Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for naphthalene

SCOEL/SUM/90

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8-hour TWA:	not feasible to derive a health-based limit at present (see "*Recommendation*")
STEL (15 mins):	not feasible to derive a health-based limit at present (see "*Recommendation*")
Additional classification:	-
SCOEL carcinogen group:	to be re-evaluated, when further data will be available (see "*Recommendation*")

Substance:

Naphthalene

Identity and Properties:

Chemical name:	Naphthalene
CAS No:	91-20-3
EINECS No:	202-049-5
Empirical formula:	$C_{10}H_8$
Molecular mass:	128.2
Synonyms:	Camphor tar, naphthalin, naphthene, naphthaline
Melting point:	80°C
Conversion factor:	1 ppm = 5.24 mgm^{-3} at 25°C, 760 mm Hg
EU classification:	Carc. Cat. 3; R40 Xn; R22 N; R50-53

Naphthalene is a colourless to brown solid with a mothball or tar-like odour and a threshold of 0.3 ppm. It is very poorly soluble in water (30 mg/L at 20°C). It is much more soluble in benzene, alcohol, ether and acetone.

1. Occurrence and Use

Naphthalene is produced by the distillation of coal tar and subsequent crystallisation of the appropriate fraction. It also occurs in mixed coal-tar distillates, including creosote. The principal use for naphthalene is in the manufacture of phthalic anhydride. It is also used in the manufacture of plasticisers for concrete, in the manufacture of an ingredient for plaster board, as dispersants in synthetic and natural rubbers and in tanning agents for the leather industries. The manufacture of a number of other chemicals such as azo dye intermediates and the insecticide 1-naphyl-N-methylcarbamate (Carbaryl, Sevin) is carried out using naphthalene. It has been used in the manufacture of mothballs and has limited use in theatrical pyrotechnics.

Naphthalene has also been addressed as an indoor air pollutant (Preuss et al., 2003; Loh et al. 2007).

2 Health significance

2.1. Metabolism and toxicokinetics

Limited information on the effects on humans (see below) indicates that naphthalene must be readily absorbed by all routes of exposure; animal data show that rapid and almost complete absorption occurs following ingestion (Bakke et al., 1985). In humans, naphthalene is metabolised via cytochrome P450 oxidation to 1-naphthol, 2-naphthol and 1,2- and 1,4-naphthoquinone (Mackell et al., 1951; Hansen et al., 1993). *In vitro* studies in human liver microsomes and human lung preparations indicate that naphthalene is also metabolised to naphthalene-1,2-dihydrodiol (Buckpitt and Bahnson, 1986; Tingle et al., 1993). Similarly, metabolism in rodents is chiefly by oxidation, with subsequent glutathione conjugation, or conversion to napththalene-1,2-dihydrodiol (Bakke et al., 1985). The respiratory tract toxicity of naphthalene in rodents has been ascribed to reactive metabolite(s) produced mainly by CYP2F2, which deplete glutathione and thereby cause cytotoxicity (Phimister et al. 2004, Genter et al. 2006, Morris and Buckpitt 2009). *In vitro* studies show that the rate of naphthalene metabolism in mouse lung tissue is approximately 3, 8 and 100 times greater than that observed in lung tissue from hamsters, rats and monkeys respectively (Buckpitt et al., 1986; Buckpitt et al., 1992). In humans and experimental animals, excretion is rapid, primarily via the urine.

Although there are studies in humans that cover a wide range of urinary naphthol concentrations at different workplaces, the present data of field investigations are not sufficient to quantitatively correlate these with ambient naphthalene concentration data (Preuss et al., 2003).

2.1.1. Health effects

In terms of the overall toxicity profile for naphthalene, there is a reasonable animal toxicity database. However, the main experimental species used (rats, mice and rabbits) do not exhibit naphthalene-induced haemolytic anaemia, the principal toxicological effect of naphthalene that has been observed in humans (see below). The reason for this is not clearly established. There is some evidence from a single dog study to indicate that this species may develop naphthalene-induced haemolytic anaemia (Zuelzer and Apt, 1949), but owing to the limited nature of the study few conclusions can be drawn. Hence, at least for this endpoint, there are difficulties in extrapolating from the experimental animal database to the human situation.

As regards acute toxicity, naphthalene is of low single-dose toxicity in rats, but there appear to be some species differences, in that the mouse shows a greater sensitivity to the acutely lethal effects of naphthalene than the rat, presumably reflecting differences in metabolism (Gaines 1969; Shopp et al., 1984).

Animal studies indicate that naphthalene is only a slight skin and eye irritant (Reprotox, 1980 a, b). In skin sensitisation studies, negative results were obtained in both a maximisation and a Buehler study, and although both had limitations in either conduct or reporting, the balance of evidence suggests that naphthalene does not cause skin sensitisation (Pharmakon, 1985a, b; Okada et al., 1985). There is no information available on respiratory sensitisation in animals. There is no useful human information on the irritant properties of naphthalene. There are also no data available on skin or respiratory sensitisation in humans. However, in view of the longstanding and widespread use of naphthalene (including domestic use), the absence of reports of skin or respiratory sensitisation suggests that naphthalene lacks these properties.

With regard to repeat-dose toxicity, in inhalation studies in rats, nasal olfactory epithelial damage, on a scale described as "minimal", was seen with repeated exposure to 1 ppm in a 28-day study and at 2 ppm in a 90-day study, the lowest exposure levels investigated (Huntingdon Research Centre, 1993 a, b). According to the EU Risk Assessment Report (2003), a LOAEL for lesions of the rat nasal epithelium is 5 mg/m^3. At higher exposures, damage to the olfactory epithelium was more pronounced. In 2-year inhalation studies in the rat and mouse, inflammation was seen in the lungs and nasal passages at 10 ppm (50 mg/m^3), the lowest exposure level tested (NTP 1992, 2000). In humans, the occurrence of haemolytic anaemia has been reported in at least 30 individuals, typically following single or repeated oral intake of naphthalene mothballs, but also following inhalation and dermal exposure to naphthalene from clothing (Shannon and Buchannon, 1982; Valaes et al., 1963; Dawson et al., 1958; Cock, 1957; Grigor et al., 1966). In some cases (particularly neonates) the naphthalene-induced haemolytic anaemia proved fatal, although it is not possible to determine the doses involved from the reports available.

Naphthalene causes cataracts in humans, rabbits and mice. Humans accidentally exposed to naphthalene by ingestion develop haemolytic anaemia, but there is no evidence of haemolytic anaemia in rodents. Cases of haemolytic anaemia have been reported in children and infants after oral or inhalation exposure to naphthalene or after maternal exposure in pregnancy (IARC 2002).

As regards mutagenicity, naphthalene has given reproducible negative results in bacterial mutation assays and was negative in an *in vitro* unscheduled DNA synthesis (UDS) assay in mammalian cells (NTP, 1992; Pharmakon, 1985c). However, naphthalene was found to be clastogenic in Chinese hamster ovary cells in the presence but not in the absence of S9, showing that following metabolic activation the substance expresses clastogenicity *in vitro* (NTP, 1992; Galloway et al., 1987). *In vivo*, naphthalene was found to be negative in two bone-marrow micronucleus tests in mice and in a well-conducted liver UDS assay in rats (Harper et al., 1984, Pharmakon, 1985 d, RTC, 1999). This suggests that naphthalene does not express genotoxicity *in vivo (IARC, 2002)*. This conclusion is confirmed by a critical assessment of the available studies by Brusick (2008) and Brusick et al. (2008). However, depurinating DNA adducts have been described in mouse skin after topical application of naphthalene. This was discussed to be related to the generation of the o-quinone metabilite, 1,2-naphthoquinone (Saeed et al., 2009).

In essence, it is not apparent that genetic lesions produced by naphthalene or its metabolites drive the carcinogenic activity that is experimentally observed (IARC 2002, Brusick, 2008).

In a standard lifetime inhalation carcinogenicity study in rats, exposed to 0, 10, 30 or 60 ppm naphthalene vapour for 6 hours/day, 5 days/week for two years, chronic inflammation of the nasal epithelium was seen at all exposure levels, the severity increasing with dose (NTP, 2000). Neuroblastoma of the nasal olfactory epithelium was observed in males from the 30 ppm and 60 ppm groups (4/48 and 3/48 respectively) and in all naphthalene-exposed groups of females (2/49, 3/49 and 12/49 respectively). (NTP uses the term "olfactory neuroblastoma" for all malignant neoplasms arising in the olfactory epithelium). This tumour did not occur in the controls, nor has it ever been noted in the chamber control rats used in NTP 2-year inhalation studies. Naphthalene produced a positive carcinogenic response in rats in this study. Significant increases were also observed in the occurrence of nasal respiratory epithelium adenomas in the naphthalene-exposed animals of both sexes (see also IARC, 2002).

In a carcinogenicity study on mice exposed to 0, 10 or 30 ppm naphthalene, the females showed an increase in the incidence of benign lung tumours (alveolar/bronchiolar adenomas), to which this species is prone, at the highest naphthalene inhalation exposure level of 30 ppm (150 mg/m^3) used in the study (NTP, 1992). The adenomas seen developed from a background of inflammatory changes in the tissues affected. From the limited information available on humans no conclusions on carcinogenicity can be drawn (see also IARC, 2002; North et al., 2008).

Human data on cancer following naphthalene exposure are only limited. No cohort or case control studies are available. Only one case report comprising 4 cases of larygeal cancer in a naphthalene purification plant was noted by Griego et al., 2008).

Concerning reproductive endpoints, there are no animal fertility studies. However, in a two-year carcinogenicity study, mice showed no histopathological changes in the gonads or accessory sex organs following inhalation of 30 ppm (150 mg/m^3) naphthalene (NTP, 1992). No testicular changes were observed in a 90-day inhalation study in rats at 60 ppm (300 mg/m^3) (Huntingdon Research Centre, 1993a). Overall, there are no grounds to indicate that naphthalene would adversely affect fertility.

With respect to developmental toxicity, in rats a twofold increase in the number of resorptions, but no malformations, was observed at doses causing maternal toxicity (450 mg/kg/day) (Navarro et al., 1991). Maternal toxicity was also noted at a lower dose at which there was no evidence of resorptions (150 mg/kg/day). Foetotoxicity (18% decrease in the number of live pups/litter) was also observed in mice at a maternally toxic dose (300 mg/kg/day). In rabbits, no developmental effects were seen in one study at a dose causing mild maternal toxicity, or in another study at a dose close to those producing maternal toxicity (Navarro et al., 1992). Overall, it appears that naphthalene does not show developmental toxicity at doses which are not maternally toxic; some adverse consequences for the foetus have been noted at maternally toxic doses.

In humans, there is no information concerning effects on fertility. The only information available with respect to human developmental toxicity comes from cases of haemolytic anaemia in infants born to mothers also suffering haemolytic anaemia, following ingestion of unquantified doses of naphthalene during their pregnancy (Zinkham and Childs, 1958).

2.2. Discussion of modes of action regarding carcinogenicity

The state of knowledge and uncertainty concerning the mode of action of the experimental tumour formation has been matter of an expert panel at the "Naphthalene State-of-the-Science Symposium", Monterey/CA, in 2006 (Bogen et al. 2008):

"Major conclusions were as follows: (1) rat nasal tumour occurrence was greatly enhanced, if not enabled, by adjacent, histologically related focal cellular proliferation; (2) elevated incidence of mouse lung tumours occurred at a concentration (30ppm) cytotoxic to the same lung region at which tumours occurred, but not at a lower and less cytotoxic concentration (NOAEL for tumour formation: 10 ppm); (3) naphthalene cytotoxicity requires metabolic activation (unmetabolized naphthalene is not the proximate cause of observed toxicity or tumors); (4) there are clear regional and species differences in naphthalene bioactivation; and (5) target tissue anatomy and physiology is sufficiently well understood for rodents, non-human primates and humans to parameterize species-specific physiologically based pharmacokinetic (PBPK) models for nasal and lung effects.

Critical areas of uncertainty requiring resolution to enable improved human cancer risk assessment were considered to be the following: (1) cytotoxic naphthalene metabolites, their modes of cytotoxic action, and detailed low-dose dose-response need to be clarified, including in primate and human tissues, and neonatal tissues; (2) mouse, rat, and monkey inhalation studies are needed to better define in vivo naphthalene uptake and metabolism in the upper respiratory tract; (3) in vivo validation studies are needed for a PBPK (physiologically-bases pharmacokinetic) model for monkeys exposed to naphthalene by inhalation, coupled to cytotoxicity studies referred to above; and (4) in vivo studies are needed to validate a human PBPK model for naphthalene."

The critical points to be resolved and the perspectives of a reliable cancer risk assessment have further been discussed in detail by Small (2008).

In view of SCOEL's strategy in the derivation of OELs for carcinogens (Bolt and Huici-Montagud 2008), the apparent non-genotoxicity of naphthalene under relevant conditions in vivo and the likely involvement of cytotoxic metabolites in carcinogenesis of the rodent respiratory tract argue in favour of the existence of a threshold. However, the definition and positioning of such a threshold and, in consequence, the justification of an health-based OEL, requires solid data for a cross-species scaling that could be provided by PBPK modelling.

Recommendation

The principal health concerns for naphthalene are haemolytic anaemia, respiratory tract damage and respiratory tract carcinogenicity.

For haemolytic anaemia, most of the human data derive from case reports involving ingestion in adults or relate to infants exposed to linen stored with naphthalene mothballs. No useful information is available on the dose-response relationship for this effect. Unfortunately, standard experimental rodents and rabbits do not exhibit this effect on exposure to naphthalene, and there are no useful experimental data from which to extrapolate to humans for this endpoint.

For respiratory tract damage, no human data are available; minimal nasal olfactory epithelium damage has been observed in rats repeatedly exposed to 1 ppm, the lowest exposure level investigated. At higher exposures the damage to the nasal epithelium was more pronounced. In 2-year studies on rats and mice, nasal and lung inflammation was seen at 10 ppm, the lowest exposure level investigated. Other studies (EU Risk Assessment Report, 2003) support a LOAEL for damage to the rat nasal epithelium of 5 ppm. A NOAEL for such effects is not evident from the available data, but the threshold in rodents clearly lies below 5ppm.

In lifetime inhalation exposure studies, naphthalene was carcinogenic towards the nasal epithelium in rats and the tumours are considered of relevance for human health. The results in mice (focused on lung adenomas) were less convincing. Naphthalene appears not to express genotoxic activity under relevant exposure conditions *in vivo*, and the respiratory tract tumours seen in rats (and mice), at the exposure levels used of 10 ppm and above, were accompanied by evidence of cytotoxicity and chronic inflammation at the sites involved. Hence one may argue that the tumours produced in rodents arose from a background of chronic cytoxicity, and that controlling exposure to avoid such cytotoxicity would also prevent carcinogenicity. However, there are still critical areas of uncertainty, which have been addressed above (see preceding chapter).

Therefore, in relation to occupational exposure limits, the position of SCOEL is that there is insufficient clarity at present in the picture surrounding the carcinogenic potential of naphthalene towards the nasal epithelium. The majority of arguments are towards a classification of naphthalene as a non-genotoxic carcinogen, for which a OEL may be established (SCOEL carcinogen group D). As clearly stated by the "Naphthalene State-of-the-Science Symposium" (Bogen et al. 2008) there are remaining uncertainties. Currently, experiments are being performed to eliminate these uncertainties (Small, 2008). When these are available, SCOEL will reconsider the situation, and eventually propose a health-based OEL for naphthalene. This also applies in respect of a STEL.

If an EU limit value (e.g. a Binding Limit Value) is eventually established, then in view of the evidence for appreciable absorption of naphthalene through the skin, a "Sk" notation would be appropriate.

Biological monitoring by the analysis of 1-naphthol in urine may be a useful aid to assessing exposure to naphthalene, particularly where control of exposure may rely on respiratory protection or where there may be scope for absorption of naphthalene through the skin (Preuss et al. 2003).

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