International Journal for Environmental Rehabilitation and Conservation
Volume III No. 1 2012 [56 – 67] [ISSN 0975 - 6272]

N-Nitrosodiethylamine and carcinogenicity: An Over review

Veena Sharma[1], Pracheta Janmeda[1], Lokendra Singh[2]

Received: November 28, 2011 | **Accepted**: April 22, 2012 | **Online**: July 28, 2012

Abstract

Cancer remains the major cause of death in the developed, developing and underdeveloped countries next only to cardiovascular disease and hence is a major cause of morbidity and mortality worldwide. N-Nitrosodiethylamine ($C_4H_{10}N_2O$) is the most important environmental carcinogen among the nitrosamines, present in our environment and food chain. *N*-Nitrosodiethylamine is present in a variety of Foodstuffs including milk, cheeses (0.5 to 30 µg/kg), meat products such as various salted and dried fishes (<1 to 147 µg/kg), cured meats (up to 40 µg/kg), alcoholic beverages (0.1 µg/kg), and a few varieties of vegetables such as soybeans (0.2 µg/kg). DENA has been suggested to cause oxidative stress and cellular injury due to involvement of free radicals. It is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals. The essential nature of any cancer in humans or in animals continues to challenge scientists and practitioners interested in the patho-physiology, prevention and therapy of this disease. Despite recent advances in our understanding of the biological processes leading to the development of cancer, there is still a need for new and effective agents to keep this disease under control.

Keywords: Chemoprevention | Environnemental impact | N-Nitrosodiethylamine | Oxidative damage

For correspondence:

[1]Department of Bioscience and Biotechnology, Banasthali University, Banasthali-304022, Rajasthan, India
[2]Department of Botany, Meerut College, Meerut
E-mail: drvshs@gmail.com

Introduction

N-nitroso compounds (NOCs) are one of the important groups of carcinogens frequently present in human environment and food chain (Preussmann, and Stewar 1984)**.** NOCs, like N-nitrosodimethylamine (NDMA), N-

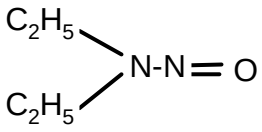
nitrosomethylethylamine (NMEA) and N-nitrosodiethylamine (DENA) are highly mutagenic compounds that are suspected of carcinogenicity (Ohkawa *et al*., 1979; Ohsawa *et al*., 2003). The presence of nitroso compounds and their precursors in human environment together with the possibility of their endogenous formation in human body have led to suggestions of their potential involvement in human cancers (Bartsch and Montesano, 1984; Kaplan *et al*., 1997).

DENA is an N-Nitroso alkyl compound and was chosen as a carcinogenic model because this well-investigated, classic carcinogen is present in our environment and suggested to increase the generation of reactive oxygen species (ROS) resulting in oxidative stress and cellular injury (Preussmann, 1984; Bartsch *et al*., 1989; Bansal *et al*., 2000; Aiub *et al*., 2003). There is considerable support to the concept that oxygen free radicals and related lipid peroxides also play a key role in the pathogenesis of normal senescence and of age-related chronic degenerative diseases, including cancer (Maxwell, 2000). *N*-Nitrosodiethylamine is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity in experimental animals (IARC 1978, 1982, 1987).

Synonyms

DEN (mutagen); NDEA; DANA; Diethylnitrosamine; Diaethylnitrosamin (German); Diethylnitrosamide; Diethylnitroso-amine; Ethanamine; N-ethyl-N-nitroso; N,N-Diethylnitrosamine; N-Nitrosdi; N-Ethyl-N-nitroso-ethanamine; Nitrosodiethylamine.

Chemical Structure



Properties

N-Nitrosodiethylamine is volatile, clear yellow oil that is soluble in water, alcohol, ether, other organic solvents, and lipids. The compound is sensitive to light, especially ultraviolet light, and undergoes relatively rapid photolytic degradation (IARC 1978, HSDB, 2002).

Principle sources of DENA

DENA is found in a drinking water, wide variety of foodstuffs such as milk products, meat products, number of alcoholic beverages, soft drinks, tobacco smoke and a few varieties of vegetables are the principal sources of nitroso compounds (Tricker *et al*., 1991; Kumar and Kuttan, 2000; Liao *et al*., 2001; Bansal *et al*., 2005).

Uses

N-Nitrosodiethylamine is used primarily as a research chemical. It is used as a gasoline and lubricant additive, antioxidant, stabilizer in plastics, fiber industry solvent, copolymer softener, and starting material for synthesis of 1,1-diethylhydrazine. It is also used to increase dielectric constants in condensers (IARC 1972, HSDB, 2002).

Primary routes of exposure

The primary routes of potential human exposure to DENA are ingestion, dermal contact, Inhalation, eye contact, skin absorption.

Air, diet, and smoking contribute to potential human exposure at levels of a few µg per day. *N*-Nitrosodiethylamine is present in a variety of foods, including cheeses at concentrations of 0.5 to 30 µg/kg, soybeans at 0.2 µg/kg, various fish at <1 to 147 µg/kg, cured meats at up to 40 µg/kg, and alcoholic beverages at 0.1 µg/kg (IARC, 1978). *N*-Nitrosamines such as *N*-nitrosodiethylamine are frequently produced during rubber processing and may be present as contaminants in the final rubber product. *N*-Nitrosodiethylamine has also been detected in tobacco smoke condensate at concentrations of 1.0 to 28 ng/cigarette. Up to 8.3 ng/cigarette were found in mainstream smoke and 8 to 73 ng/cigarette were found in side stream smoke. An analysis of indoor air polluted with tobacco smoke indicated levels of up to 0.2 ng/L of *N*-nitrosodiethylamine (Brunnemann *et al.*, 1977). The compound has been found in high-nitrate well water for drinking at concentrations of 0.010 µg/L and in deionized water at 0.33 to 0.83 µg/L. Wastewater from two chemical plants contained 0.07 and 0.24 µg/L (IARC 1978).

Chronic Health Effects and Hazard identification

N-Nitrosodiethylamine is on the Hazardous Substance List because it is cited by NTP, DEP, IARC, HHAG and EPA. The Potential symptoms are Irritation of eyes, skin, respiratory tract and liver damage. This compound affects the different organs in animals such as Liver, bladder, kidney, esophagus, brain, nasal sinuses, stomach, and lungs.

The following chronic (long-term) health effects can occur at some time after exposure to N-Nitrosodiethylamine and can last for months or years: (i) N-Nitrosodiethylamine is a probable carcinogen in humans. There is some evidence that it causes liver, nose and lung cancer in humans. Further, scientists believe there is no safe level of exposure to a carcinogen. (ii) N-Nitrosodiethylamine has caused cancer in the offspring of animals exposed during pregnancy. N-Nitrosodiethylamine may damage the developing fetus. The acute chronic hazardous effect is that, when heated to decomposition this compound emits toxic fumes of nitrogen oxides (NTP, 1992).

Reactivity Profile of DENA

N-Nitrosodiethylamine reacts with strong oxidizing agents. Incompatible with reducing agents and can be hydrolyzed by hydrogen bromide in acetic acid (NTP, 1992).

Human/ Animal Carcinogenicity Data

It is well known that N-Nitroso compounds act as strong carcinogens in various mammals including primates (Leoppky and Li, 1991). Human exposure to nitrosamines results from contact with mixtures containing these compounds (e.g., cutting oils, tobacco products). Because of potential confounding by the other substances in these mixtures, data from human exposure is of limited use in the evaluation of carcinogenicity of individual nitrosamines. Further, no adequate human studies of the relationship between exposure to *N*-nitrosodiethylamine and human cancer have been reported (IARC 1978, HSDB, 2002).

There is a large database on the carcinogenicity of nitrosamines, most of which pertains to structure-activity relationships rather than to dose- response. Diethylnitrosamine administered by gavage, in drinking water, or

by feeding produces liver tumors in the following species: rat, mice, hamster, guinea pig, rabbit, dog, and monkey (Druckrey *et al*., 1963, 1967; Rajewsky *et al*., 1966; Yamamoto *et al*., 1972; Tomatis, 1973; Magee *et al*., 1976).

Tracheal and lung tumors have been observed in Syrian golden hamsters upon administration of diethylnitrosamine by gavage or inhalation (Magee *et al.,* 1976). Diethylnitrosamine administered to pregnant mice, rats, and hamsters has been shown to act transplacentally, inducing tumors in the progeny (Mohr, 1966; Tomatis, 1973; Druckrey, 1973a, b). Dose-related increases in incidence of upper GI tumors and liver cell tumors were observed in C57-BO mice, and tracheal and liver cell tumors were observed in Syrian hamsters (Peto *et al*., 1984).

Diethylnitrosamine is mutagenic for *S. typhimurium*, *E. coli*, and *Neurospora crassa*, and produced mitotic recombination in S. cerevisiae, recessive lethal mutations in *D. melanogaster*, and chromosomal aberrations in mammalian cells. Positive responses in bacterial cells are dependent upon the addition of a mammalian metabolic system (Montesano and Bartsch, 1976). Diethylnitrosamine is structurally related to known carcinogens. Lee *et al*., 1989 demonstrate the Inhibition of N-Nitrosodiethylamine Carcinogenesis in Mice by Naturally Occurring Organosulfur Compounds and Monoterpenes'. These results provide evidence for an increasing diversity of naturally occurring compounds having the capacity to inhibit nitrosoamine carcinogenesis (Wattenberg, 1985). The impact of such inhibitory effects on environmental exposure of human populations to this class of carcinogens could be of importance, but clear evidence for such inhibitory effects remains to be demonstrated.

Environmental and Drinking water impact

DENA may also form in the environment from the reaction of nitrite with Rhodamine B and Rhodamine WT tracer dyes. Because of its low estimated Koc (adsorption coefficient) value of 43, DENA is expected to be moderately to highly mobile in soil. Volatilization from soil surfaces will be rapid while volatilization of DENA incorporated into the soil will be slower but may nevertheless be significant. The half-life for N-Nitrosodiethylamine (DENA) was found to be about 1-2 hours in a Teflon outdoor smog chamber irradiated with sunlight. The primary fate mechanism for DENA in water may be photolysis

In water, DENA is not expected to partition to sediments, suspended organic matter or biota. Volatilization from water is probably not significant. Hydrolysis is probably not a significant removal process. Estimated atmospheric residence time for DENA is < 0.3 days with photolysis probably the primary removal mechanism. DENA has been found in the air at dye, rubber and foundry industries. DENA has also been found in Philadelphia drinking water, in the passenger area of new cars, in cigarette smoke, and in cheese, bacon, beer and fish. Thus, the general population may be exposed to DENA from riding in new cars, breathing cigarette smoke, drinking beer, or eating certain foods such as cheese, bacon, and fish.

Philadelphia tap water contained <0.1-0.7 ng/l N-nitrosodiethylamine. EFFL: Chemical plant effluent released to a river contained 132 ng N-nitrosodiethylamine/l. In human esophageal

mucosa, the de-ethylation of N-nitrosodiethylamine to form acetaldehyde appears to be catalyzed by the cytochrome P450, CYP2A6, but not by CYP2E1. It is also catalyzed by human CYP2A13.

Single doses of N-nitrosodiethylamine in rodents have been used to initiate liver cancer for research on tumor promoters. Researchers may be subject to inhalational exposure to this chemical in animal rooms where animals injected with it are kept. N-Nitrosodiethylamine constituted 5% of all airborne nitrosamines found in one study of the vulcanized rubber industry.

N-Nitrosodiethylamine (DENA) released to water is expected to stay in solution and not partition to organic matter (Koc= 43). The estimated Henry's Law constant for DENA is 1.1X10-8 atm-cu m/mol; therefore, volatilization from water will probably not be significant. Photolysis may be the most significant removal process for DENA since 89% degradation occurs in 7 hours with sunlight. Incubation studies for 108 days in lake water at 30°C in the dark indicate that hydrolysis and bio-concentration are not significant processes.

Mechanism for DENA-induced oxidative damage and carcinogenesis

ROS and Oxidative stress

Oxidative stress has recently been suggested to participate in both the metabolism (activation and detoxification) and the carcinogenic actions of nitrosamines, including DENA (Bartsch *et al*., 1989; Loeppky and Li, 1991). There are experimental, clinical and epidemiological reports that oxygen free radicals and related lipid peroxides play a key role in the pathogenesis of age-related chronic degenerative diseases and etiology of cancer (Marklund and Marklund, 1974; Ray *et al*., 2000).

N-nitrosodiethylamine (DENA) has been suggested to enhanced free radicals, disturbing the ROS status and ultimately leading to oxidative stress and carcinogenesis (Ames *et al*., 1993; Gey, 1993; Noguchi *et al*., 2000). It is metabolized to its active ethyl radical ($CH_3CH_2^+$) metabolite by cytochrome and the reactive product interacts with DNA causing mutation and further which would lead to carcinogenesis (Anis *et al*., 2001).

Szatrowski and Nathan (1991) suggested that tumor cells produce substantial amount of hydrogen peroxide and reactive oxygen metabolites that are released into the circulation. Therefore, the increased susceptibility of plasma and red blood cells of DENA-administered rats could be due to the production of ROS during the metabolism of DENA or during the process of carcinogenesis.

It is widely accepted that DENA undergoes metabolic activation by cytochrome P450 enzyme to reactive electrophiles that are cytotoxic, mutagenic and carcinogenic. Because of its relatively simple metabolic pathway and potent carcinogenic activity, DENA has found widespread use as an experimental model in the field of carcinogenesis and in chemoprevention. A single administration of DENA induced liver tumor is evidenced by the increase in liver weight increased level of hepatic enzyme like SGPT, SGOT, ALP, total bilirubin and decrease in total proteins and increased levels of GGPT, GPX, GST and LPO (oxidant enzymes), decrease in SOD and catalase (free radical scavengers) and morphological changes

noted by histopathological studies (Surender *et al*., 2011).

Herrold and Dunham, (1963) experiment suggests three possible mechanisms for the carcinogenic effect of DENA on the respiratory system, liver, and ethmoturbinals. These indude: (a) a local action of DENA; (b) that the DENA or a metabolite present in the circulating blood is selectively deposited in various tissues where it is metabolized to a carcinogen; or (c) that a carcinogenic metabolite is excreted via the respiratory system.

The work of Druckrey and his colleagues (1961 and 1962) has been considered as supporting a theory that the dialkylnitnosamines are carcinogenic by virtue of their metabolic conversion to active alkylating agents, diazoalkanes. The theory proposed that a specific "dealkylizing" enzyme is not required for each tissue and that enzymatic oxidation in the alpha carbon atom is sufficient, with the result that the alkyl residue is quickly split off because the oxidation products are chemically unstable, and the diazoalkanes are formed (Druckret and Preussmann, 1962).

An estimation of lipid peroxidation products and antioxidants has accepted them as significant biomarkers of cancer chemoprevention (Hayes and Pulford, 1995). Decreased activities of GPx, SOD and CAT in DENA-treated rats could be due to overutilization of these non-enzymatic and enzymatic antioxidants to scavenge the products of lipid peroxidation. Tumor cells have been reported to sequester essential antioxidants from the circulation, in order to meet the demands of the growing tumor (Buzby *et al*., 1980; Corrocher *et al*., 1986).

Effect of DENA on Soft Tissues and their Prevention

DENA is one of the most well-known liver, lungs and kidney carcinogens. Tumors of the liver, kidneys, and lungs have been induced in rats by the feeding diethylnitrosamine (Magee and Barnes, 1956; Zak *et al*., 1960; Argus and HochLigeti, 1961; Magee and Barnes, 1962).

N-Nitrosodiethylamine is a powerful and potent hepatocarcinogenic dialkyl nitrosamine that has been used as an initiating agent in some 2 stage (initiation and promotion) protocols for hepatocarcinogenic studies. It is metabolized to reactive electrophilic reactants that alter the structure of DNA and forms alkyl DNA adducts (Yoshiji *et al*., 1991). Sundaresan, and Subramanian (2003) showed that administration of s-allylcysteine could prevent DENA-induced hepatocarcinogenesis in rats. It has been reported that DENA is metabolized to alkylating reactants, which could interact with DNA molecule and initiate carcinogenesis (Anis *et al*., 2001).

Shaarawy *et al*, (2009) reported the protective effects of garlic and silymarin on DENA-induced rats hepatotoxicity. In this study, they demonstrated that the injection of DENA to rats lead to a marked elevation in the levels of serum AST, ALT and ALP which is indicative of hepatocellular damage, as previously reported (Bansal *et al*., 2005).

Melatonin Modulates the oxidant–antioxidant Imbalance during N-Nitrosodiethylamine Induced hepatocarcinogenesis in rats was reported by Dakshayani *et al*. (2005). Chodon *et al*., (2008) find out the effect of Genistein on modulating lipid peroxidation and membrane-bound enzymes in N-Nitrosodithylamine induced and Phenobarbital- promoted rat liver carcinogenesis.

Hydro-ethanolic extract of *E. neriifolia* leaves have been observed to possess chemopreventive effect against DENA-induced renal carcinogenesis in mice (Janmeda *et al*., 2011). We have also reported the chemoprotective activity of hydro-ethanolic extract of *euphorbia neriifolia* Linn. leaves against DENA-induced liver carcinogenesis in mice (Pracheta *et al*., 2011). EN extract restored SOD and CAT enzyme levels in the liver and kidney.

Zak et al. (1960) demonstrated that DENA produced lesions in the kidney, as well as tumors of the trachea and bronchus. They believe that the kidney lesions may represent an early stage in tumor development. This can be supported by Magee and Barnes (1962). Dontenwill *et al*. (1961; 1962) reported that squamous-cell carcinoma of the trachea and lung of Syrian hamsters followed administration of DENA by each of three approaches-tube feeding, inhalation, and subcutaneous injection.

In lungs, administration of DENA resulted in chronic interstitial pneumonia along with infiltration of leukocytes. Under hypercholesterolemic conditions, liver showed vacuolar degeneration and swelling of hepatocytes but more severe changes were seen upon DENA administration, such as accumulation of lipid droplets in hepatocyte, granular degeneration along with infiltration of fibroblasts indicating chronic change. In spleen, there was a depletion of lymphocytes from lymphoid follicles under hypercholesterolemic conditions. Administration of DENA, however, also resulted in congestion and hemorrhage in spleen along with severe depletion of lymphoid cells. Kidneys showed mild congestion under hypercholesterolemic conditions but DENA administration caused severe granular degeneration and coagulative necrosis in kidneys (Mittal *et al*., 2006).

Chemoprevention

Chemoprevention is a major area that has been intensively investigated in recent years. A large number of agents including natural and synthetic compounds have been shown to possess chemopreventive value. This warrants the exploration and evaluation of effective anticancer drugs which could be easily available. Chemopreventive agents can be divided into two groups: antimutagenic and antiproliferative: Antimutagens reduce the formation of carcinogens or mutagens there by preventing DNA damage through suppression of phase I enzymes or enhancement of Phase II detoxifying enzymes and alternatively chemopreventive agents may exert antiproliferative effects via induction of cell cycle arrest or apoptosis, inhibition of terminal differentiation and inhibition of oncogene activity or DNA synthesis (Wu *et al*. 2001; Wu, Kassie and Mersch– Sundermann 2004). The search for new chemopreventive and antitumor agents that are more effective and less toxic than existing agents has kindled great interest in phytochemicals.

Synthetic or Natural Approach

In the recent times focus on plant research has increased all over the world and a large body of evidence has collected to show immense potential of medicinal plants used in various traditional systems (Modzelewska *et al*., 2005). One of the oldest, most effective strategies for developing new chemotherapeutics is the

isolation and evaluation of chemicals of natural origin. The importance of natural products for drug discovery has been impressive. Chemoprevention involving the use of natural products to inhibit or reverse the carcinogenic process is an effective approach to control cancer.

Acknowledgement

The authors are thankful to the authorities of Banasthali University for providing support to the study.

References

Aiub, C.A., Pinto, L.F. and Felzenszwalb, I., 2003. N-Nitrosodiethylamine mutagenicity at low concentrations. *Toxicol Lett,* 145:36-45.

Anis, K.V., kumar R.N.V. and Kuttan, R., 2001. Inhibition of chemical carcinogenesis by

Argus, M.F. and Hoch-Ligeti, C., 1961. Comparative Study of the Carcinogenic Activity of Nitrosamines. *Journal of NatI. Cancer Institute,* 27:695-709.

Bansal, A.K., Bansal, M., Soni, G. and Bhatnagar, D., 2005. Modulation of NDEA induced oxidative stress by vitamin E in rat erythrocytes. *Hum Exp Toxicol,* 24:297−302.

Bansal, A.K., Trivedi, R., Soni, G.L. and Bhatnagar, D., 2000. Hepatic and renal oxidative stress in acute toxicity of N-nitrosodiethylamine in rats. *Indian Journal of Experimental Biology*, 38:916–920.

Bartsch, H. and Montesano, R., 1984. Relevance of nitrosamines to human cancer. *Carcinogenesis,* 5:1381–1393.

Bartsch, H., Hietanen, E. and Malaveille, C., 1989. Carcinogenic nitrosamines: free radical aspects of their action. *Free Radic Med Biol*, 7:637–644.

Brunnemann, K.D., Yu, L. and Hoffmann, D., 1977. Assessment of carcinogenic volatile *N*-nitrosamines in tobacco and in mainstream and sidestream smoke from cigarettes. *Cancer Research,* 37(9): 3218-22.

Buzby, G.P., Mullen, J.H., Stein, T.P. and Roasto, E.F., 1980. Host tumor interactions and nutrient supply. *Cancer,* 45:2940–2947.

Chodon, D., Arumugam, A., Rajasekaran, D. and Dhanapal, S., 2008. Effect of Genistein on modulating lipid peroxidation and membrane- bound enzymes in N-Nitrosodithylamine induced and Phenobarbital- promoted rat liver carcinogenesis. *Journal of Health Science,* 54(2):137-142.

Corrocher, R., Casani, M., Bellisola, G.B., Nicoli, N., Guidi, G.C. and Sandre, G., 1986. Severe impairment of antioxidants system in human hepatoma. *Cancer,* 58:1658–1662.

Dakshayani, K.B., Subramanian, P., Manivasagam, T., Essa, M and Manoharan, S., 2005. Melatonin Modulates The Oxidant– Antioxidant Imbalance During N-Nitrosodiethylamine Induced Hepatocarcinogenesis In Rats. J *Pharm Pharmaceut Sci.,* 8(2):316-321.

Dontenwill, W. and Mohr, U., 1961. Carcinome des Respirationstractus nach Behandlung von Goldhamstern mit Diathylmtrosamin. *Z. Krebsforsch*., 64:305-12.

Dontenwill, W., Mohr U. and Zagel, M., 1962. Uber die unterschiedliche Lungen-carcinogene Wirkung des Diathylnitrosamin bei Hamster und Ratte. *Z. Krebsforsch*, 64:499-502.

Druckrey, H, Preussmann, R., Ivankovic S., and Schmaehl. D., 1967. Organotropism and carcinogenic effects of 65 different N-nitroso compounds in BD-rats. *Z. Kerbsforsch,* 69(2):103-201.

Druckrey, H. 1973b. Specific carcinogenic and teratogenic effects of "indirect" alkylating methyl and ethyl compounds, and their dependency on stages of oncogenic development. *Xenobiotica,* 3:271.

Druckrey, H. and Schmahl, D., 1962. Quantitative Analyse der experimentellen Krebserzeugung. *Naturwissenschaften,* 49:217-2189.

Druckrey, H., 1973a. Chemical structure and action in transplacental carcinogenesis and teratogenesis. IARC Sci. Publ., Lyon, France. No. 4. p. 45-58.

Druckrey, H., Preussmann, R., Schmahl, D. and Muller, M, 1961. Chemische Konstitution und carcinogene Wir hung bei Nitrosaminen. *Naturwissensehaften*, 48:134-35.

Druckrey, H., Schildbach, D., Schmahl, D., Preussmann, R. and Ivankovic S., 1963. Quantitative analyse der carcinogen Wirking von Diathylnitrosamin. Arzneimittel-*Forsch.* 13:841-851.

Gey, K.F., Prospects for the prevention of free radical disease, regarding cancer and cardiovascular disease. *Br Med Bull*, 49:679-99.

Hayes, J.D. and Pulford, D.J., 1995. The GST supergene family: regulation of GST and the contribution of isoenzymes to cancer chemoprevention and resistance. *Crit. Rev. Biochem. Mol. Biol.,* 30:445–600.

HSDB., 2002. Hazardous Substances Database. National Library of Medicine. http://toxnet.nlm.nih.gov/cgibin/sis/htmlgen?HSDB.

IARC. 1987. Overall Evaluations of Carcinogenicity. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Supplement 7. Lyon, France: *International Agency for Research on Cancer*. 440 pp.

IARC., 1972. Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, *N*-Nitroso Compounds and Natural Products. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 1. Lyon, France: *International Agency for Research on Cancer*. pp. 184

IARC, 1978. Some *N*-Nitroso Compounds. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 17. Lyon, France: *International Agency for Research on Cancer*. pp. 365

IARC, 1982. Chemicals, Industrial Processes and Industries Associated with Cancer

in Humans. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, Supplement 4. Lyon, France: *International Agency for Research on Cancer*. pp. 292 .

Janmeda, P., Sharma, V., Singh, L.K., Paliwal, R., Sharma, S., Yadav, S. and Sharma, S.H., 2011. Chemopreventive effect of hydro-ethanolic extract of *Euphorbia neriifolia* Leaves against DENA-induced renal carcinogenesis in mice. *Asian Pacific Journal of Cancer Prevention*, 12(3):1-6.

Kaplan, S., Novikov, I. and Modan, B., 1997. Nutritional factors in the etiology of brain tumors: potential role of nitrosamines, fat, and cholesterol. *Am J Epidemiol.*, 146:832-841.

Kumar, R.N.V. and Kuttan R., 2000. Inhibition of NNitrosodiethylamine induced hepatocarcinogenesis by picroliv. *J. Exp. Clin. Cancer Res*., 19:459–465.

Lee, W., Velia, L., Sparnins, and Barany, G., 1989. Inhibition of N-Nitrosodiethylamine Carcinogenesis in Mice by Naturally Occurring Organosulfur Compounds and Monoterpenes'. *Cancer Research,* 49:2689-2692.

Leoppky, R.N., and Li, Y.E., 1991. Nitrosamine activation and detoxification through free radicals and their derived cations. In: Relevance to Human Cancer of Nitroso Compounds, Tobacco and Mycotoxins. Eds. Neill I.K.O., *Chem J., Bartsch H.,* LARC Scientific Publication. No. 105, Lyan, 375–382.

Liao, D.J., Blanck, A. and Eneroth, P., 2001. Diethylnitrosamine causes pituitary damage, disturbs hormone levels, and reduces sexual dimorphism of certain liver functions in the rat. *Environ Health Perspect,* 109:943-7.

Loeppky, R.N. and Li, Y.H., 1991. *Nitrosamine activation and detoxication through free radicals and their derived cations.* In: 1. K. O'Neill, J. Chen, and H. Bartsch (eds.), Relevanceto HumanCancerof N-NitrosoCompounds,Tobaccoand Mycotoxins, IARC Scientific Publications No. 105, pp. 375-382.Lyon: IARC, 1991.

Magee, P.N. and Barnes, J.M., 1956. The Production of Malignant Primary Hepatic Tumours in the Rat by Feeding Dimethylnitrosamine. *British Journal of Cancer,* 10:114-22.

Magee, P.N. and Hultin, T., 1962. Toxic Liver Injury and Carcinogenesis. Methylation of Proteins of Rat-Liver Slices by Dimethylnitrosamine in vitro. *Biochem. J*., 83:106-14.

Magee, P.N., Montesano R. and Preussman, R., 1976. N-Nitroso compounds and related carcinogens. *ACS Monograph*, 173:491-625.

Marklund, S. and Marklund, G., 1974. Involvement of the superoxide anion radical in the auto-oxidation of pyrogallol and a convenient assay for superoxide dismutase. *Eur J Biochem.,* 47: 469−474.

Maxwell, S.R., 2000. Coronary artery disease-free radical damage, antioxidant protection and the role of homocysteine. *Basic Res Cardiol.,* 95(1):165-171.

Modzelewska, A., Sur, S., Kumar, S.K. and Khan, S.R., 2005. Sesquiterpenes: natural products that decrease cancer growth. *Curr. Med. Chem. Anticancer Agents*, 5: 477.

Mohr, U., Althoff J., and Authaler, A., 1966. Diaplacental effect of the carcinogen diethylnitrosamine in the golden hamster. *Cancer Research,* 26:2349-2352.

Montesano, R. and Bartsch, H., 1976. Mutagenic and carcinogenic N-Nitroso compounds: Possible environmental Hazards. *Mutat. Res.* 32: 179-228.

Noguchi, N., Watanabe, A. and Shi, H., 2000. Diverse functions of antioxidants. *Free Radical Research,* 33: 809−817.

Ohkawa, H., Ohishi, N. and Yagi, K., 1979. Assay for lipid peroxides in animal tissues by thiobarbituric reaction. *Anal Biochem.,* 95:351−358.

Ohsawa, K., Nakagawa, S.Y., Kimura, M., Shimada, C., Tsuda, S., Kabasawa, K., Kawaguchi, S. and Sasaki, Y.F., 2003. Detection of *in vivo* genotoxicity of endogenously formed N-nitroso compounds and suppression by ascorbic acid, teas and fruit juices. *Mutat Res.,* 539:65-76.

Peto, R., Gray, R., Brantom P., and Grasso, P., 1984. Nitrosamine carcinogenesis in 5120 rodents: Chronic administration of sixteen different concentrations of NDEA, NDMA, NPYR and NPIP in the water of 4440 inbread rats, with parallel studies on NDEA alone of the effect of age starting (3, 6 or 20 weeks) and of species (rats, mice, hamsters). IARC Sci. Publ., Lyon, France, 57:627-665.

Pracheta, Sharma, V., Paliwal, R., Sharma, S., Singh, L.K., Janmeda, B.S., Savita, Yadav, S. and Sharma, S.H., 2011. Chemo-protective activity of hydro-ethanolic extract of *Euphorbia neriifolia* Linn. leaves against DENA-induced liver carcinogenesis in mice. *Biology and Medicine*, 3(2):36-44.

Preussmann, R., 1984. *Occurrence and exposure to N-nitroso compounds and precursors*. In: I. K. O'Neill, R. C. von Borstel,C. T. Miller,J. Long, and H. Bartsch(ads.), N-Nitroso Compounds: Occurrence, Biological Effects and Relevance to Human Cancer, IARC Scientific Publications No. 57, pp. 3-15. Lyon: IARC.

Rajewsky, M.F., Dauber W. and Frankenberg, H., 1966. Liver carcinogenesis by diethylnitrosamine in the rat. *Science,* 152:83-85.

Ray, G., Batra, S., Shkula, N.K., Deo, S., Raina, V., Asok, S. and Husain, S.A., 2000. Lipid peroxidation, free radicals production and antioxidant status in breast cancer. *Breast Cancer Res. Treat.,* 59:163–170.

Sunderasen, S. and Subramanian, P., 2003a. S-allyl cysteine inhibits circulatory lipid peroxidation and promotes antioxidants in Nnitrosodiethylamine induced carcinogenesis. *Pol. J. Pharmacol.* 55:37-42.

Szatrowski, T.P. and Nathan, C.F., 1991. Production of large amounts of hydrogen peroxide by human tumor cells. *Cancer Research,* 51:794–798.

Tomatis, L., (ed.) 1973. Transplacental carcinogenesis. In: Modern Trends in Oncology, Part I, R.W. Raven, Butterworths, London.

Tricker, A.R., Pfundstein, B., Theobald, E., Preussmann, R. and Spiegelhalder, B., 1991. Mean daily intake of volatile Nnitrosamines from food and beverages in West Germany in 1989–90. *Food Chem Toxicol.,* 29:729-732.

Wattenberg, L.W., 1985. Chemoprevention of cancer. *Cancer Research,* 45:1-8.

Wu, C.C., Sheen, L.Y., Chen, H.W., 2001. Effects of organosulfur compounds from garlic oil on the antioxidant system in rat liver and red blood cells. *Food and Chem. Toxicol.,* 39:563-569.

Wu, X., Kassie, F. and Mersch–Sundermann, V., 2004. Induction of apoptosis in tumor cells by naturally occurring sulfur containing compounds. *Mutation Res.* 589:81-102.

Yamamoto, R.S., Kroes R. and Weisburger, J.H., 1972. Carcinogenicity of diethylnitrosamine in Mystromys albicaudatus (African white-tailed rat). (36573). *Proc. Soc. Exp. Biol. Med.*, 140: 890.

Yoshiji, H., Nakae, D., Kinugasa, T., Matsuzaki, M., Denda, A., Tsujii, T. and Konishi, Y., 1991. Inhibitory effect of dietary iron deficiency on the induction of putative preneoplastic foci in rat liver initiated with diethyl-nitrosamine and promoted by phenobarbital. *British Journal of Cancer*, 64:839.

Zak, F.G., Holzner, J.H., Singer, E.J. and Popper, H., 1960. Renal and Pulmonary Tumors in Rats Fed Dimethylnitrosamine. *Cancer Research,* 20:96-99.