



## Carcinogenic effects of N-nitroso compounds in the environment

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### Abstract

N-nitroso compounds (NOC) are produced by the acid catalyzed reaction of nitrite with certain nitrogen compounds. The gastrointestinal tract (GI) is the main site for the formation of reactive nitrogen species (RNS). Bacteria present on the GI tract surface reduced the dietary nitrate or nitrite into Nitric oxide (NO) and other related compounds. The clinical sign of NOC carcinogenicity varies according to species, dose, and route of administration. Humans are exposed to preformed N-nitroso compounds and endogenous NOC via the environmental food chain. Several NOC are potential human carcinogens, including DENA and NDMA, but evidence from population studies is inconsistent.

**Key Words:** *Environmental problem, Gastrointestinal tract, Human carcinogen, N-nitroso compounds, Reactive species*

### Introduction

N-nitroso compounds (NOC) can be classified on the basis of their properties like chemical determination, structure, decomposition, carcinogenicity, and stability, etc. Based on their chemical structure, NOC are classified into two major groups: N-nitrosamines and N-nitrosamides. Both groups of NOC are characterized by a nitroso group ( $-N=O$ ) attached to an atom of nitrogen ( $-N-N=O$ ). The nitrite compounds with amides or amines are inducing these reactions. N-nitrosamines are produced from nitrosation (reaction with nitrite) of secondary amines containing alkyl aryl, N-alkyl amides, N-alkyl ureas, N-alkyl carbamates, dialkyl, and their substituent's (Tricker, 1992). It is influenced by many factors, like pH, contact time, substrate concentration and basicity of the amine (Alaba *et al.*, 2017). Nitrosamines are the main N-nitroso compounds as shown in Fig. 1, they originate from the reactions of secondary amines and nitrosamides (e.g., urea and carbamates) with nitrite. The N-nitrosamines, shown by Dimethylnitrosamine (DMN), is thermally and chemically resistant under the phenomenon of physiological conditions, and are now generally known to have an undesirable biological impact, primarily by microsomal mixed-function oxidases, to reactive intermediates, after their metabolic activation (Shaik *et al.*, 2020).

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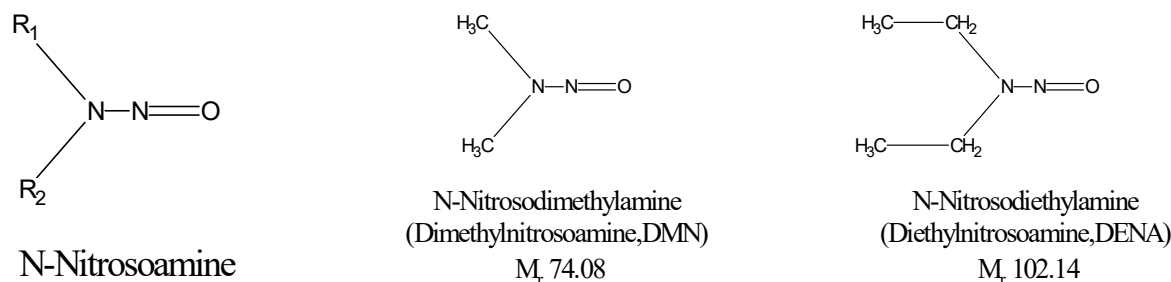
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There are many N-nitrosamines like N-Nitroso-N-methylurea (NMU), which are physiologically toxic, decompose non-enzymatically, and unstable at pH concentrations to reactive alkylating derivatives in most of the conditions. Carcinogenic N-nitroso compounds became more interesting in 1937 as a result of liver damage observed by men which are caused by exposure of DMN, used for an industry solvent (Freund, 1937). The carcinogenic and toxic function of DMN in animals was revealed by Magee and Barnes (Barnes *et al.*, 1954; Magee, 1956). The biological functions and their mechanism of a majority of N-nitroso compounds have been studied. The formation of carcinogenic nitrosamines can evolve through the interactions between nitrogen oxides and tobacco amines in tobacco smoke (Druckrey and Preussmann, 1962; West, 2017).

### Occurrence and formation of N-nitroso compounds

Ender *et al.* (1964) provided the first verified environmental proof of occurrence of N-nitrosamines. He noticed the residues of N-nitrosodimethylamine (NDMA) in a fish meal which is preserved in nitrite for sheep fodder, prepared for an outbreak of hepatosis in sheep. This indicates the possible importance and features of NOC compounds for human beings. It led to the contribution of significant research on nitrosamines certainty in nitrite-stored fish and meat (Sakshaug *et al.*, 1965).



**Fig 1: Structures of nitrosamines, DMN, and DENA**

Sander in 1967, presented the first unambiguous evidence of the endogenous development of nitrosamines (i.e. *In vivo* production from precursor compounds) in laboratory animal models strengthened the issue over the health problems caused by these compounds. They noticed that N-nitroso compounds triggered a broad range of tumors, including monkeys, rats, and many other species. It seems that before alkylate cell macromolecules “carcinogenic event”, nitrosamines necessitate metabolic activation through alpha-hydroxylation, while nitrosamines act as alkylating agents directly (Magee and Barnes, 1967). Since monkeys are particularly prone to nitrosamine and slices of human liver metabolize DMN (Montesano and Magee, 1970), human beings are likely susceptible too. Many researchers also reviewed on their carcinogenicity, toxicity, teratogenicity, and metabolism (Magee and Barnes, 1967; Druckrey 1973a and 1973b; Magee 1976). The occurrence and formation of N-nitroso compounds in the human body environment have been discussed (Magee *et al.*, 1956; Mirvish, 1975). Compounds carcinogenic effects in experimental test models and their impact on humans in causing a different kind of cancer have also been widely studied (Bartsch and Montesano, 1984; Preussmann and Stewart, 1984; Lijinsky, 1987; Magee, 1989). There are methods and techniques commonly accessible for the estimation of both extremely reactive volatile nitroso compounds by GC-MS, and in recent days for the creation of volatile and nonvolatile nitrosamines with the help of “thermal energy analyzer” (Fine *et al.*, 1975). In other studies, N-nitrosamines are evaluated by less precise methods, like, thin-layer chromatography, colorimetry, and polarography. Later, the foregoing

instruments rely on the removal of the nitric oxide by catalytic methods from the N-nitroso compounds. The nitric oxide is oxidized with ozone to give excited nitrogen dioxide, which decays to ground-state nitrogen dioxide with the emission of infrared light, which is measured. Such approaches can identify nitrosamine/kg food down to 1-5 µg. Exposure of N-nitroso compounds to humans were established carcinogenic, which can occur via diet. Smaller amounts of nitrosamines like NPY and NDMA, it takes place intermittently in many fish and meat products which are nitrite preserved. Nitrosopyrrolidine (NPY) is currently reported in fried bacon, upto 100 µg/kg (Scanlan, 1975). Nitrosamines were also recorded in urban air samples, in cosmetics, agricultural chemicals, and cutting oils in large (Fine *et al.*, 1976; Fan *et al.*, 1977; Vlachou *et al.*, 2020).

Druckrey and Preussman proposed that N-nitrosamines also occur in cigarette smoke on the appearance of certain precursors for their synthesis and formation in tobacco e.g. nitrosating agents and secondary amines (Druckrey and Preussman, 1962; Sharma *et al.*, 2012). Many N-nitrosamines were identified in condensates of cigarette, 180 ng per cigarette is maximal concentration which is found in those made up of tobacco and raise in a soil rich in nitrogen (Rhoades *et al.*, 1972; Cormick *et al.*, 1973; Hoffman *et al.*, 1974). The Occupational risks linked with the use of N-nitroso compounds have been identified in the industry (Magee, 1972). Although such compounds do not appear to be commonly used, some have been used as antioxidants and organic accelerators for the rubber production, including polymerized N-Nitroso-2, 2, 4-trimethyl-1,2-dihydroquinoline, N, N'-Dinitroso pentamethylenetetramine, N-Methyl-N-4-



dinitrosoaniline, and N-Nitrosodiphenylamine (Boyland *et al.*, 1968). N-nitrosamines formation has been reviewed by many eminent scientist and researchers (IARC, 1974; Mirvish, 1975; Magee *et al.*, 1976). As an air pollutant, DMN is spreading in the atmosphere by factories during the production of dimethylamine, which has been detected at the concentration varying from 0.001 to 0.43 ppb, their frequency is associated with the secondary amine and nitrogen dioxide concentrations in the air (Bretschneider *et al.*, 1973). Dimethylamine hydrochloride treatments with sodium nitrite in the alkaline phase have been reported since 1865 to generate DMN at an acidic pH (Fridman, 1971), there is also significant evidence for the production of N-nitrosamines in the acidic atmosphere prevailing in the stomach of mammals. The nitro reductase containing bacteria can also derive from nitrate enzyme reduction. Such bacteria usually exist in the lower intestines of humans. They penetrate the upper portion of the gastro-intestinal tract especially in adults with achlorhydria, while in infants having gastric acid secretion in low amount (Philipps, 1971).

Quaternary ammonium compounds, secondary and tertiary amines, guanidines, carbamates, and ureas are the nitrostable compounds which occurs in the environment and found in the nature, nitrosation of a variety of chemicals used in agriculture have been also observed (Elespuru, 1973; Eisenbrand, 1974; Sen, 1974). In certain vegetables including spinach and manufactured food and dairy products, bacterial conversion of nitrate or nitrite to nitric oxide has been observed in gastrointestinal tracts (Lee, 1970). Later on, this nitric oxide again converted to nitrate or nitrite in bloodstream and react further with secondary amines and amides to form N-nitroso compounds (Kobayashi, 2018). Evidence that the amine precursors form N-nitroso compounds in the body which is based on the detection of chemicals in gastric juices (*In vitro*), in human stomach (*In vivo*), disruption to cellular macromolecules, carcinogenic, and acute toxic effects were observed after amides, amines, and nitrite being continuously administered (IARC, 1974; Magee *et al.*, 1976).

#### Human exposure of N-nitroso compounds

A summary of the present human exposure to environmental N-nitroso compounds is attempted in Fig 2. The apparently dynamic pattern of overall

exposure may be divided into exogenous and endogenous exposure. Exogenous exposure is an intake of environmentally preformed N-nitroso compounds, which can be validated only in terms of volatile nitrosamine. On the other hand, endogenous exposure is a formation of carcinogenic compounds (*In vivo*) from the precursors of nitrosating agents and amines (Preussmann, 1984).

#### Toxicity and carcinogenicity

Although nitrite and nitrate raise a toxicologic risk, the most difficult issues lie in their appearance in the production and formation of carcinogenic N-nitroso compounds.

Thus, various chemical reactivities or stabilities are partly due to the various toxicities of N-nitrosamides and N-nitrosamines. In experiments of acute and sub-acute toxicity, glycogen loss, necrosis of centrilobular, testis, and of the renal tubes were observed after inducing DMN and DENA in rats (Hard *et al.*, 1970a, 1970b; Svoboda *et al.*, 1975). The two N-nitroso compounds groups observed significant organ potency for the carcinogenic effect. The N-nitrosamines exerted particularly carcinogenic action of the N-nitrosamides specifically in the tissues of the respiratory system, central nervous systems, oesophagus, the gastro-intestinal tract, the peripheral, liver, and kidney. The presence of N-nitrosamines tumor insertion is highly influenced by the length of the alkyl chain in chemical structures. Offspring of maternal animals can be affected by cancer while treating with different N-nitroso compounds during pregnancy. The duration of medication through the gestation period is a key consideration for the emergence of tumors in the offspring, few overlapping cycles also exists. Embryotoxic impact in rats generates after induction of N-nitroso compounds was administered via different routes between days of 1 to 10, a carcinogenic effect observed from day 10 till delivery, and a tetraogenic response between 9 to 16 days (Druckrey, 1973a and 1973b; Napalkov, 1974; Tomatis *et al.*, 1974). N-nitroso compounds having potential for causing cancer and they are distributed in the environment for their chemical synthesis, and now it is being wondered whether N-nitroso compounds are liable for certain part of the human cancer incidences (Lijinsky, 1970; Sharma *et al.*, 2011).



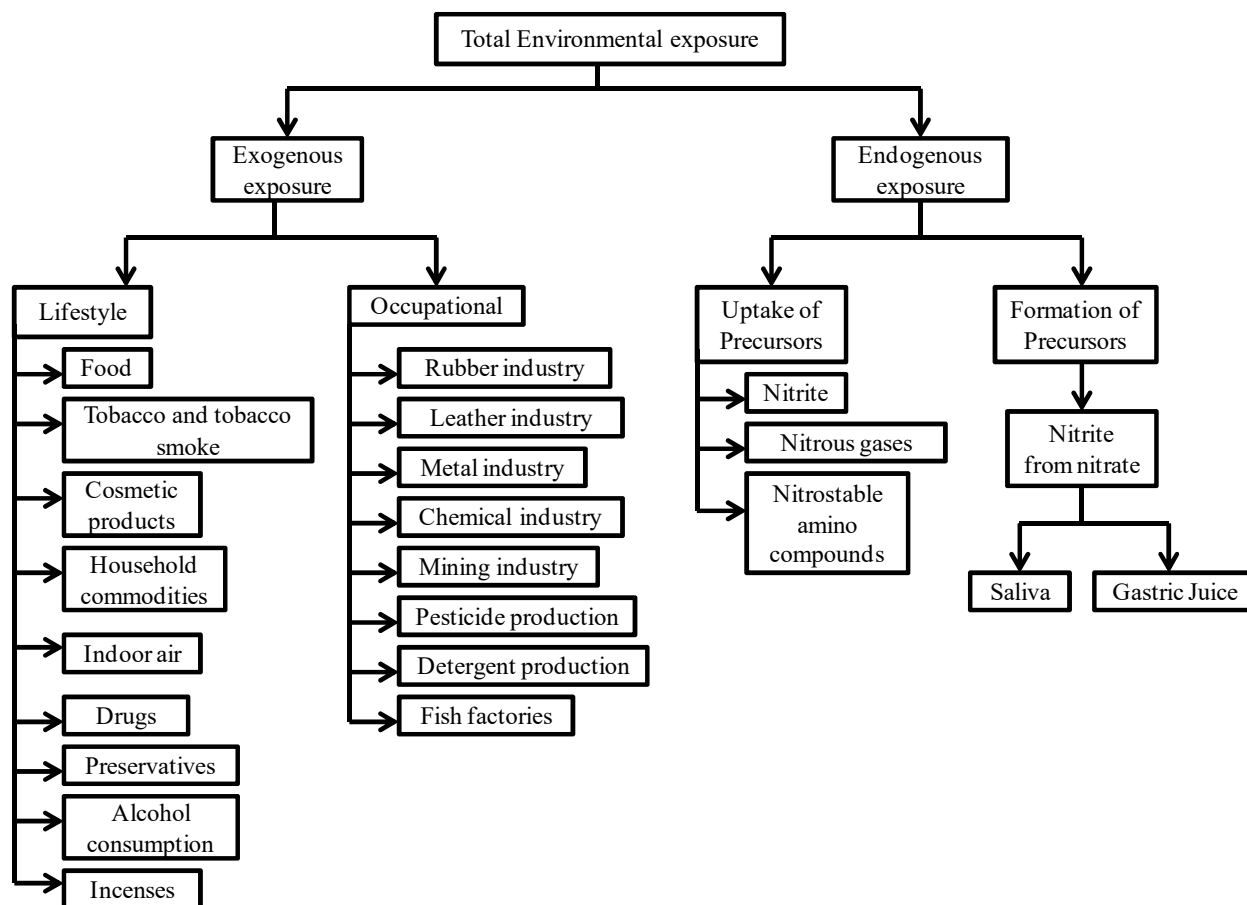


Fig 2. Total environment exposure by humans

### Sources of N-nitroso compounds

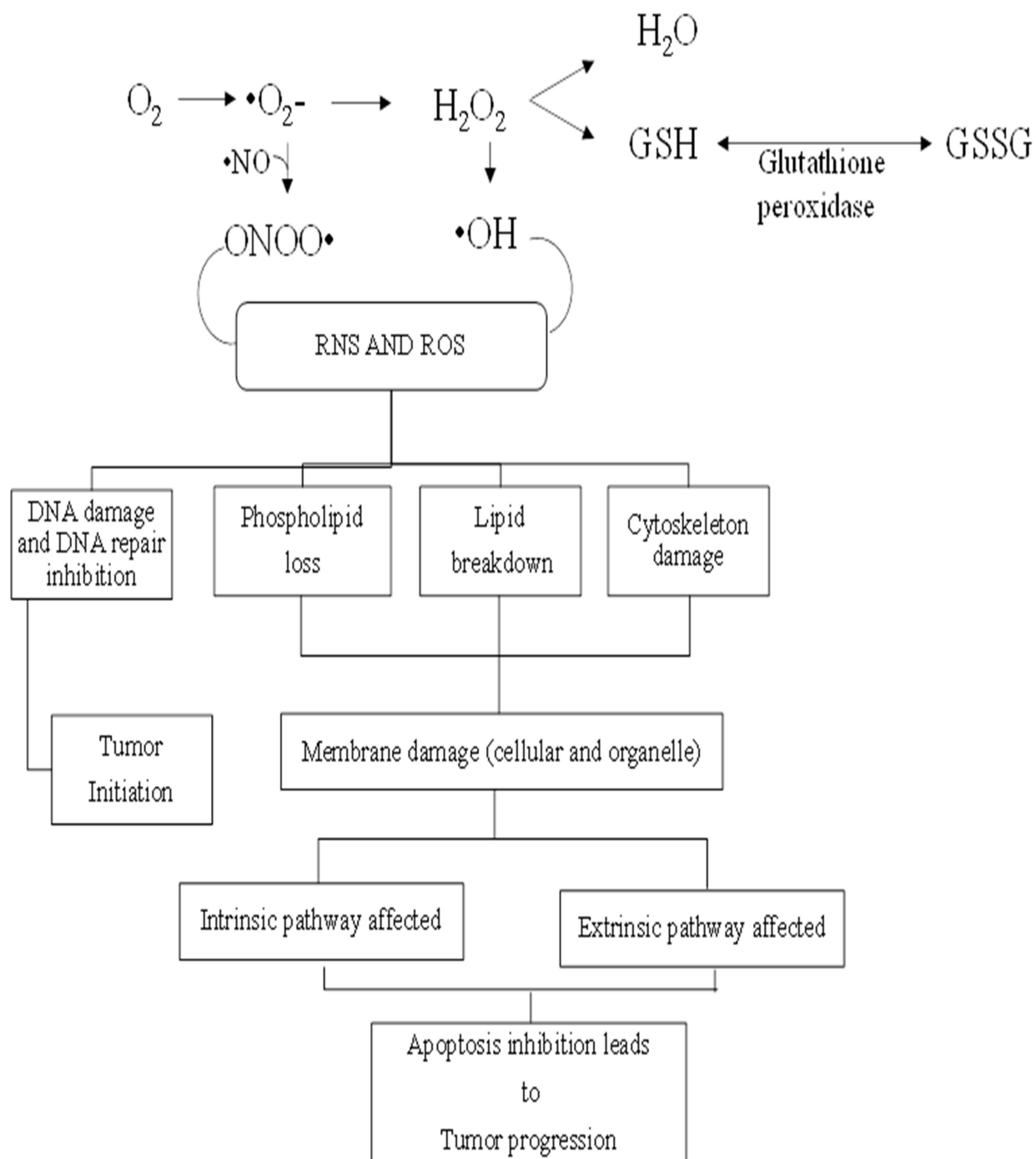
Human beings are susceptible to preformed N-nitroso compounds which produced *In vivo* from different sources such as, alcohol, heavy metals, drugs, tobacco or tobacco products, occupational environments, and diet, etc. (Mirvish, 1995). Increased production of N-nitroso compounds was observed in the human colon because of consumption of red-meat containing hemoglobin in large amount (Bingham *et al.*, 1996; Silvester *et al.*, 1997; Hughes *et al.*, 2001; Cross *et al.*, 2003; Loh *et al.*, 2011).

N-nitroso compounds are etiologically related to childhood brain tumors (CBT, Dietrich *et al.*, 2005). There are a few risk factors causing CBT, includes ionizing radiation, e.g., X-rays or radiotherapy for leukemia (Martin *et al.*, 1982; Monson and MacMahon, 1984; Rimm *et al.*, 1987; Shapiro *et al.*, 1989; Rodvall *et al.*, 1990), and PGS such as neurofibromatosis or Von-Recklinghausen's disease (Kleihues *et al.*, 1995;

Davis and Martin, 1998).

In many biological processes, ROS/RNS act as signaling molecules in the cellular system (Hancock *et al.*, 2001; Chatterjee and Fisher, 2004).  $O_2^-$  radical is considered as the primary ROS, among the several types of reactive species produced during normal and inflammatory responses.  $\bullet OH$  radicals that are generated from superoxide dismutase after production of  $H_2O_2$  in the presence of redox-active transition metals, react spontaneously, causing DNA strand breaks and base modifications during phagocytosis (Hancock *et al.*, 2001; Shacter and Weitzman, 2002). Moreover,  $NO\bullet$  radical (RNS) can induce nitration of guanine, producing G:C; T:A transversions, and thus are involved in inflammation-induced carcinogenesis (Ohshima *et al.*, 2006; Terasaki *et al.*, 2006). The products of nitric oxide synthesis induce mutations through N-nitrosation of secondary amines. These N-nitrosamines are

markedly mutagenic and hence may play a critical role in carcinogenesis induced during chronic inflammation (Szabo and Ohshima, 1997). The generation of free radicals in complex III of mitochondria to the initiation of tumor formation and progression is shown in Fig.3.



**Fig 3.** The progression and initiation of tumor from reactive species. GSSG-oxidized glutathione; GSH-reduced glutathione; H<sub>2</sub>O<sub>2</sub>- hydrogen peroxide; H<sub>2</sub>O-water; RNS- reactive nitrogen species; ROS- reactive oxygen species; O<sub>2</sub>- oxygen.

### Human carcinogenesis by N-nitroso compounds

There are different types of N-nitroso human carcinogen compound which leads to diverse types of carcinomas in various human organs as shown in

Fig 4. It is also used in studying the carcinogenicity in human being after inducing cancer in rodents. The lung, liver, and kidney cancer are described as further.

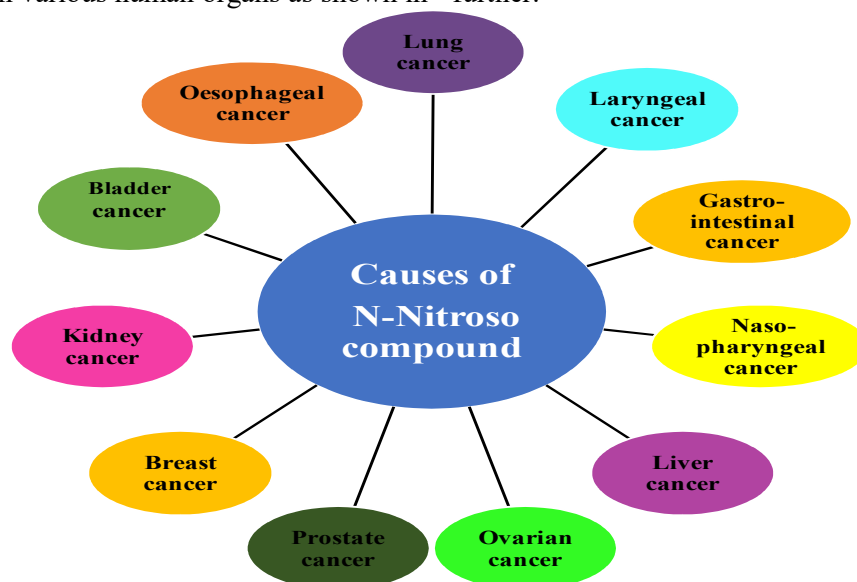


Fig 4. Different types of cancer caused by N-nitroso compounds

**Lung:** It has been suggested that NOC are more effective as carcinogens in animals when taken as orally and given in small quantities for a period of time (Stefani *et al.*, 1996). It is studied that intake of NDMA from any source can cause or increase the risk of lung cancer (Goodman *et al.*, 1992) and a study on rat also gives similar evidence (Zak *et al.*, 1960). Certain foods like salted meat and beer also contained NDMA (Stefani *et al.*, 1996). The tumorigenic effect was dependent on dose, e.g., if the dose of both reactants were lowered by 10 times, production of the nitrosamine (i.e., Mono-nitrosopiperazine) should drop by 1000 times and in one experiment with 6.25 g piperazine/kg food and 1.0 g NaNO<sub>2</sub> per litre water, an average of 9 lung adenomas/mouse were induced and by comparison with experiments where preformed mono-nitrosopiperazine (MNP) was given, it was estimated that 2.5% of the nitrite was converted to nitrosamine (Mirvish, 1977).

**Liver:** In 1937, carcinogenicity of NOC was firstly reported in DMN which found to cause liver cancer in men (Freund, 1937) and later confirmed by Barnes and Magee in 1954. The study revealed that there was the demarcation of a sharp line between seemingly safe liver cell and completely destroyed

parenchyma area in the liver and also continues administration of DMN leads to the occurrence of hepatic tumor in rats (Barnes *et al.*, 1954; Magee and Barnes, 1956). Later, another NOC i.e., DENA also found to possess the hepatotoxic and carcinogenic effects by ethylation of the N7 atom in the guanines of nucleic acids that were extracted from the liver and is a most common carcinogen (Schmahl *et al.*, 1960; Magee and Lee, 1963; Druckrey *et al.*, 1967; Janmeda *et al.*, 2011; Sharma and Janmeda, 2019). Oral administration of DENA (at 50mg/kg b.wt.) responsible to initiate the hepatic carcinogenicity and to damage tissue architecture in swiss albino mice (Pracheta *et al.*, 2011; Sharma *et al.*, 2012; Sharma and Janmeda, 2014). The experiments by Tolba *et al.* (2015) found that the intraperitoneal administration of DENA at body weight of 10 mg/kg for 100 days on 2-week-old male mice can induce hepatic tumors. Nitroso compounds especially DMN found to become one of the recognized carcinogens for induction of liver cancer in rodents to study human hepatocarcinogenesis and understanding of pathogenic alteration. Recently, in China nitroso compound was used on C57BL/6 mice aged 4 weeks to induced liver tumor by increasing its dose

weekly (Bao *et al.*, 2019). Along with the NOC, some promoters can also be used to escalate the carcinogenicity. During experiments on rats for hepatic carcinomas study Phenobarbitone is used as a promoter to induce cancer faster with an increase in the dose of N-Nitrosodiethylamine it leads to metastasis (Upreti *et al.*, 2018).

**Kidney:** In fact, Nitroso dimethylamine (NDMA) induces benign and malignant tumors after its administration by various routes (including ingestion) in the kidney and various other organs (IARC, 1978). The kidney tumors induced in rats by several other N-nitroso compounds, including DENA, Nitroso ethyl hydroxyl ethylamine, Nitroso diethanolamine, Nitroso hydroxyl ethyl chloro ethylurea, and Nitroso hydroxyl ethyl urea are tubular cell neoplasmas, not of mesenchymal origin. In an experiment of DENA via oral administration which is given to mice which gives rise to initiation of renal carcinoma formation (Sharma and Pracheta, 2013 and Sharma and Janmeda, 2014). Formation of this type of kidney

tumor seems related to the hydroxyethyl group in the NOC (Lijinsky, 1987).

Long-term low-dose feeding of rats with NDMA produced only liver tumors, while higher concentrations given for short periods or even as a single dose resulted in kidney tumors (Magee and Barnes, 1967). In 9 months, one dose of NDMA via intraperitoneal administration of 30 mg/kg body wt. induced large kidney tumors in rats (Magee, 1987). Several studies reported cancer of the kidney after single-dose exposures. A single intravenous dose of MNU produced 11 different types of tumors among 16 rats, and a single oral dose resulted in tumors of different parts of the gut and in the kidney (Pruckrey *et al.*, 1964; Magee and Barnes, 1967). MNU is the most active methylating agent and carcinogen in the kidney (Low, 1974).

#### Mechanism of action

The mechanism of action of N-nitroso compounds in the animal body has been described below and presented in Fig. 5.

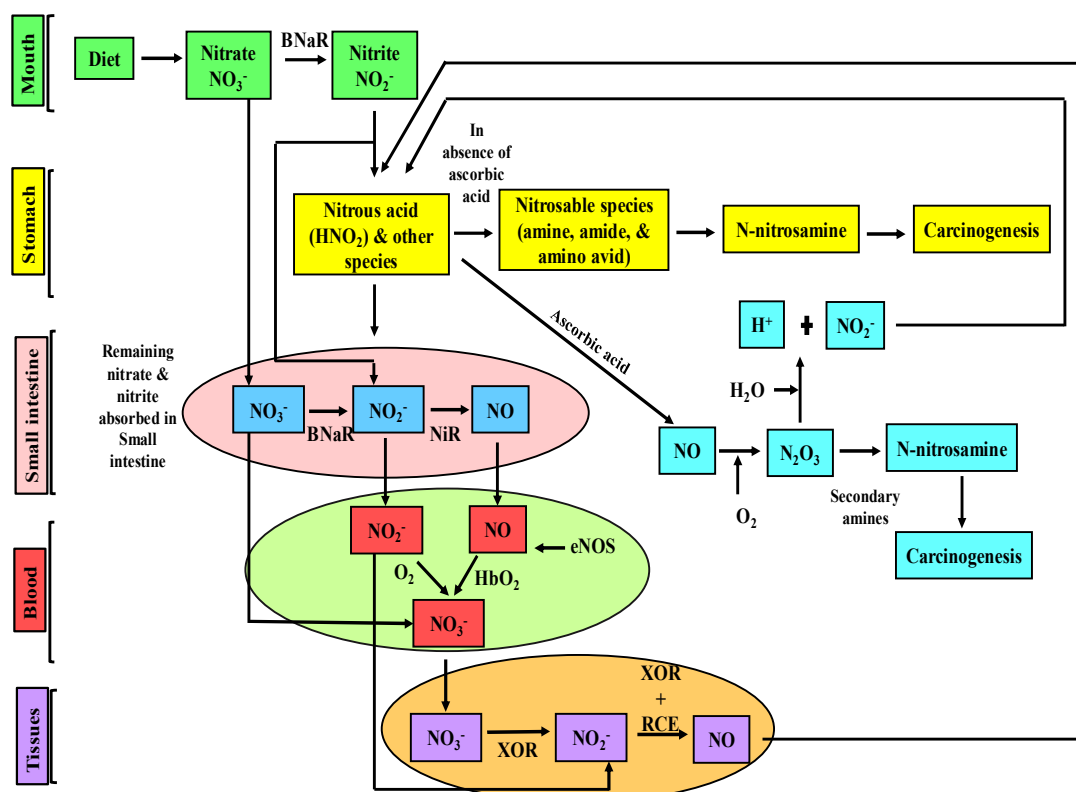


Fig 5. Mechanism of action of N-nitroso compounds in animal body. BNaR: bacterial nitrate reductase; eNOS: endothelial nitric oxide synthase;  $\text{HbO}_2$ : oxygenated hemoglobin; XOR: xanthine oxidoreductase; RCE: respiratory chain enzymes.

### Conversion of nitrate ( $\text{NO}_3^-$ ) to nitrite ( $\text{NO}_2^-$ ) in oral cavity

*Diet, salivary gland, and Mouth:* Nitrosamine usually present in dairy products (butter & cheese), vegetable and fruit crops, and meat. The main sources of nitrosamine in these products are nitrate  $\text{NO}_3^-$ , nitrite  $\text{NO}_2^-$ , and other amine products (Ma *et al.*, 2018). The first step of formation of these products is seen in the mouth, where nitrate ( $\text{NO}_3^-$ ) is converted into the nitrite ( $\text{NO}_2^-$ ) by the help of bacterial nitrate reductase enzyme (Winter *et al.*, 2007).

### Conversion of $\text{NO}_2^-$ to NO in gastric tract and formation of nitrosamine

*Stomach:* Then the  $\text{NO}_2^-$  enters to gastric tract and converted to nitrous acid ( $\text{HNO}_3$ ) and other nitrosating species ( $\text{NOSCN}$ ,  $\text{NO}^+$ , &  $\text{N}_2\text{O}_3$ ). In ascorbic acid absence, these species react with other secondary amines, amides, and lead to the production of N-nitrosamine. Ascorbic acid present in gastric juice prevents the nitrosation reaction by the formation of nitric oxide from nitrosating species. This nitric oxide in the presence of oxygen leads to the formation of nitrosating species i.e.  $\text{N}_2\text{O}_3$ , that on further reaction results in N-nitrosamine formation. There is a formation of nitrite which is reported by the reaction of  $\text{H}_2\text{O}$  with  $\text{N}_2\text{O}_3$  (Winter, 2007).

*Small intestine:* The large proportion of remaining nitrite and nitrate is absorbed in the small intestine and further reaches to the blood. Bacteria produce NO locally in the lumen of the gut through the reduction of remaining nitrate and nitrite (Tiso and Schechter, 2015).

*Blood:* There is a mixing of nitric oxide, nitrites, and nitrates with the coming nitric oxide from the small intestine in the presence of endothelial nitric oxide synthase (eNOS) and oxygenated hemoglobin ( $\text{HbO}_2$ ). In blood, oxidation of NO and nitrite leads to the generation of nitrate in the blood (Chen *et al.*, 2008).

*Tissues:* In tissues, xanthin oxidase (XOR) produces nitrite from nitrate via reduction. In further catalysis, nitrite is reduced to bioactive NO in the presence of respiratory chain enzymes then these NO and other species leads to the formation of nitrosamine in an animal body (Lundberg and Weitzberg, 2013).

### Effect of nitrosamine

The amino acids decarboxylation in nitrate ingested with diet by the help of bacteria, which results in the formation of amides and amines. The reaction of nitrosonium ions and other related species with these amides or amine lead to the production of nitrosamine and nitrosamide (Özogul and Özogul, 2019). They are reported to have carcinogenic, teratogenic, and mutagenic effects (Rostkowska *et al.*, 1998). For example: DMN is an important carcinogen that can cause tumors in variable species in different tissues, such as stomach, liver, and lung (Song *et al.*, 2015). The metabolic activation of DMN found in the liver. It is determined that the metabolism of DMN is done by the cytochrome P-450 monooxygenase enzyme which further initiates their toxic effects. So, instead of their excretion with urine, they initiate the onset of necrosis, cancer, and mutations through the formation of a covalent bond with the biomolecules (Atakisi and Merhan, 2017).

There is a direct association between the synthesis of N-nitroso compounds with the help of bacteria and raised risk for nasopharynx, esophagus, stomach, and liver cancer (Kamangar *et al.*, 2010). The toxic effects of Diethylnitrosamine and other N-nitroso compounds can be decreased by the administration of antioxidant molecules such as  $\alpha$ -lipoic acid, beta-carotene, blueberry, omega-3 and other secondary metabolites (like tannins, terpenoids, alkaloids, glycosides, and phenols) procured from the medicinal plants (Atakisi and Merhan, 2017; Jain *et al.*, 2020; Prakash *et al.*, 2019; Razzak *et al.*, 2020; Verma *et al.*, 2020).

### Carcinogenicity of N-nitroso compounds in different species

The carcinogenicity of N-nitroso compounds is based on the variable factors. Primary important factors are the type of N-nitroso compounds, different species for experimentation, the route, and the dosage of administration as listed in Table 1.

### Preventions that need to be taken care for the reduction of exposure

Following preventions should be taken in order to reduce the exposure of human beings to N-nitroso compounds:

- To prevent the extreme accumulation of nitrate in the plants, care must be exercised while fertilizing the crops (Ahmed *et al.*, 2017). Sufficient time period must elapse between the





- usage of fertilizers and harvesting. As drought condition raises the accumulation of nitrate content in the leaves of cultivated crops (Bruning-Fann, 1993).
- The application of nitrites and nitrates as food preservatives should be minimized to a level that provides protection against botulism. This is mainly for canned and cured meat, bacons, and for fish (Cammack *et al.*, 1999; Ferysiuk and Wójciak, 2020)
  - The level of nitrate in public drinking water should be less than the limit i.e. 45 mg/l as described by the International Standard of Drinking Water (WHO, 1971).
  - The preparation of dried milk of infant baby should be done with water containing less nitrate level. If nitrate-free water is not present, then breast feeding and utilization of cow milk must be done (Yeh *et al.*, 2013).
  - Food crops with low content of nitrate should be utilized for preparing foods. If vegetables with a high content of nitrate is utilized, then appropriate precautions of food processing must be encouraged (WHO, 1978).
  - Discharge of industrial and municipal wastes are another source of nitrogen that released directly into the surface water. Around 5 kg per person per year of nitrogen is present in animal waste. So, proper treatment of waste is required in order to decrease the accumulation of nitrogen waste into the water and further into the soil (Ferronato and Torretta, 2019).
  - By limiting contact with the smoke of tobacco or by avoiding the consumption of beer and other beverages, one can prevent the accumulation of nitrate in the body (Schildt *et al.*, 1998).

**Table 1. The carcinogenicity of N-nitroso compounds in different animal models.**

N-nitroso compounds	Species	Dose	Route	Carcinogenicity	References
Dimethylnitrosamine (DMN)	Rat	50 mg/ 5	Oral	+++	Maduagwu and Bassir, 1980
	Guinea pig	mg/ 1 mg		+++	
	Cat			+++	
	Monkey			++	
	Duck			-	
	Lizard			-	
N-Nitrosomethyl-n-propylamine	Syrian golden hamsters	2.1 mg/wk	Oral	+++	Linjinsky and Kovatsch, 1988
Nitrosomethyl-n-butylamine		2.5 mg/wk		+++	
N-Nitrosomethyl-n-heptylamine		6.8 mg/wk		+++	
N-Nitrosomethyl-n-octylamine		7.4 mg/wk		+++	
N-Nitrosodiethylamine (NDEA)	Albino rats	200 µg/ml	Oral	+++	Mittal <i>et al.</i> , 2002
	Swiss Albino Mice	50 mg/kg			Sharma and Pracheta, 2013; Sharma and Janmeda, 2014
N-Methyl-N-nitrosourea	Monkey	10 mg/kg	Oral	+++	Tsubura <i>et al.</i> , 2010
	Shrew	5 and 10 mg/kg		+++	
N, N-Dinitrosopiperazine	Strain SWR (inbred swiss) mice	1.00 m mole/kg	Intraperitoneal	+	Stoner and Shimkin, 1982
N-Nitrosopiperidine		0.94 mmole/kg		+	
N-Nitrosodibutylamine		1.58 mmole/kg		+	



N-Nitrosomethylurea		1.00 mmole/kg		+	
N-Nitrosodiethylamine		1.96 mmole/kg		+	
N-Nitrosodimethylamine		0.27 mmole/kg		+	
N-Nitrosomethylurethane		0.08 mmole/kg		+	
N'-Nitrosornicotine (NNN)	F344 rat	30 & 80 ppm	Oral	++	Rivenson <i>et al.</i> , 1988
	Strain A/J inbred mice	0.12 mmole	Intraperitoneal	+	Castonguay <i>et al.</i> , 1983
4-(Methylnitrosamino)-1-(3-pyridyl)-1-Butanone (NNK)	F344 rat	1-0 mmole/kg	Oral	++	Hoffmann <i>et al.</i> , 1984
	Strain A/J inbred mice	0.10 mmol	Intraperitoneal	+	Castonguay <i>et al.</i> , 1983
N-Nitrosomethyl(2-oxopropyl) amine	Syrian hamster	25 mg/kg b.w.	Sub cutaneous injection	+	Pour <i>et al.</i> , 1980
Benzo(a)pyrene	Swiss albino mice	50 mg/kg b.w. twice per week for 4 weeks	Oral	+++	Hassan, 2019
Diethylnitrosamine	Balb C Mice	3.5 l/mg once in a week	Intraperitoneal	+++	Dar <i>et al.</i> , 2019
Dimethylbenz(a)anthracene (DMBA)	Rat	80 mg/kg b.w.	Oral	+++	Zingue <i>et al.</i> , 2018
N-Nitrosobis(2-oxopropyl) amine (BOP)	MRC Rats	2.5, 5, and 10 mg/kg	Intragastric injection	+	Pour <i>et al.</i> , 1983
	Syrian golden hamster	10 mg/kg b.w.	Sub cutaneous injection	+	Zalatnai and Schally, 1989
N-Nitrosobis (2-hydroxypropyl) amine (BHP)	MRC Rats	125, 250, and 500 mg/kg	Intragastric injection	+	Pour <i>et al.</i> , 1983
N-Nitroso-N-methylurea	Wistar rats	50 mg/kg b.w.	Intraperitoneal	+++	Singh, 2020
N-Methylcyclohexylamine	Rat	400 mg/kg	Oral	-	Deichmann, 1969
	Rabbit	2000 mg/kg	Skin	-	
	Guinea Pig	7000 mg/kg	Inhalation	-	
N-Nitrosoguvacoline (NGC)	Sprague-Dawley Rats	4.4 mmoles	Oral	+	Lijinsky and Taylor, 1976
N-Nitroso-1,2,3,6-tetrahydropyridine (NTP)	Sprague-Dawley Rats	2.3 mmoles	Oral	+	
N-Nitrosopiperidine (NP)	Sprague-Dawley Rats	3.9 mmoles	Oral	+	
N-Nitrosodiethylamine	Mouse	3 mg/kg	Oral	++	Schmähl and



(DENA)	Rat	1.5 mg/kg	Oral	++	Habs, 1980
	Golden hamster	1.6 mg/kg	Oral	++	
	Guinea Pig	8-40 mg/kg	Subcutaneous	++	
	Cat	1.5-2 mg/kg	Oral	++	
	Dog	3 mg/kg	Oral	++	
	Monkey	2-50 mg/kg	Oral	++	
	Pig	0.4 mg/kg	Oral	++	

Symbols: - not present; + present in trace amount; ++ present in moderate amount; +++ present in high amount

Abbreviations: mg/kg- milligrams per kilogram; mmoles- millimoles; mg/kg b.w- milligrams per kilogram body weight; µg/ml- micrograms per milliliter; ppm- parts per million; mg/wk- milligram of dose per week; MRC- midnands rat club; SWR/A/J/Balb C- inbred swiss mice strains; F344 rat- fischer 344 rat.

## Conclusion

There are sufficient evidences to support the hypothesis that humans are susceptible to NOC induced carcinogenesis. Thus, continuous exposure to low concentrations of several different N-nitroso compounds in the diet would be expected to be etiological risk factors for certain human cancers. The response of NO is cell-specific, and they are based upon the presence of variable NOS isoforms at differed concentration, and their regulation at the post- and pre-transcriptional process is quite complicated. The recent development of strategies

for preventing or treating pathological processes in relation to the inhibition or stimulation of excessive generation of NO and N-nitrosamine presents vital importance in the field of medicine.

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## Abbreviations used

<b>NOC</b> - N-Nitroso compounds	<b>GSH</b> - Reduced glutathione
<b>DMN</b> - Dimethylnitrosamine	<b>GSSG</b> : Oxidized glutathione
<b>NDMA</b> - N-Nitrosodimethylamine	<b>BNaR</b> - Bacterial nitrate reductase
<b>NPY</b> - Nitrosopyrrolidine	<b>eNOS</b> - Endothelial nitric oxide synthase
<b>DENA</b> - N-Nitrosodiethylamine	<b>HbO<sub>2</sub></b> - Oxygenated hemoglobin
<b>NMU</b> - N-Nitroso-N-methylurea	<b>XOR</b> - Xanthine oxidoreductase
<b>GC-MS</b> -Gas chromatographic-mass spectrometry	<b>RCE</b> - Respiratory chain enzymes
<b>PGS</b> - Predisposing genetic syndromes	<b>Nitrate</b> - -NO <sub>3</sub>
<b>ROS</b> - Reactive oxygen species	<b>Nitrite</b> - -NO <sub>2</sub>
<b>RNS</b> - Reactive nitrogen species	<b>Nitrous acid</b> - HNO <sub>3</sub>
<b>MNP</b> - Mononitrosopiperazine	<b>ppb</b> - Parts per billion

