

Naphthalene

Toxicological overview

Key Points

Kinetics and metabolism

- Naphthalene is readily absorbed into the systemic circulation following inhalation, ingestion or dermal exposure
- Naphthalene is initially metabolised into a number of reactive epoxide and quinone metabolites by cytochrome P450 oxidation
- Metabolites of naphthalene are excreted in the urine as mercapturic acids, methylthio derivatives and glucuronide conjugates
- Glutathione and cysteine conjugates are excreted in the bile
- Following ingestion the urinary excretion of naphthalene metabolites is prolonged due to delayed absorption from the gastrointestinal tract

Health effects of acute exposure

- Acute exposure to naphthalene can cause adverse effects such as nausea, vomiting, abdominal pain, diarrhoea, headache, confusion, profuse sweating, fever, tachycardia, tachypnoea and agitation which may lead to convulsions and coma
- Naphthalene exposure can cause acute haemolysis, particularly in individuals with glucose 6-phosphate dehydrogenase deficiency, which is accompanied by anaemia, leukocytosis, fever, haematuria, jaundice and renal and hepatic dysfunction which can possibly be fatal
- Dermal exposure to naphthalene causes mild dermal irritation and in some sensitive individuals may cause dermatitis
- Ocular exposure to naphthalene may cause eye irritation, corneal damage, formation of lens opacities and cataracts

Health effects of chronic exposure

- Chronic exposure to naphthalene by inhalation will give rise to similar effects as observed following acute exposure
- Children are more susceptible to the haemolytic effects of naphthalene than adults
- Naphthalene is considered to be a possible human carcinogen

Toxicological Overview

Summary of Health Effects

The principal route of exposure for naphthalene is by inhalation of vapours due to its uses in industry and its release as a product of the combustion of organic materials [1]. Ingestion of naphthalene is not a common route of exposure, although it may occur in some cases.

Naphthalene is readily absorbed into the systemic circulation following either inhalation or ingestion and may result in systemic toxicity. Systemic absorption of naphthalene can also occur following dermal contact [1-3].

An acute inhalation exposure to naphthalene can cause signs and symptoms such as nausea, vomiting, abdominal pain, diarrhoea, headache, confusion, profuse sweating, fever, tachycardia, tachypnoea and agitation. In some cases this may lead to convulsions and coma [1, 3]. The most characteristic sign of naphthalene toxicity is acute intravascular haemolysis, particularly in individuals with a deficiency of glucose 6-phosphate dehydrogenase (G6-PD) which can cause anaemia, leukocytosis, fever, haematuria, jaundice and liver and kidney dysfunction [1, 3].

Ingestion of naphthalene is not a common route of exposure, however the effects observed would be similar to those seen following acute inhalation, with the likely addition of abdominal pain [1, 2].

Acute dermal exposure to naphthalene will give rise to mild irritation and in some sensitive individuals may cause dermatitis [1, 3]. Dermal exposure to sufficient amounts of naphthalene may result in dermal absorption, thus causing systemic toxicity similar to that observed following inhalation or ingestion [1]. Ocular exposure may cause eye irritation, corneal damage and can lead to the formation of lens opacities and in some cases can result in the formation of cataracts [1-3].

Chronic inhalation exposure to naphthalene may give rise to similar effects as observed following acute exposure, including nausea, headache, malaise and haemolytic anaemia and its related hepatic and renal effects. Due to the adverse health effects of acute exposure, chronic exposure to amounts sufficient to cause significant toxicity is relatively uncommon [2].

There is some limited evidence that naphthalene may cause developmental toxicity as it may cross the placenta giving rise to neonatal haemolytic anaemia [2]. However, the dose required to produce developmental toxicity is also likely to cause significant maternal toxicity [3, 4].

There is insufficient data available regarding the carcinogenicity of naphthalene in humans. The International Agency for Research on Cancer (IARC) classified naphthalene as possibly carcinogenic to humans (group 2B) based on the evidence of carcinogenicity in animals [4]. The EU system classifies naphthalene as a category 3 carcinogen, meaning that it has limited evidence of a carcinogenic effect. Naphthalene is not mutagenic in animals and the carcinogenicity is due to a non-genotoxic mechanism.

Kinetics and metabolism

Naphthalene is readily absorbed into the systemic circulation following inhalation of vapour. Dermal absorption of naphthalene may also be a significant route of systemic absorption in humans, particularly in infants. Absorption of naphthalene following ingestion is not as clearly defined as for inhalation of naphthalene vapour. However, systemic absorption following ingestion has been shown in some people to be rapid [1]. Following systemic absorption in mothers who consumed naphthalene during pregnancy, naphthalene has been shown to distribute across the human placenta in concentrations high enough to cause adverse effects, leading to haemolysis and anaemia in newborn infants [1, 2].

The metabolism of naphthalene has been extensively studied in experimental animals. The metabolism of naphthalene forms a number of reactive metabolites, which may be responsible for its toxicity, including 1,2-naphthalene oxide, 1,2-naphthoquinone and 1,4-naphthoquinone [2]. The initial stage of naphthalene metabolism is the formation of the epoxide, 1,2-naphthalene oxide by cytochrome P450 (CYP) oxidation. The epoxide is relatively unstable and can undergo spontaneous rearrangement to 1-naphthol or 2-naphthol, which can be conjugated to either glucuronides or sulphates and excreted in the urine. The 1-naphthol metabolite is the most common of the two formed and alternatively to conjugation, it may undergo further metabolism by CYP 450 into 1,4-naphthoquinone resulting in toxicity and adduct formation. Another toxic metabolite formed from 1,2-naphthalene oxide first by epoxide hydrolase and then by dihydrodiol dehydrogenase is 1,2-naphthoquinone [2]. Mercapturic acids and methylthio derivatives of naphthalene are excreted in the urine along with naphthalene dihydrodiol and 2-naphthol as glucuronide conjugates [1, 2]. Conjugates with glutathione and cysteine are excreted in the bile [1].

The excretion rate of 1-naphthol in workers exposed to naphthalene by inhalation was calculated to have a half-life of approximately 4 hours [2]. Additional case studies following ingestion of naphthalene have indicated that the urinary excretion of metabolites is prolonged following an exposure, possibly due to delayed absorption from the gastrointestinal tract [2].

Sources and route of human exposure

Naphthalene toxicity may occur by all routes of exposure, whether by inhalation of vapours, ingestion and by dermal or ocular contact [1-3]. The most likely source of exposure to significant amounts of naphthalene is occupational inhalation of the vapour, since its principal use is in industry [1]. In occupations where naphthalene is used, personal protective equipment is recommended to minimise the potential for exposure [5]. Exposure to naphthalene may also occur from the burning of fossil fuels and organic material, in vehicle exhaust emissions and from cigarette smoke, as it is one of the constituent chemicals. However, such exposure would not be limited solely to naphthalene, as many other toxic chemicals are also present in smoke from these sources [2]. The amount of naphthalene released from the burning of organic material is also expected to be much lower than would be experienced from an occupational exposure [1, 2]. Exposure to naphthalene in the home has classically occurred from its use in mothballs as a moth repellent, although this use is becoming less common due to the toxicity and flammability of naphthalene.

Health Effects of Acute / Single Exposure

Human Data

General toxicity

Naphthalene is readily absorbed into the systemic circulation following all routes of exposure, and as such elicits systemic toxicity [1-3]. Individuals who have a deficiency in glucose-6-phosphate dehydrogenase are particularly susceptible to haemolysis following naphthalene exposure [2].

Inhalation

Naphthalene readily forms a vapour at room temperature and therefore, poses an inhalation hazard. Some of the common signs and symptoms of an acute inhalation exposure to naphthalene include headache, confusion, nausea, vomiting and profuse perspiration [1, 3]. The most characteristic sign of naphthalene toxicity is acute intravascular haemolysis, particularly in individuals with a deficiency of glucose-6-phosphate dehydrogenase (G6-PD), which is accompanied by haemolytic anaemia, leukocytosis, fever, haematuria, jaundice and renal and hepatic dysfunction which are secondary to the anaemia [1, 3]. Further symptoms of naphthalene exposure related to the haemolytic anaemia, include dysuria and haemoglobinuria, observed by the passing of dark brown or black urine [1-3]. In serious cases, renal failure resulting from naphthalene inhalation can be fatal [1].

Ingestion

Ingestion of naphthalene commonly gives rise to abdominal cramps, nausea, vomiting and diarrhoea. Some additional signs and symptoms of naphthalene ingestion include headache, profuse sweating, tachycardia, respiratory distress, listlessness, confusion [1, 2]. In some cases ingestion of naphthalene may also cause arrhythmias, convulsions and coma and could possibly be fatal [1]. Ingestion of sufficient amounts of naphthalene may also give rise to adverse health effects as seen following inhalation, including acute intravascular haemolysis, haemolytic anaemia, haematuria and hepatic and renal failure which may be fatal [1].

Dermal / ocular exposure

Dermal exposure to naphthalene causes mild skin irritation, however, some individuals may be more sensitive to naphthalene and dermal contact may give rise to severe dermatitis [1, 3]. Ocular exposure to naphthalene has been seen to result in eye irritation, corneal damage, lens opacities and the formation of cataracts [1].

Delayed effects following an acute exposure

Symptoms including nausea, vomiting and diarrhoea may be delayed up to 48 hours following an acute exposure to naphthalene [1]. The onset of haemolysis and

haemoglobinuria leading to acute renal failure can also be delayed for between 3-5 days following exposure [6].

Animal and In-Vitro Data

General toxicity

The acute toxicity of naphthalene in laboratory animals has been extensively studied, particularly following oral exposure and has demonstrated that rodents are not sensitive to the haemolytic effect of naphthalene, as is observed in humans [2].

Inhalation

Mice are more susceptible to lung damage following naphthalene exposure than rats. An acute inhalation exposure (4 hours) of 10 ppm naphthalene to mice induced necrosis of the Clara cells in the proximal airways of the lung. However, exposure of rats to up to 100 ppm naphthalene for the same duration had no effect on lung tissue [2]. No studies have been located which have investigated the formation of lesions in the nasal passages following an acute exposure to naphthalene, although these are common targets for naphthalene toxicity following chronic exposure [2].

Ingestion

The haemolytic effects of naphthalene toxicity as seen in humans have not been observed in common laboratory species such as rats and mice. However, acute haemolytic anaemia has been observed in dogs orally administered with greater than 411 mg kg⁻¹ naphthalene [1]. Heinz bodies were evident in the circulating red blood cells before haemolysis was observed [1]. The oral LD₅₀ for acute naphthalene ingestion in mice are 533 mg kg⁻¹ for males and 710 mg kg⁻¹ for females [2]. Rats are less sensitive to the effects of naphthalene toxicity than mice, as the oral LD₅₀ for rats ranged from 1760 mg kg⁻¹ to 2400 mg kg⁻¹ [1, 2].

Dermal

Dermal exposure of naphthalene in rabbits have shown that it is a mild irritant, giving rise to erythema and fissuring, which healed approximately 6-7 days after removal from the exposure. Acute dermal exposure of naphthalene to rats has also been shown to cause mild dermal irritation [2]. Acute toxicity by this route is relatively low, with an LD₅₀ of greater than 2500 mg kg⁻¹ body weight being reported [7, 8].

Health Effects of Chronic / Repeated Exposure

Human Data

Inhalation

Adverse effects following chronic inhalation of naphthalene are similar to those seen following acute exposure, such as nausea, headache, malaise and haemolytic anaemia and its related hepatic and renal effects. In cases of human exposure to naphthalene vapours, the dose and duration of exposure is often unknown and as such it is difficult to assess the effect of chronic naphthalene exposure. Also, due to the adverse health effects of acute exposure to naphthalene, chronic exposure to amounts sufficient to cause significant toxicity is relatively uncommon [2]. Newborn children are more at risk from naphthalene-induced haemolysis than adults as they are less able to effectively metabolise naphthalene [1]. Infants have died following inhalation and dermal absorption of naphthalene, from naphthalene treated clothing, nappies or blankets [2, 8]. Children exposed to naphthalene are susceptible to kernicterus (permanent neurological damage) due to the increased levels of bilirubin from the associated jaundice, this can lead to convulsions and in some cases may be fatal [2]. There is limited evidence linking occupational inhalation of naphthalene with cataracts, however, these studies are old and typically involve co-exposure to other substances [2, 7, 8].

Dermal / Ocular

No studies were located specifically documenting chronic dermal exposure of humans to naphthalene. As naphthalene is a mild irritant however, chronic exposure would be expected to cause dermal irritation with some susceptible individuals developing dermatitis [3]. An investigation of workers with ocular exposure to naphthalene vapours in a factory manufacturing dye intermediates over a period of 5 years showed an increase in lens opacities which had no correlation with the age of the workers, and were judged to be due to naphthalene exposure [2, 3].

Genotoxicity

No studies were available concerning the genotoxicity of naphthalene in humans.

Carcinogenicity

There were no studies available investigating the carcinogenicity of naphthalene in humans via any route of exposure. The International Agency for Research on Cancer (IARC) has evaluated that there is inadequate evidence for the carcinogenicity of naphthalene in humans. However, based on evidence from animal studies, IARC has concluded overall that naphthalene is possibly carcinogenic to humans (group 2B) [4].

Reproductive and developmental toxicity

Following ingestion by a pregnant mother, naphthalene has been shown to cross the placenta into the fetus, resulting in neonatal haemolytic anaemia [2].

Animal and In-Vitro Data

Inhalation

The nose and lungs are the principal target for naphthalene toxicity following inhalation in rats and mice. Chronic inhalation exposure to naphthalene resulted in an increased incidence of neoplastic and non-neoplastic lesions in the nose and lungs of rats. In mice, an increase in non-neoplastic lesions was seen in the nose, whilst the incidence of both neoplastic and non-neoplastic lesions were increased in the lungs [2]. The non-neoplastic lesions observed in the nasal cavity of rats and mice included hyperplasia, atrophy, chronic inflammation and hyaline degeneration of the olfactory epithelium and hyperplasia, metaplasia or degeneration of the respiratory epithelium. Neoplastic lesions include respiratory epithelial adenoma and olfactory epithelial neuroblastoma [2].

Ingestion

Chronic oral exposure of naphthalene to rats and rabbits has been shown to increase ocular lens density followed by the formation of cataracts after approximately 4 weeks exposure to 500 and 1000 mg kg⁻¹ day⁻¹ [1, 2]. Pregnant female rats that were orally exposed to naphthalene at 50, 150 and 450 mg kg⁻¹ day⁻¹ during organogenesis exhibited lethargy, slow respiration, had periods of apnoea, appeared to be dazed and were unable to move following exposure. The rats administered 50 mg kg⁻¹ day⁻¹ were seen to acclimatise quickly, with symptoms only apparent during the first 2 days of dosing. A significant reduction in body weight gain was also observed in the animals treated with either 150 or 450 mg kg⁻¹ day⁻¹. These effects were not observed in non-pregnant rats or mice, suggesting that pregnant animals are more susceptible to naphthalene toxicity [2].

Genotoxicity

Naphthalene has consistently given negative results in the well established *Salmonella* assay for gene mutation in bacteria. There is some evidence that naphthalene is clastogenic *in-vitro*, but negative results were obtained in the bone marrow assay for clastogenicity *in-vivo* in mice. Negative results were also obtained in an *in-vivo* assay for DNA damage in the liver of rats in an unscheduled DNA synthesis (UDS) study. A number of expert groups have concluded that on-balance naphthalene is not an *in-vivo* genotoxin [7-10].

Carcinogenicity

The carcinogenicity of naphthalene has been studied in rats and mice following inhalation exposure. Neuroblastomas of the olfactory epithelium and adenomas of the nasal respiratory epithelium were induced in both male and female rats exposed to naphthalene. In mice exposed to naphthalene by inhalation there was an increased incidence of bronchiolar-alveolar adenomas in females, but this was not seen in males [2-4]. The International Agency for Research on Cancer (IARC) has evaluated that there is sufficient evidence for the carcinogenicity of naphthalene in experimental animals [4].

Reproductive and developmental toxicity

There is some evidence of developmental toxicity in rats and mice exposed to naphthalene by oral ingestion. However, this was observed only at levels which produced significant maternal toxicity [3, 4]. Studies in pregnant rats and rabbits have not shown any evidence for developmental toxicity using dose levels of up to about $500 \text{ mg kg}^{-1} \text{ bw}^{-1} \text{ day}^{-1}$ [7, 8, 11, 12].

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