Cancer Association of South Africa (CANSA)

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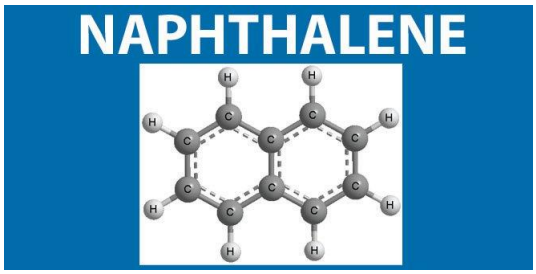
Fact Sheet
on
Naphthalene

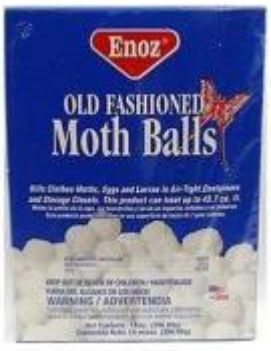
Introduction

Naphthalene is made from crude oil or coal tar. It is also produced when various things burn, so naphthalene is found in cigarette smoke, car exhaust, and smoke from forest fires. It is used as an insecticide and pest repellent. Naphthalene was first registered as a pesticide in the United States in 1948. Mothballs and other products containing naphthalene are solids that turn into toxic gas. The toxic gas kills insects and may repel animals.



[Picture Credit: Naphthalene]

[Picture Credit: Moth Balls]



IARC Classification of Naphthalene

Naphthalene is classified as a Group 2B substance by the International Agency for Research on Cancer (IARC). This means that this agent is possibly carcinogenic (cancer causing) to humans. This category is used for agents, mixtures and exposure circumstances for which there is limited evidence of carcinogenicity in humans but there is sufficient evidence of carcinogenicity in experimental animals. In some instances, an agent, mixture or exposure for which there is inadequate evidence of carcinogenicity in humans but limited evidence of carcinogenicity in experimental animals together with supporting evidence from other relevant data may be placed in this group.

Buchholz, B.A., Carratt, S.A., Kuhn, E.A., Collette, N.M., Ding, X. & Van Winkle, L.S. 2019.
"Naphthalene (NA) is a respiratory toxicant and possible human carcinogen. NA is a ubiquitous combustion product and significant component of jet fuel. The National Toxicology Program found that NA forms tumors in two species, in rats (nose) and mice (lung). However, it has been argued that NA does not pose a cancer risk to humans because NA is bioactivated by cytochrome P450 monooxygenase enzymes that have very high efficiency in the lung tissue of rodents but low efficiency in the lung tissue of humans. It is thought that NA carcinogenesis in rodents is related to repeated cycles of lung epithelial injury and repair, an indirect mechanism. Repeated *in*

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vivo exposure to NA leads to development of tolerance, with the emergence of cells more resistant to NA insult. We tested the hypothesis that tolerance involves reduced susceptibility to the formation of NA-DNA adducts. NA-DNA adduct formation in tolerant mice was examined in individual, metabolically-active mouse airways exposed *ex vivo* to 250 µM ^{14}C-NA. *Ex vivo* dosing was used since it had been done previously and the act of creating a radioactive aerosol of a potential carcinogen posed too many safety and regulatory obstacles. Following extensive rinsing to remove unbound ^{14}C-NA, DNA was extracted and ^{14}C-NA-DNA adducts were quantified by AMS. The tolerant mice appeared to have slightly lower NA-DNA adduct levels than non-tolerant controls, but intra-group variations were large and the difference was statistically insignificant. It appears the tolerance may be more related to other mechanisms, such as NA-protein interactions in the airway, than DNA-adduct formation."

Bailey, L.A., Nascarella, M.A., Kerper, L.E. & Rhomberg, L.R. 2016.
"Inhalation of naphthalene causes olfactory epithelial nasal tumors in rats (but not in mice) and benign lung adenomas in mice (but not in rats). The limited available human data have not identified an association between naphthalene exposure and increased respiratory cancer risk. Assessing naphthalene's carcinogenicity in humans, therefore, depends entirely on experimental evidence from rodents. We evaluated the respiratory carcinogenicity of naphthalene in rodents, and its potential relevance to humans, using our Hypothesis-Based Weight-of-Evidence (HBWoE) approach. We systematically and comparatively reviewed data relevant to key elements in the hypothesized modes of action (MoA) to determine which is best supported by the available data, allowing all of the data from each realm of investigation to inform interpretation of one another. Our analysis supports a mechanism that involves initial metabolism of naphthalene to the epoxide, followed by GSH depletion, cytotoxicity, chronic inflammation, regenerative hyperplasia, and tumor formation, with possible weak genotoxicity from downstream metabolites occurring only at high cytotoxic doses, strongly supporting a non-mutagenic threshold MoA in the rat nose. We also conducted a dose-response analysis, based on the likely MoA, which suggests that the rat nasal MoA is not relevant in human respiratory tissues at typical environmental exposures. Our analysis illustrates how a thorough WoE evaluation can be used to support a MoA, even when a mechanism of action cannot be fully elucidated. A non-mutagenic threshold MoA for naphthalene-induced rat nasal tumors should be considered as a basis to determine human relevance and to guide regulatory and risk-management decisions."

Naphthalene
Naphthalene is a white crystalline, volatile solid with an odour of mothballs. It sublimes (transition of a substance directly from the solid to the gas phase) at room temperature. Naphthalene is insoluble in water and is soluble in benzene, absolute alcohol, ether, carbon tetrachloride, carbon disulphide, hydronaphthalenes, and in fixed and volatile oils.

Naphthalene is produced from petroleum refining and coal tar distillation. It is used as a chemical intermediate in the production of phthalic anhydride, naphthol, and chlorinated naphthalenes. It is also used in smokeless powder, cutting fluids, lubricants, antiseptics, synthetic resins, tanning products, preservatives, textile chemicals, emulsion breakers, and scintillation counters. It is also found in combustion processes including refuse combustion, tobacco smoke, coal tar pitch fumes, and oil spills.

The primary stationary sources that have reported emissions of naphthalene are paper mills, manufacturers of miscellaneous wood products, and electrical services. Naphthalene has also been detected, but not quantified, in motor vehicle exhaust by the Air Resources Board (ARB).

It is also known as:

- Tar Camphor
- White Tar
- Moth Flakes

Its main hazards include:

- It is flammable
- Its dust can form an explosive mixtures with air
- It is a sensitiser
- It is a possible carcinogen

Weiss T, Breuer D, Bury D, Friedrich C, Werner S, Aziz M, Hummel T, Raulf M, Zschiesche W, Sucker K, Pallapies D, Bünger J, Brüning T. 2020.
"Exposure to the bicyclic aromatic hydrocarbon naphthalene occurs in most cases along with other polycyclic aromatic hydrocarbons. Here we report from an investigation of 63 healthy, non-smoking male employees in the abrasives industry where naphthalene is the only relevant chemical exposure. Exposure assessment was performed using a combination of Air and Biological Monitoring over nearly a whole working week (Mo.-Th.). Air measurements were carried out during the shift on Thursday with the GGP mini-sampling system, combining particle and vapour sampling at low flow rates. In urine spot samples, the metabolites 1- and 2-naphthol were measured Mo.-Th. pre- and post-shift (for the reference group only Mo. pre- and Th. post-shift). With regard to naphthalene concentrations measured in air and concentrations of its metabolites (1- and 2-naphthol) in urine, study participants could be divided into a high and a low exposure group, and a reference group. The naphthalene concentration in air was in the range of 0.1-11.6 mg m-3, and naphthol concentrations (sum of 1- and 2-naphthol) in post-shift urine were in the range of <1 to 10 127 µg l-1. Naphthalene concentrations in air and naphthol concentrations in urine were closely correlated, indicating mainly airborne exposure at the investigated workplaces. As expected from toxicokinetic data, internal body burden increased slightly during a working week and did not completely decline over a work-free weekend to background concentrations observed in occupationally not exposed persons. Taking into account the observed increase in pre- and post-shift values during the working week, urine sampling for Biological Monitoring at workplaces should be carried out after several preceding shifts. Our data allow the derivation of biological limit values for the sum of 1- and 2-naphthol in urine corresponding to occupational exposure limits for naphthalene in air."

Uses of Naphthalene

- Naphthalene's most familiar use is as a household fumigant, such as in mothballs. In a sealed container of naphthalene pellets, naphthalene vapours build up to levels toxic to both the adult and larval forms of many moths that are destructive to textiles. Other fumigant uses of naphthalene include use in soil as a fumigant pesticide, and in attic spaces to repel animals.
- In the past, naphthalene was administered orally to kill parasitic worms in livestock.
- Larger volumes of naphthalene are used as a chemical intermediate to produce other chemicals. The single largest use of naphthalene is the industrial production of phthalic anhydride, although

more phthalic anhydride is made from o-xylene than from naphthalene. Other naphthalene-derived chemicals include alkyl naphthalene sulfonate surfactants, and the insecticide carbaryl.

- Naphthalenes substituted with combinations of strongly electron-donating functional groups, such as alcohols and amines, and strongly electron-withdrawing groups, especially sulfonic acids, are intermediates in the preparation of many synthetic dyes.
- The hydrogenated naphthalenes tetrahydronaphthalene (Tetralin) and decahydronaph-thalene (Decalin) are used as low-volatility solvents.
- Naphthalene vapour can also slow the onset of rust, and, thus, sometimes moth balls are used in places like tool boxes.
- Naphthalene is used to make products like moth balls that repel and keep moths away.
- Naphthalene is also used in the manufacturing of certain leather goods.
- Naphthalene (mothballs) is also used as a deodorant air freshener, especially in male urinals.
- It could not be determined whether the following is an urban legend or not. There appears to be evidence that before World War II naphthalene was used as a fuel. Race drivers used it to boost octane by adding 1 moth ball to every 5 litres of fuel. Today, many people are apparently still using it to get better mileage out of gasoline and diesel engines. It is said that engine performance is improved and fuel economy is much better if one add 1 naphthalene moth ball to 20 litres of gasoline or diesel fuel.

Health Hazards of Naphthalene

Acute Effects:

- Acute exposure of humans to naphthalene by inhalation, ingestion, and dermal contact is associated with haemolytic anaemia, damage to the liver, and, in infants, neurological damage. Symptoms of acute exposure include headache, nausea, vomiting, diarrhoea, malaise, confusion, anaemia, jaundice, convulsions, and coma.
- Cataracts have been reported in humans acutely exposed to naphthalene by inhalation and ingestion. Cataracts have also been reported in animals following acute oral exposure.
- Tests involving acute exposure of rats, mice, rabbits, and guinea pigs have demonstrated naphthalene to have moderate to high acute toxicity from ingestion and low to moderate acute toxicity from dermal exposure.

[Picture Credit: Mothballs 1]

Chronic Effects (Non-cancer):

- Chronic exposure of workers to naphthalene has been reported to cause cataracts and retinal haemorrhage.
- Chronic inflammation of the lung, chronic nasal inflammation, hyperplasia of the respiratory epithelium in the nose, and metaplasia of the olfactory epithelium were reported in mice chronically exposed to naphthalene via inhalation.
- Rats, rabbits, and mice chronically exposed to naphthalene via ingestion have developed cataracts and degeneration of the retina.

- Diarrhoea, lethargy, hunched posture, rough coats, decreased body weight, and lesions in the kidneys and thymus were observed in rats and mice chronically exposed via gavage (experimentally placing the chemical in the stomach).

Reproductive/Developmental Effects:

- Haemolytic anaemia has been reported in infants born to mothers who "sniffed" and ingested naphthalene (as mothballs) during pregnancy. The mothers themselves were anaemic, but to a lesser extent than the infants.
- Signs of maternal toxicity (e.g., decreased body weight and lethargy) but no foetal effects were reported in rats and rabbits exposed to naphthalene via gavage.
- Maternal toxicity (increased mortality and reduced weight gain) and foetotoxicity (reduced number of live pups per litter) were observed in mice exposed via gavage (force-feeding a person or an animal against their will).

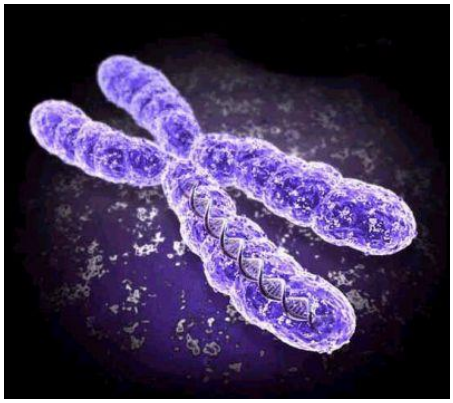
Cancer Risk:

- Workers occupationally exposed to vapours of naphthalene and coal tar may develop laryngeal carcinomas or neoplasms of the pylorus and caecum.
- Di-, tri-, and tetramethyl naphthalene contaminants of coal tar were found to be carcinogenic when applied to the skin of mice, but naphthalene alone was not.
- An increased number of alveolar/bronchiolar adenomas and carcinomas were reported in female mice exposed by inhalation.
- No carcinogenic responses were reported in rats exposed to naphthalene in their diet and by injection.
- EPA has classified naphthalene as a Group C, possible human carcinogen.

Bailey, L.A. & Rhomberg, L.R. 2020.
"Chronic inhalation of naphthalene causes nasal olfactory epithelial tumors in rats and benign lung adenomas in mice. The available human data do not establish an association between naphthalene and increased respiratory cancer risk. Therefore, cancer risk assessment of naphthalene in humans depends predominantly on experimental evidence from rodents. The United States Environmental Protection Agency's (US EPA) Toxicity Forecaster (ToxCast™) database contains data from 710 in vitro assays for naphthalene, the majority of which were conducted in human cells. Of these assays, only 18 were active for naphthalene, and all were in human liver cells. No assays were active in human bronchial epithelial cells. In our analysis, all of the active naphthalene ToxCast assay data were reviewed and used to: 1) determine naphthalene human inhalation concentrations corresponding to relevant activity concentrations for all active naphthalene assays, using a physiologically based pharmacokinetic (PBPK) model; and 2) evaluate the transcriptional responses for active assays in the context of consistency with the larger naphthalene data set and proposed modes of action (MoAs) for naphthalene toxicity and carcinogenicity. The transcriptional responses in liver cells largely reflect cellular activities related to oxidative stress and chronic inflammation. Overall, the results from our analysis of the active ToxCast assays for naphthalene are consistent with conclusions from our earlier weight-of-evidence evaluation for naphthalene carcinogenesis."

Chromosomal Aberrations Due to Naphthalene

According to a new study, children exposed to high levels of the common air pollutant naphthalene are at increased risk for chromosomal aberrations (CAs), which have been previously associated with cancer. These include chromosomal translocations, a potentially more harmful and long-lasting subtype of CAs.



[Picture Credit: Chromosomal Aberration]

Researchers from the Columbia Center for Children's Environmental Health (CCCEH) at the Mailman School of Public Health, Columbia University Medical Center, and the Centers for Disease Control and Prevention (CDC) report the new findings in *Cancer, Epidemiology, Biomarkers & Prevention*, a journal of the American Association for Cancer Research.

The researchers followed 113 children, age 5, who are part of a larger cohort study in New York City. They assessed the children's exposure to naphthalene; a CDC laboratory measured levels of its metabolites--1- and 2-naphthol--in urine samples. (Metabolites are products of the body's metabolism, and can serve as marker for the presence of a chemical.) Researchers also measured CAs in the children's white blood cells using a technique called fluorescent *in situ* hybridisation. Chromosomal aberrations were present in 30 children; of these, 11 had translocations. With every doubling of levels of 1- and 2-naphthol, translocations were 1.55 and 1.92 times more likely, respectively, to occur.

Naphthalene Poisoning

Poisoning from naphthalene destroys or changes red blood cells so they cannot carry oxygen. This can cause organ damage.

Symptoms of Naphthalene Poisoning - Stomach problems may not occur until 2 days after coming in contact with the poison. They can include:

- Abdominal pain
- Nausea and vomiting
- Diarrhoea

The person may also have a fever. Over time, the following symptoms also may occur:

- Coma
- Confusion
- Convulsions
- Drowsiness
- Headache
- Increased heart rate (tachycardia)
- Low blood pressure
- Low urine output (may stop completely)
- Pain when urinating (may be blood in the urine)

- Shortness of breath
- Yellowing of skin (jaundice)

NOTE: People with a condition called glucose-6-phosphate dehydrogenase deficiency are more vulnerable to the effects of naphthalene.

Important Facts About Naphthalene

- Naphthalene is possibly carcinogenic to humans according to Environmental Protection Agency (EPA)
- Naphthalene can damage one's health
- Naphthalene is a chemical found in moth balls and commonly used as a pesticide
- Always follow the instructions provided on the product label
- Integrated Pest Management (IPM) is a comprehensive approach to pest control that emphasizes environmental responsibility and reducing the use of chemical pesticides

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/ estate/heirs) relating to the use of any information contained in this Fact Sheet.

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