zaštite, uključujući kontrolu procesa, radnu praksu, zaštitnu odeću, upotrebu respiratora, zakonske propise.*

Ključne reči: *N*-nitrozamini, *N*-nitrozo jedinjenja, izloženost na radnom mestu, karcinogenost, monitoring.