

Naphthalene

CAS RN 91-20-3

Synopsis

The Ministers of the Environment and of Health have conducted a screening assessment of naphthalene, Chemical Abstracts Service Registry Number (CAS RN) 91-20-3, a substance identified in the categorization of the Domestic Substances List as a high priority for action under the Ministerial Challenge. Naphthalene was identified as a high priority as it was considered to pose greatest potential for exposure to individuals in Canada (GPE) and had been classified by other agencies on the basis of carcinogenicity. While the substance did meet the ecological categorization criteria for inherent toxicity to aquatic organisms, it did not meet the criteria for persistence or bioaccumulation. Therefore, the focus of this assessment of naphthalene relates to human health aspects.

Based on a survey conducted under Section 71 of CEPA 1999, in 2000 Canadian companies reported manufacturing more than 52 000 000 kg of naphthalene, and importing more than 150 000 000 kg into the country. Naphthalene has a wide variety of industrial uses and is also a component of a variety of consumer products.

Population exposure to naphthalene in Canada is expected to be predominantly via inhalation of indoor air, accounting for more than 95% of the total daily intake across age groups.

Based principally on weight of evidence based assessments by several international and national agencies, a critical effect for the characterization of risk to human health is carcinogenicity, based on the observation of respiratory tract tumours in rodents. Naphthalene was also genotoxic in some assays. Therefore, although the mode of induction of tumours has not been fully elucidated, it cannot be precluded that the tumours observed in experimental animals resulted from direct interaction with genetic material. In addition, the upper-bounding concentration of naphthalene in indoor air may approach the critical effect level for non-cancer effects of the respiratory system.

On the basis of the carcinogenicity of naphthalene, for which there may be a probability of harm at any level of exposure, as well as the potential inadequacy of the margin between the upper-bounding concentration of naphthalene in indoor air and the critical effect level for non-cancer effects, it is concluded that naphthalene is a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is concluded that this substance is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends. Additionally, naphthalene does not meet criteria for persistence and bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations*.

This substance will be included in the Domestic Substances List inventory update initiative, to be launched in 2009. In addition and where relevant, research and monitoring will support verification of assumptions used during the screening assessment and, where appropriate, the performance of potential control measures identified during the risk management phase.

Based on the information available, naphthalene meets one or more of the criteria set out in section 64 of the *Canadian Environmental Protection Act, 1999*.

Introduction

The *Canadian Environmental Protection Act, 1999* (CEPA 1999) (Canada 1999) requires the Minister of the Environment and the Minister of Health to conduct screening assessments of substances that have met the categorization criteria set out in the Act to determine whether these substances present or may present a risk to the environment or human health. Based on the results of a screening assessment, the Ministers can propose to take no further action with respect to the substance, to add the substance to the Priority Substances List (PSL) for further assessment, or to recommend that the substance be added to the List of Toxic Substances in Schedule 1 of the Act and, where applicable, the implementation of virtual elimination.

Based on the information obtained through the categorization process, the Ministers identified a number of substances as high priorities for action. These include substances that

- met all of the ecological categorization criteria, including persistence, bioaccumulation potential and inherent toxicity (PBiT) to aquatic organisms, and were believed to be in commerce ; and/or
- met the categorization criteria for greatest potential for human exposure (GPE) or presented an intermediate potential for exposure (IPE), and had been identified as posing a high hazard to human health based on classifications by other national or international agencies for carcinogenicity, genotoxicity, developmental toxicity or reproductive toxicity.

The Ministers therefore published a notice of intent in the *Canada Gazette*, Part I, on December 9, 2006 (Canada 2006), that challenged industry and other interested stakeholders to submit, within specified timelines, specific information that may be used to inform risk

assessment and to develop and benchmark best practices for the risk management and product stewardship of those substances identified as the highest priorities.

The substance naphthalene was identified as a high priority for assessment of human health risk because it was considered to present GPE and had been classified by other agencies on the basis of carcinogenicity. The Challenge for naphthalene was published in the *Canada Gazette* on February 3, 2007 (Canada 2007a). A substance profile was released at the same time. The substance profile presented the technical information available prior to December 2005 that formed the basis for categorization of this substance. As a result of the Challenge, submissions of information were received.

Although naphthalene was determined to be a high priority for assessment with respect to human health and it also met the ecological categorization criterion for inherent toxicity for aquatic organisms, it did not meet the criteria for potential for persistence or bioaccumulation. Therefore, this assessment focuses principally on information relevant to the evaluation of risks to human health.

Under CEPA 1999, screening assessments focus on information critical to determining whether a substance meets the criteria for defining a chemical as toxic as set out in section 64 of the Act, where

“64. [...] a substance is toxic if it is entering or may enter the environment in a quantity or concentration or under conditions that

- (a) have or may have an immediate or long-term harmful effect on the environment or its biological diversity;
- (b) constitute or may constitute a danger to the environment on which life depends; or
- (c) constitute or may constitute a danger in Canada to human life or health.”

Screening assessments examine scientific information and develop conclusions by incorporating a weight of evidence approach and precaution.

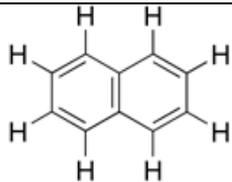
This screening assessment includes consideration of information on chemical properties, hazards, uses and exposure, including the additional information submitted under the Challenge. Data relevant to the screening assessment of this substance were identified in original literature, review and assessment documents, stakeholder research reports and from recent literature searches, up to January 2007. Key studies were critically evaluated; modelling results may have been used to reach conclusions. Evaluation of risk to human health involves consideration of data relevant to estimation of exposure (non-occupational) of the general population, as well as information on health hazards (based principally on the weight of evidence assessments of other agencies that were used for prioritization the substance). Decisions for human health are based on the nature of the critical effect and/or margins between conservative effect levels and estimates of exposure, taking into account confidence in the completeness of the identified databases on both exposure and effects, within a screening context. The screening assessment

does not represent an exhaustive or critical review of all available data. Rather, it presents a summary of the critical information upon which the conclusion is based.

This screening assessment was prepared by staff in the Existing Substances Programs at Health Canada and Environment Canada and incorporates input from other programs within these departments. This assessment has undergone external written peer review/consultation. Comments on the technical portions relevant to human health were received from Meridian Environmental Inc. and Starodub & Associates. While external comments were taken into consideration, the final content and outcome of the screening risk assessment remain the responsibility of Health Canada and Environment Canada. Additionally, the draft of this screening assessment was subject to a 60-day public comment period. The critical information and considerations upon which the assessment is based are summarized below.

Substance Identity

Table 1. Substance identity

| | |
|--|---|
| CAS Registry Number | 91-20-3 |
| DSL name | Naphthalene |
| Inventory names ¹ | Naphthalene (TSCA, EINECS, ENCS, AICS, ECL, SWISS, PICCS, ASIA-PAC, NZIoC) NAPHTHALENE SCALES (PICCS) |
| Other names | Albocarbon; Camphor Tar; Dezodorator; Mighty 150; Mighty RD1; Moth Balls; Moth flakes; Naftalen; Naphtalene; Naphthalin; Naphthaline; Naphthene; Tar Camphor; White tar |
| Chemical group | Discrete organics |
| Chemical sub-group | Aromatic |
| Chemical formula | C ₁₀ H ₈ |
| Chemical structure |  |
| SMILES | <chem>c(c1ccc2)ccc2(c1)c2</chem> |
| Molecular mass | 128.18 g/mol |
| The primary focus of this screening assessment report is on the uses of naphthalene as a discrete substance rather than its presence in complex mixtures such as petroleum-based streams and products. | |

¹ **Source:** National Chemical Inventories (NCI), 2007: AICS (Australian Inventory of Chemical Substances); ECL (Korean Existing Chemicals List); EINECS (European Inventory of Existing Chemical Substances); ELINCS (European List of Notified Chemical Substances), ENCS (Japanese Existing and New Chemical Substances); PICCS (Philippine Inventory of Chemicals and Chemical Substances); TSCA (Toxic Substances Control Act Chemical Substance Inventory); ASIA-PAC (Combined Inventories from the Asia-Pacific Region); and NZIoC (New Zealand Inventory of Chemicals)

Physical and Chemical Properties

A summary of the physical and chemical properties of naphthalene is presented in Table 2.

Table 2: Physical and chemical properties of naphthalene

| Property | Type | Value | Temperature (°C) | Reference |
|--|------------------------|--|------------------|------------------------------|
| Melting Point (°C) | Experimental | 80.5 | - | Weast et al. 1985 |
| Boiling Point (°C) | Experimental | 218 | - | Weast et al. 1985 |
| Density (kg/m ³) | Experimental | 1.145 | 20 | Weast et al. 1985 |
| Vapour pressure (Pa) | Experimental | 11.6 | 25 | US EPA 1982e |
| Henry's Law constant (Pa•m ³ /mol) | Experimental | 46.6 (4.6x10 ⁻⁴ atm•m ³ /mol) | - | Weast et al. 1985 |
| Log K _{ow} (Octanol-water partition coefficient) (dimensionless) | Experimental | 3.29 | - | Weast et al. 1985 |
| Log K _{oc} (Organic carbon-water partition coefficient) (dimensionless) | Experimental | 2.97 | - | Weast et al. 1985 |
| Water solubility (mg/L) | Experimental | 31.7 | 25 | Weast et al. 1985 |
| Other solubilities (g/L) | Experimental (alcohol) | 20 | 20–25 | GDCh-Advisory Committee 1989 |
| | Experimental (benzene) | 1130 | 41 | GDCh-Advisory Committee 1989 |
| | Experimental (toluene) | 910 | 41 | GDCh-Advisory Committee 1989 |

Sources

Naphthalene is found in eroded geologic deposits of lignite, anthracite, bituminous and sub-bituminous coal. Based on a survey conducted under Section 71 of CEPA 1999, in 2000 Canadian companies reported manufacturing more than 52 000 000 kg of naphthalene, and importing more than 150 000 000 kg into the country (Environment Canada 2006).

Uses

The primary focus of this screening assessment report is on the uses of naphthalene as a discrete substance rather than its presence in complex mixtures such as petroleum-based streams and products.

According to submissions made under section 71 of CEPA 1999, from the Challenge questionnaire submission and other data voluntarily submitted (Environment Canada 2006), naphthalene is reported to be used in the petroleum sector as an oilfield chemical, solvent, refinery cleaner, fuel additive and feedstock. Other non-petroleum stream uses that were reported included its use as a solvent and intermediate in automotive paint manufacturing and driveway sealants, in pest control products such as moth repellants, as a chemical intermediate in the manufacture of pharmaceutical, agricultural and construction products, and as a feedstock for the production of naphthalene sulfonate plasticizers and surfactants. Consumer product uses of naphthalene may include some commercially available paints, stains and coatings (NIH 2007).

In Canada, four end-use products containing naphthalene are registered for use as moth repellents under the *Pest Control Products Act* (PMRA 2007). Naphthalene was reported in two notifications of cosmetic products (wig glue removers) filed with Health Canada under the *Cosmetic Regulations* of the *Food and Drug Act* (Health Canada, Product Safety Programme; personal communication, September 2007; unreferenced). Naphthalene is also a component of tobacco combustion products.

Releases to the Environment

The National Pollutant Release Inventory reports that 120 tonnes of naphthalene were released by Canadian industries in 2005, with 34 out of 73 facilities reporting releases. The top four releasing facilities were located in Ontario (NPRI 2007).

Persistence and Bioaccumulation Potential

Persistence

As a polycyclic aromatic hydrocarbon (PAH), naphthalene was included in a risk assessment of PAHs that was previously conducted under CEPA's Priority Substances Assessment Program (Canada 1994). In that assessment PAHs in general were considered persistent in the environment, however naphthalene was identified as one of the more labile substances.

Based on its physical and chemical properties (Table 2) and the empirical degradation data for naphthalene presented below (Table 3), naphthalene does not meet the persistence criteria (half-lives in soil and water ≥ 182 days, in sediments ≥ 365 days and in air ≥ 2 days) set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Table 3. Empirical data for persistence of naphthalene

| Medium | Fate process | Degradation value | Degradation endpoint/units | Reference |
|----------|-----------------------|-------------------|----------------------------|----------------------------|
| Air | • OH radical reaction | 24.0 | Half-life, hours | Güsten et al. 1984 |
| Air | • OH radical reaction | 19.0 | Half-life, hours | Klöpffer et al. 1986 |
| Air | • OH radical reaction | 8.9 | Half-life, hours | Atkinson and Aschmann 1987 |
| Air | • OH radical reaction | 8.2 | Half-life, hours | Biermann et al. 1985 |
| Air | • OH radical reaction | 8.0 | Half-life, hours | Masclet and Mouvier 1988 |
| Air | • OH radical reaction | 8.0 | Half-life, hours | Biermann et al. 1985 |
| Air | • OH radical reaction | 7.4 | Half-life, hours | Atkinson and Aschmann 1986 |
| Soil | Degradation | Approx. 2 | Half-life, days | Park et al. 1990a, 1990b |
| Sediment | Biodegradation | 0.125-→88 | Half-life, days | ATSDR 2005 |
| Sludge | Biodegradation | 2 | Biodegradation, % | MITI 1992 |

Bioaccumulation

The experimental data (Table 4) indicate that the substance naphthalene does not meet the bioaccumulation criteria—bioconcentration factor (BCF) / bioaccumulation factor (BAF) ≥ 5000 —as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000).

Table 4. Experimental data for bioaccumulation of naphthalene

| Test organism | Endpoint | Value wet wt L/kg | Reference |
|--------------------------------|----------|-------------------|---------------------------|
| <i>Arenicola marina</i> | BCF | 4.07 | Lyes 1979 |
| <i>Leucisus idus melanotus</i> | BCF | 30.20 | Freitag et al. 1985 |
| <i>Chlorella fusca</i> | BCF | 128.82 | Geyer et al. 1984 |
| <i>Daphnia pulex</i> | BCF | 131.83 | Southworth et al. 1978 |
| <i>Pimephales promelas</i> | BCF | 426.58 | Veith et al. 1979 |
| <i>Daphnia magna</i> | BCF | 50 | Eastmond et al. 1984 |
| <i>Lepomis macrochirus</i> | BCF | 310 | McCarthy and Jimenez 1985 |
| <i>Lepomis macrochirus</i> | BCF | 320 | McCarthy and Jimenez 1985 |

Environmental Fate

Based on moderate vapour pressure, log K_{oc} and water solubility values, as well as the results of Level III fugacity modelling (Table 5), there is the indication that naphthalene will remain in the media to which it was released.

Table 5. Results of the Level III fugacity modelling (EPIWIN V3.12) for naphthalene

| Substance released to: | Fraction of substance partitioning into each compartment medium (%) | | | |
|-------------------------------|---|-------|-------|----------|
| | Air | Water | Soil | Sediment |
| Air (100%) | 90.5 | 4.81 | 4.44 | 0.218 |
| Water (100%) | 2.19 | 93.5 | 0.107 | 4.23 |
| Soil (100%) | 0.143 | 0.379 | 99.5 | 0.0172 |
| Air, water, soil (33.3% each) | 1.03 | 12.8 | 85.6 | 0.578 |

Potential to Cause Ecological Harm

As indicated earlier, naphthalene does not meet the persistence or bioaccumulation criteria as set out in the *Persistence and Bioaccumulation Regulations* (Canada 2000). Experimental ecotoxicological data indicate that naphthalene poses a high hazard for aquatic organisms. LC_{50} s of 96 to 680 $\mu\text{g/L}$ have been reported for fish (Black et al. 1983; Rice and Thomas 1989; Milleman et al. 1984; US EPA 1992). For non-mammalian organisms in other media, toxicity values of 18665 $\mu\text{g/kg}$ in sediment and 205 $\mu\text{g/kg}$ in soil can be derived through equilibrium partitioning from an acute toxicity LC_{50} of 1000 $\mu\text{g/L}$ for *Daphnia pulex* (Trucco et al., 1983), using the experimental K_{oc} of 2.97 and a fraction of organic carbon of 0.2 (Mackay, 1991). The National Pollutant Release Inventory reports releases by Canadian industries of 120 tonnes of naphthalene in 2005, mainly to air where it is not persistent (NPRI 2007).

Ecological effects of naphthalene and exposure of biota were considered as part of previous ecological components of the Priority Substances List assessments of polycyclic aromatic hydrocarbons (PAHs) (Canada 1994) and creosote-impregnated waste materials (Canada 1993). As a result of those assessments, Polycyclic aromatic hydrocarbons and Creosote-impregnated

waste materials from creosote-contaminated sites have been added to Schedule 1 (List of Toxic Substances) of CEPA 1999. Those assessments had considered ecological impacts of exposure to total PAHs rather than to individual components such as naphthalene. In that context, ecologically-relevant releases had been found to be related to sources of total PAHs, rather than to sources of individual commercial components. Since ecological exposure and impacts are expected to be associated with total PAHs, it is not considered at this time that naphthalene, as an individual commercial compound, is likely to cause ecological harm. Should evidence be identified in the future that indicates that naphthalene on its own may have ecological impacts, revision of this conclusion may be warranted.

Potential to Cause Harm to Human Health

Exposure Assessment

Appendix 1 presents upper-bounding estimates of intake for each age group in the general population of Canada, based upon maximum identified concentrations in environmental media. The upper-bounding estimates of exposure to naphthalene for the general population range from 25.84 $\mu\text{g}/\text{kg}\text{-bw}$ (kilogram of body weight) per day in the 60+ years age group to 78.01 $\mu\text{g}/\text{kg}\text{-bw}/\text{day}$ in the 0.5 to 4 year age group. Inhalation of indoor air was the greatest source of intake of naphthalene, accounting for more than 95.0 % of the total daily intake across all age groups. A Health Canada survey of homes in Windsor, Canada in 2005 and 2006 (Health Canada 2008) identified maximum indoor air concentrations of 158.05 $\mu\text{g}/\text{m}^3$. The corresponding mean and 90th percentile values from this study were significantly lower (6.778 and 9.405 $\mu\text{g}/\text{m}^3$ respectively). Another Health Canada study conducted in Ottawa, Canada (Zhu et al. 2005) reported maximum indoor air concentrations of 144.44 $\mu\text{g}/\text{m}^3$. The corresponding arithmetic mean and 90th percentile values from this study were also significantly lower (3.87 and 4.75 $\mu\text{g}/\text{m}^3$ respectively). The maximum value from the Windsor survey was considered to be more appropriate for use in deriving upper-bounding estimates of intake than the maximum value of 398.70 $\mu\text{g}/\text{m}^3$ as reported in an earlier Canadian survey (Fellin et al. 1992), as it is considered to be more representative of current exposures. However, the Windsor survey was conducted on non-smoking homes and since cigarette smoke is a source of naphthalene, smoking households may potentially have higher indoor air concentrations than those reported above for non-smoking homes. Therefore it is considered appropriate to use the maximum values in deriving upper-bounding estimates of exposure.

Measured values of indoor air and ambient air are believed to generally capture emissions from consumer products and other sources such as migration of volatile organic compounds from attached garages (Batterman et al. 2007). It is notable that air concentrations of 520–820 $\mu\text{g}/\text{m}^3$ were reported in a limited study which simulated moth ball use in 3 homes (EURAR 2003). Relevance of this data to the Canadian use pattern for moth balls is uncertain.

Dermal exposure to naphthalene from use of consumer products containing naphthalene can contribute to general population exposure.

Confidence in the general population exposure assessment is moderate to high given the completeness of the dataset, critical study design and thoroughness and quantity of literature currently available. Confidence in the estimates of exposure from use of consumer products is low due to uncertainties in the assumptions used.

Health Effects Assessment

Appendix 2 contains a summary of the available health effects information for naphthalene in laboratory animals. An overview of health effects reported in humans is presented in Appendix 4.

The International Agency for Research on Cancer (IARC 2002) has classified naphthalene as “possibly carcinogenic to humans” (Group 2B) on the basis of “inadequate evidence in humans” and “sufficient evidence in experimental animals” for determination of carcinogenicity. The European Commission (EURAR 2003) has classified naphthalene as Category 3 for carcinogenicity (“causes concerns for humans owing to possible carcinogenic effects”). It was noted by the European Commission that a satisfactory assessment of carcinogenic effects in humans was not possible based on inadequate available information and that evidence for carcinogenicity from appropriate animal studies was insufficient to classify the substance in Category 2 (“regarded as if carcinogenic to humans”) (EURAR 2003). The National Toxicology Program (NTP) has classified naphthalene as being “reasonably anticipated to be a human carcinogen based on sufficient evidence from studies in experimental animals” (NTP 2004). The United States Environmental Protection Agency (US EPA 1998) has classified naphthalene as Group C (“possible human carcinogen”) based on inadequate human carcinogenicity data and limited evidence of carcinogenicity after oral and inhalation exposures in experimental animals. These classifications were based on increased incidence of neoplastic effects observed in both mice and rats exposed to naphthalene via inhalation. Groups of male and female B6C3F1 mice exposed to up to 30 ppm (157 mg/m³) naphthalene for 104 weeks (NTP 1992a) had a significant increase in incidence of alveolar/bronchiolar adenoma (females only). Increased incidences of alveolar/ bronchiolar adenoma and carcinoma in males were not statistically significant (NTP 1992a). In a screening study summarized in IARC (2002), female A/J mice were exposed via inhalation to up to 30 ppm (157 mg/m³) naphthalene for 6 months. A significant increase in the number of adenomas per tumour-bearing mouse, but not adenomas per mouse, was reported (Adkins et al. 1986). However IARC (2002) noted that this particular strain of mouse is highly susceptible to lung tumours. Groups of male and female F344/N rats exposed to up to 60 ppm (314 mg/m³) naphthalene for 105 weeks had increased incidence of olfactory epithelium neuroblastoma and respiratory epithelium adenoma (NTP 2000). IARC (2002) reported that these nasal tumours were rare, and had not been observed in the NTP historical control database for two-year inhalation studies or the NTP database of studies conducted via all routes of exposure. IARC (2002) reports that the utility of carcinogenicity studies via the oral route in rats

as well as by injection in mice and rats (Schmähl 1955; LaVoie et al. 1988; Knake 1956) was limited for evaluation of the carcinogenicity of naphthalene.

Assays investigating mutagenicity *in vitro* provide little evidence for induction of gene mutations; however IARC (2002) noted that positive results were obtained in assays investigating micronucleus formation, chromosomal aberrations and chromosomal recombinations *in vitro* which are consistent with clastogenic potential. Similarly, the European Commission (EURAR 2003) stated that results of an *in vitro* assay indicate that naphthalene was clastogenic, but that assays were negative for induction of sister chromatid exchange *in vitro*. Assays were negative in two *in vivo* bone-marrow micronucleus tests and an *in vivo* rat liver unscheduled DNA synthesis test.

Although a mode of action analysis is beyond the scope of a screening assessment, nongenotoxic mechanisms have been proposed but not fully elucidated for the carcinogenicity of naphthalene (IARC 2002; EURAR 2003). IARC (2002) notes that, for mice, higher rates of metabolism leading to cytotoxic metabolites and increased cell turnover may lead to tumour development. Similarly, the European Commission (EURAR 2003) indicates that, for the rat nasal tissue, tumour development is considered to be the result of chronic tissue injury, for which an identifiable threshold will exist. The European Commission (EURAR 2003) concluded that uncertainty exists concerning the relevance of the rat nasal effects to human health, but that it is not possible to dismiss the rat nasal olfactory data as being of no relevance for humans. IARC (2002) stated that there is no full understanding of the formation of these nasal tumours, particularly the neuroblastomas. The US EPA (2005) is currently assessing the mode of action of the carcinogenicity of naphthalene. In addition, the US EPA Reregistration Eligibility Decision (RED) document for naphthalene is expected to be made publicly available in July 2008 (US EPA 2008). An industry research program is also in place from 2007-2011, where efforts are focussed on defining the mode of action for tumourgenicity (Naphthalene Council Inc.; letter dated March 12, 2008; unreferenced).

The following text presents a summary of non-cancer effects observed in laboratory animals at the lowest levels of exposure via inhalation, the predominant route of exposure for the general population.

The National Toxicology Program (NTP) conducted two-year inhalation studies with mice and rats. Groups of male and female B6C3F1 mice were exposed to approximately 0, 52 or 157 mg/m³ naphthalene. Non-neoplastic effects included inflammation of the nose and lungs, metaplasia of the olfactory epithelium and hyperplasia of the nasal respiratory epithelium (NTP 1992a). Groups of male and female F344/N rats were exposed to approximately 0, 52, 157 or 314 mg/m³ naphthalene. Non-neoplastic effects observed in rats included atypical hyperplasia, atrophy, chronic inflammation and hyaline degeneration of the olfactory epithelium as well as hyperplasia, squamous metaplasia, hyaline degeneration, goblet cell hyperplasia and glandular hyperplasia of the respiratory epithelium (NTP 2000). For both the rat and mouse studies, a lowest-observed-(adverse)-effect concentration (LO(A)EC) of 52 mg/m³ was identified.

The European Commission (EURAR 2003) reported that naphthalene was administered via inhalation in a well-conducted unpublished study (Huntingdon Research Centre 1993a), 6 hours/day, 5 days a week for 13 weeks to male and female rats at dose levels of approximately 0, 10, 50 or 3000 mg/m³. Effects in the olfactory epithelium at the 10 mg/m³ dose level (LOEC) were reported to include slight disorganization, mild erosion, minimal atrophy, rosette formation, occasional degenerate cells, loss of Bowman's glands and minimal hyperplasia (EURAR 2003). The European Commission (EURAR 2003) noted that a no-observed-adverse-effect concentration (NOAEC) could not be identified for local effects.

The European Commission (EURAR 2003) reported that naphthalene was administered via inhalation in a second well-conducted unpublished study (Huntingdon Research Centre 1993b), 6 hours/day, 5 days a week for 4 weeks to groups of male and female rats at dose levels of approximately 0, 5, 15, 50, 150 or 370 mg/m³. A lowest-observed-adverse-effect-concentration (LOAEC) of 5 mg/m³ was identified by the European Commission, where observed effects in the nasal olfactory epithelium included local effects with signs of proliferative repair; a NOAEC could not be identified (EURAR 2003).

Confidence in the toxicological database is considered to be moderate to high, as a number of studies exist for acute, short-term and chronic durations, via inhalation, dermal and oral routes.

Characterization of Risk to Human Health

Based principally on the weight of evidence-based assessments of several international and national agencies (IARC 2002; EURAR 2003; US EPA 1998; NTP 2004), a critical effect for characterization of risk to human health is carcinogenicity. Although a mode of action for induction of tumours has not been fully elucidated, it cannot be precluded that the tumours observed involved direct interaction with genetic material.

With respect to non-cancer effects, the lowest identified concentrations at which effects were observed in animals were 5 mg/m³, in a 4-week inhalation study with rats (Huntingdon Research Centre 1993b) and 10 mg/m³, in a 13-week inhalation study with rats (Huntingdon Research Centre 1993a). These effect concentrations are 32 to 63 times higher, respectively, than the upper-bounding concentration of naphthalene in indoor air (158.05 µg/m³) in Canada (Health Canada 2008). Comparison of the same effect levels to the 90th percentile concentrations measured in indoor air (9.405 µg/m³ – Health Canada 2008) result in margins of exposure of 532 to 1063. These margins may not be adequate to account for uncertainties in the database on exposure and effects. For example, the indoor air survey (Health Canada, 2008) was conducted in non-smoking homes and smoking households may potentially have higher indoor air concentrations of naphthalene. Additionally, dermal exposure from use of consumer products could contribute to exposure to the general population.

Uncertainties in Evaluation of Risk to Human Health

There were uncertainties in the assumptions used in the estimates of exposure from the use of consumer products. Estimates were, however, considered to be conservative. Estimates of intake did not address potential intake from breast milk, in which naphthalene has been detected, but not quantified (Pellizzari et al. 1982).

The lack of developmental and reproductive studies by the predominant route of exposure in the general population (i.e., inhalation) is a limitation in the effects database. The scope of this screening assessment does not take into account potential interspecies differences in sensitivity to naphthalene. Uncertainty exists regarding the mode of action for tumour induction from exposure to naphthalene. Data suggest nongenotoxic mechanisms may play a role. There is uncertainty regarding the relevance to human health of nasal tumours in rats exposed chronically by inhalation (IARC 2002; EURAR 2003). The scope of this screening assessment does not take into consideration a thorough analysis of the mode of action for tumour induction from exposure to naphthalene or thorough review of individual study design.

Conclusion

Based on the available information, it is concluded that naphthalene is not entering the environment in a quantity or concentration or under conditions that have or may have an immediate or long-term harmful effect on the environment or its biological diversity, or that constitute or may constitute a danger to the environment on which life depends.

On the basis of the carcinogenicity of naphthalene, for which there may be a possibility of harm at any level of exposure, as well as the potential inadequacy of the margin between the upper – bounding concentration of naphthalene in indoor air and the critical effect level for non-cancer effects, it is concluded that naphthalene is a substance that may be entering the environment in a quantity or concentration or under conditions that constitute or may constitute a danger in Canada to human life or health.

It is therefore concluded that naphthalene does not meet the criteria in paragraph 64a and 64b of CEPA 1999, but it does meet the criteria in paragraph 64c of CEPA 1999. Additionally, naphthalene does not meet criteria for persistence and bioaccumulation potential as set out in the *Persistence and Bioaccumulation Regulations*.

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Appendix 1. Upper-bounding estimates of daily intake of naphthalene for the general population in Canada

| Route of exposure | Estimated intake ($\mu\text{g}/\text{kg}\text{-bw}$ per day) of naphthalene by various age groups | | | | | | |
|----------------------------------|--|-----------------|--------------------------|-------------------------|--------------------------|--------------------------|------------------------|
| | 0–6 months ^{1, 2, 3} | | 0.5–4 years ⁴ | 5–11 years ⁵ | 12–19 years ⁶ | 20–59 years ⁷ | 60+ years ⁸ |
| | formula fed | not formula fed | | | | | |
| Ambient air ⁹ | 0.52 | 0.52 | 1.11 | 0.87 | 0.49 | 0.42 | 0.37 |
| Indoor air ¹⁰ | 38.71 | 38.71 | 82.95 | 64.67 | 36.77 | 31.59 | 27.46 |
| Drinking water ¹¹ | 0.14 | 0.05 | 0.06 | 0.05 | 0.03 | 0.03 | 0.03 |
| Food and beverages ¹² | | 1.05 | 1.01 | 0.79 | 0.51 | 0.42 | 0.34 |
| Soil ¹³ | 9.3×10^{-3} | | 3.1×10^{-2} | 2.0×10^{-2} | 9.3×10^{-3} | 9.3×10^{-3} | 9.3×10^{-3} |
| Total intake | 39.37 | 40.33 | 85.13 | 66.37 | 37.81 | 32.46 | 28.19 |

- ¹ Naphthalene was identified, but not quantified, in 6 of 8 samples of breast milk in the United States (Pellizzari et al. 1982).
- ² Assumed to weigh 7.5 kg, to breathe 2.1 m³ of air per day, to drink 0.8 L of water per day (formula fed) or 0.3 L/day (not formula fed) and to ingest 30 mg of soil per day (Health Canada 1998).
- ³ For exclusively formula-fed infants, intake from water is synonymous with intake from food. The highest Canadian concentration of naphthalene in water used to reconstitute formula was based on Williams et al. (1982). Approximately 50% of non formula-fed infants are introduced to solid foods by 4 months of age and 90% by 6 months of age (NHW 1990).
- ⁴ Assumed to weigh 15.5 kg, to breathe 9.3 m³ of air per day, to drink 0.7 L of water per day and to ingest 100 mg of soil per day (Health Canada 1998).
- ⁵ Assumed to weigh 31.0 kg, to breathe 14.5 m³ of air per day, to drink 1.1 L of water per day and to ingest 65 mg of soil per day (Health Canada 1998).
- ⁶ Assumed to weigh 59.4 kg, to breathe 15.8 m³ of air per day, to drink 1.2 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).
- ⁷ Assumed to weigh 70.9 kg, to breathe 16.2 m³ of air per day, to drink 1.5 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).
- ⁸ Assumed to weigh 72.0 kg, to breathe 14.3 m³ of air per day, to drink 1.6 L of water per day and to ingest 30 mg of soil per day (Health Canada 1998).
- ⁹ The highest Canadian concentration of naphthalene measured in outdoor air from a large survey was in Winnipeg, Manitoba, at 14.8 $\mu\text{g}/\text{m}^3$, n=443 (Manitoba Government 2007). A higher maximum was obtained from Quebec; however the sample size was considerably smaller. A higher value from a study in the U.S. was not used, as Canadian data were available. Canadians are assumed to spend 3 hours outdoors each day (Health Canada 1998). This concentration was within the range of concentrations reported in a NAPS survey of outdoor air in Canada (NAPS 2003/04/05) and other studies, e.g., Ontario's Ministry of the Environment. The critical data were identified in a data set of studies of ambient air: Dann (2002); Otson et al. (1998); Otson and Zhu (1996); Tremblay and Dann (1995); Ng and Karellas (1994); Bell et al. (1991); Hoff and Chan (1987); Otson and Benoit (1986); NAPS (2003, 2004, 2005); Canada (1993); Health Canada (2008); OMOE (2000a,b,c, 2002a,b, 2003, 2004a); Chuang et al. (1991); Zhu et al. (2005); Manitoba Conservation Authority (2006); Alberta Environment (2005); Austin et al. (2001); Stroscher (1982); Lesage et al. (1987, cited in EURAR 2003).
- ¹⁰ The maximum concentration of naphthalene of 158.05 $\mu\text{g}/\text{m}^3$ (range: 0.001–158.05 $\mu\text{g}/\text{m}^3$; arithmetic means ranging from 1.002 to 6.778 $\mu\text{g}/\text{m}^3$ depending upon year and season of sampling) in a recent indoor air survey in Windsor, Canada, based on sampling over 2 years, and 2 seasons, in 48 homes, was used to derive intake (Health Canada 2008). This value was very similar to the maximum value of 144.44 (arithmetic mean of 3.8 $\mu\text{g}/\text{m}^3$) in another indoor air survey in Ottawa, Canada (Zhu et al. 2005). These values are lower than the maximum value of 398.70 $\mu\text{g}/\text{m}^3$ reported by Fellin et al. (1992), but are considered more representative of current exposures and the analytical methodology was more robust. Canadians are assumed to spend 21 hours indoors each day (Health Canada 1998). The critical data were identified from a data set of

studies of indoor air: Otson et al. (1994, 1998); Otson and Zhu (1996); Bell et al. (1991); Fellin et al. (1992); Otson and Benoit (1986); Health Canada (2008); Chuang et al. (1991); Zhu et al. (2005).

¹¹ The maximum Canadian concentration value ($\mu\text{g/L}$) of naphthalene in drinking water was 1.3 $\mu\text{g/L}$ for 12 Great Lakes municipalities (Williams et al. 1982). This concentration falls within the range of other studies conducted on bottled water in Canada and extensive U.S. surveys. The critical data were identified in a data set of studies of drinking water: City of Toronto (1990, 2002a,b,c,d, 2003a,b); Otson et al. (1982); LeBel et al. (1987); EURAR (2003); Williams et al. (1982); Benoit et al. (1979); Laroche (2004, 2005); EPCOR (2005); Greater Vancouver Regional District (2002); City of Calgary (2003).

¹² Estimates of intake from food are based upon concentrations in foods that are selected to represent the twelve food groups addressed in calculating intake (Health Canada 1998). Amounts of foods consumed on a daily basis by each age group are described by Health Canada (Health Canada 1998):

Dairy products: a maximum concentration of 0.25 $\mu\text{g/ml}$ in dairy products was reported by the US EPA (2003). This converts to 0.24 $\mu\text{g/kg}$ using a milk density of 1036.86 kg/m^3 at 20°C. This is the only reported level in milk.

Fats: no data were identified for the general population. A mean ($n=8$) concentration of 23.5 ng/g was reported for blubber from harp seals (Zitko et al. 1998); this would result in an intake of < 0.01 $\mu\text{g/kg-bw}$ per day. [Based on mean body weight of 62 kg and 1:1 sex ratio (NHW 1980). Adult consumes 24.3 g blubber/person/day, based on a study of Inuit food harvest and consumption on an isolated island community on the east coast of Baffin Island, NWT in 1987–1988 (Kinloch et al. 1992; Kuhnlein 1989); 24-hour recall of food consumption was examined by interview every two months during 1987–1988, for a total of 7 surveys.]

Fruits and fruit products: no data identified.

Vegetables: a maximum concentration of 63 $\mu\text{g/kg}$ naphthalene in vegetables (endive, $n=3$) was reported from Kipopoulou et al. (1999) cited in US EPA (2003). Several levels in other vegetable produce were available, e.g., carrots, cabbage, leeks, lettuce.

Cereal products: the maximum concentration of naphthalene in cereal products, in this case rice, was 28 $\mu\text{g/kg}$, as reported by the US EPA (2003). This was the only cereal level identified.

Meat and poultry: the maximum concentration of naphthalene in meat and poultry was 26 $\mu\text{g/kg}$ for beef or fried chicken (Johnston et al. 1994). Other levels were reported for a number of other meat products. These were the only levels in meat products that were identified.

Fish: a maximum naphthalene concentration of 1.7 $\mu\text{g/kg}$ was reported in fish (Gabos et al. 1998). No other levels were identified.

Eggs: no data were identified.

Foods, primarily sugar: no data were identified.

Mixed dishes: no data were identified.

Nuts and seeds: no data were identified.

Beverages (soft drinks/alcohol/coffee/tea): no data were identified.

The critical data were identified in a data set of studies of foods: Gabos et al. (1998); ETL (1991, 1992); US EPA (2003); Kipopoulou et al. (1999); Johnston et al. (1994); Snyder et al. (1996); EURAR (2003); Zitko et al. (1998).

¹³ The maximum Canadian concentration of naphthalene in soil from a non-point source was reported as 310 ng/g (OMOE 1994) as a typical upper bound for Ontario soil levels. This level falls within the range identified by other studies including a study by Dillon Consulting Ltd. (2006) and others. The critical data were identified in a data set of studies of soil, sediment and sludge: Gizyn (1994); OMOE (1994); Webber (1994); OMOE (2000a,c, 2002b, 2004b); Chuang et al. (1995, 1999); Golder Associates (1990a,b); Roper et al. (2006); Canada (1993); NWP (1980); AEAB (2002); Chen et al. (1999); McCarthy et al. (1997); Balch et al. (1995); Dickman et al. (1992); Dillon Consulting Ltd. (2006); Western Canadian Coal (2005); Alberta Environment (2006); Nova Scotia Power Inc. (2003); MESL (2006); Webber and Bedford (1996); Webber and Nichols (1995); Webber (1994); Harrison et al. (2006); Bright and Healey (2003).

Appendix 2. Summary of health effects information for naphthalene

| Endpoint | Lowest effect levels ¹ /Results |
|-----------------------------------|---|
| Acute toxicity | <p>Lowest inhalation LC₅₀ > 340 mg/m³ (RTECS 2006) [Additional studies: None identified in ATSDR 2005; EURAR 2003; IARC 2002] Lowest inhalation LO(A)EC = 7.86 mg/m³; nasal olfactory epithelium injury in male NIH Swiss mice; No NO(A)EC (Phimister et al. 2004). [Additional Studies: West et al. 2001; Lee et al. 2004, 2005]</p> <p>Lowest oral LD₅₀ = 316 mg/kg in rats (RTECS 2006) [Additional studies: Gaines 1969 (oral rat); Papciak and Mallory 1990 (oral rat); Shopp et al. 1984 (oral mouse)] Lowest oral LOEL = 1000 mg/kg in rats for respiratory effects (lung lesions) and gastrointestinal effects (stomach lesions); identified by the ATSDR (2005) as a LOAEL (Papciak and Mallory 1990). [Additional studies: Zuelzer and Apt 1949 (oral dog); Vuchetich et al. 1996 (oral rat)]</p> <p>Lowest dermal LD₅₀ > 2000 mg/kg in rabbits (Landis International 1995) Lowest dermal LOEL = 125 mg/kg for reversible erythema in rabbits; single dose study (identified as LOAEL in ATSDR; no NOAEL) (PRI 1985a) [Additional studies: Gaines 1969; Reprotox 1980a,b; Okada et al. 1985; Papciak and Mallory 1990]</p> |
| Short-term repeated-dose toxicity | <p>Lowest inhalation LOAEC = 5 mg/m³ (1 ppm); local effects with signs of proliferative repair in nasal olfactory epithelium of male and female rats. Animals dosed at 370 mg/m³ (71 ppm), the highest dose level, were reported by the European Commission (EURAR 2003) to have a 50% reduction in body weight associated with reduced food consumption. No no-observed-adverse-effect level (NOAEL) was identified, as the lowest-observed-adverse-effect level (LOAEC) identified by the European Commission was at the lowest exposure level tested (Huntingdon Research Centre 1993b; unpublished study). [Additional studies: NO(A)EC = 157.2 mg/m³ (30 ppm); 14-day exposure; identified by ATSDR (2005) for hematologic effects in mice (NTP 1992a)]</p> <p>Lowest oral LOEL = 50 mg/kg/day for neurological effects in a developmental toxicity study; Sprague-Dawley rats; maternal effects: slow respiration, lethargy, apnea, inability to move at lowest dose tested; no NOEL as maternal LOEL was at lowest exposure level tested; identified as LOAEL by ATSDR (2005); body weight effects and fetotoxicity identified at higher exposure levels (NTP 1991). [Additional studies: Srivastava and Nath 1969; Rao and Pandya 1981; Yamauchi et al. 1986; Kojima 1992; Plasterer et al. 1985; van Heyningen 1970; van Heyningen and Pirie 1967; Shopp et al. 1984; Rossa and Pau 1988; Germansky and Jamall 1988; Murano et al. 1993; Xu et al. 1992; Rathbun et al. 1990; Orzalesi et al. 1994; Holmen et al. 1999; Lakritz et al. 1996; Zuelzer and Apt 1949; van Heyningen and Pirie 1976; Cataracts were observed in experimental animals at oral exposure levels above the LOAEL (approx. 500–2000 mg/kg/day in rabbits and rats)]</p> <p>Lowest dermal LOEL = N/A NOAEL = 1000 mg/kg in guinea pig (PRI 1985b) [Additional studies: Frantz et al. 1986; Papciak and Mallory 1990]</p> |
| Subchronic toxicity | <p>Lowest inhalation LOEC = 10 mg/m³ (2 ppm); damage to nasal epithelium of rats (mild</p> |

| Endpoint | Lowest effect levels ¹ /Results |
|---------------------------------------|--|
| | <p>atrophy, rosette formation in olfactory epithelium, loss of Bowman’s glands, minimal hyperplasia; no NOAEC as LOEC was the lowest exposure level of the study (Huntingdon Research Centre 1993a; unpublished study). [Additional studies: 6-month carcinogenicity screening assay in mice exposed to up to 30 ppm (Adkins et al. 1986)]</p> <p>Lowest oral LOEL = 133 mg/kg/day for decreased absolute brain, liver and spleen weights; male and female CD-1 mice exposed by gavage for 90 days; NOAEL = 53 mg/kg/day, LOAEL = 133 mg/kg/day identified by ATSDR (2005); NOAEL = 133 mg/kg/day identified by the European Commission (EURAR 2003) (Shopp et al. 1984). [Additional studies: Tao et al. 1991; NTP 1980a,b]</p> <p>Lowest dermal LOEL = 1000 mg/kg/day in rats for dermal effects; NOAEL = 300 mg/kg/day, LOAEL = 1000 mg/kg/day identified by ATSDR (2005); NOAEL = 1000 mg/kg/day by the European Commission (EURAR 2003) (Frantz et al. 1986) [Additional studies: N/A]</p> |
| Developmental / reproductive toxicity | <p>No studies specifically designed to investigate developmental and/or reproductive toxicity by inhalation exposure were identified.</p> <p>Lowest oral LOEL = 150 mg/kg/day in rats identified by ATSDR (2005) for developmental effects (decreased maternal weight gain > 20%) without fetotoxic or teratogenic effects; IARC (2002) notes decreased fetal body weight and increased percentage of adversely affected implants per litter as significant trends, as well as an increased percentage (non-significant) of malformed fetuses per litter in next highest level, 450 mg/kg/day group; European Commission (EURAR 2003) states that this “study provides some evidence of fetotoxicity occurring at maternally toxic doses with no fetotoxicity occurring at doses which were not maternally toxic”; US EPA (1998) identifies a fetal NOAEL = 450 mg/kg (NTP 1991) [Study also utilized for LOAEL for short-term toxicity (maternal toxicity)].</p> <p>[Additional Studies: oral LOEL = 200 mg/kg/day in rabbits identified by ATSDR (2005) for developmental effects in pregnant females described as: “maternal dyspnea, cyanosis, body drop, hypoactivity with no pathological aberrations”; European Commission (EURAR 2003) notes no developmental effects observed (PRI 1986); LOEL = 300 mg/kg/day in mice; identified by ATSDR (2005) for reproductive effects (> 10% maternal mortality); IARC (2002) noted that the average number of live offspring per litter was decreased; IARC (2002) suggests early embryonic absorption (Plasterer et al. 1985). [Additional studies: NOAEL = 120 mg/kg/day in rabbits; highest dose tested (NTP 1992b)]</p> |
| Chronic toxicity/ carcinogenicity | <p>Non-neoplastic endpoints: Lowest inhalation LO(A)EC = 52.4 mg/m³ (10 ppm); non-neoplastic lesions in both rats and mice. Mice: dose-response-related increase in alveolar/bronchiolar inflammation, nasal epithelium inflammation, olfactory epithelium metaplasia, respiratory epithelium hyperplasia; no NOAEC as LO(A)EC is lowest exposure level tested in the study (NTP 1992a). Rats: significant increase in nasal lesions in both sexes (atypical hyperplasia, atrophy,</p> |

| Endpoint | Lowest effect levels ¹ /Results |
|--|--|
| | <p>chronic inflammation, hyaline degeneration of the olfactory epithelium, hyperplasia, squamous metaplasia, hyaline degeneration, goblet cell hyperplasia, glandular hyperplasia of the respiratory epithelium); no NOAEC as LO(A)EC is lowest exposure level tested in the study (NTP 2000).</p> <p>Oral NO(A)EL = 41 mg/kg/day; rat exposed in feed to 10–20 mg/day, 6 days/week for 100 weeks; body weight of rats assumed to be 200 g (EURAR 2003); no tumours observed; IARC (2002) notes small group sizes, incomplete reporting of study (Schmähl 1955).</p> <p>Neoplastic endpoints: B6C3F1 mice: 0, 52 or 157 mg/m³ (0, 10 or 30 ppm); 6 hours/day, 5 days/week for 104 weeks; significant increase in incidence of alveolar/bronchiolar adenoma in 30 ppm female mice [5/69 (7%), 2/65 (3%), 28/135 (21%) at 0, 52 and 157 mg/m³, respectively] (NTP 1992a).</p> <p>F344/N rats: 0, 52, 157, 314 mg/m³ (0, 10, 30, 60 ppm); 6 hours/day, 5 days/week for 105 weeks; significant increase in incidence of nasal olfactory neuroblastoma in males and females; rare tumour type, not observed in historical controls [0/49, 0/49, 4/48 (p=0.056), 3/48 in male rats and 0/49, 2/49, 3/49, 12/49 (p=001) in female rats at 0, 52, 157 and 314 mg/m³ respectively]; significant incidence of adenoma of the respiratory epithelium of male and female rats [0/49, 6/49 (p=0.013), 8/48 (p=0.003), 15/48 (p<0.001) in male rats and 0/49, 0/49, 4/49 (p=0.053), 2/49 in female rats at 0, 52, 157, and 314 mg/m³ respectively] (NTP 2000).</p> <p>[Additional studies: A/J mice; inhalation, up to 30 ppm for 6 months; significant increase in number of adenomas per tumour-bearing mouse, but not adenomas per mouse (Adkins et al. 1986)]</p> |
| Genotoxicity and related endpoints: <i>in vivo</i> | <p>Micronuclei test: Negative: bone marrow erythrocyte, male ICR Swiss mouse, single oral exposure (Harper et al. 1984) [IARC LED or HID = 500 mg/kg-bw/day]; bone marrow, CD-1 mice, single intraperitoneal injection [250 mg/kg] (Sorg et al. 1985).</p> <p>Unscheduled DNA synthesis: Negative: liver, rat, oral exposure [0, 600, 1000, 1600 mg/kg] (RTC 1999).</p> <p>DNA damage: Negative: liver, rat, oral exposure [359 mg/kg] (Kitchin et al. 1992).</p> <p>DNA fragmentation Positive: liver and brain tissue, female C57BL/6NTac mouse; single oral exposure (Bagchi et al. 2000) [LED (liver) = 220 mg/kg-bw/day]; liver and brain tissue, female C57BL/6TSG-p53 mouse, single oral exposure (Bagchi et al. 2000) [LED (liver) = 22 mg/kg-bw/day]; liver and brain tissue, female Sprague-Dawley rat; 30 oral exposures (Bagchi et al. 1998b) [LED or HID = 110 mg/kg-bw/day]</p> <p>Adduct formation to proteins: Positive: CFW and B6C3F1 mouse liver, lung, kidney, brain tissue and blood cells;</p> |

| Endpoint | Lowest effect levels ¹ /Results |
|---|---|
| | <p>adduct formation to haemoglobin, albumin, other proteins; single intraperitoneal injection (Cho et al. 1994b; Tsuruda et al. 1995). Negative: mouse; protein adduct formation; inhalation (Phimister et al. 2004)</p> <p>Neoplastic transformation: Negative: rat; oral (gavage in corn oil) (Tsuda et al. 1980) [oral; 100 mg/kg; gamma-glutamyl transpeptidase foci]</p> <p>Non-mammalian wing spot test: Positive: <i>Drosophila melanogaster</i>; larval feed [IARC LED or HED = 640 mg/kg bw/day] (Delgado-Rodriguez et al. 1995)</p> <p>Non-mammalian micronucleus formation: Weak positive: newt larvae (<i>Pleurodeles waltl</i>) erythrocytes; naphthalene administered in tank water (Djomo et al. 1995)</p> |
| Genotoxicity and related endpoints: <i>in vitro</i> | <p>Mutagenicity: Negative: <i>Salmonella typhimurium</i> TA97, TA98, TA100, TA1535, TA1537, TA2637, UHT8413, UHT8414 with and without activation (Mortelmans et al. 1986; Sakai et al. 1985; Nohmi et al. 1985; Connor et al. 1985; Florin et al. 1980; NTP 1992a; Godek et al. 1985); <i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537, TA1538, TM677 with activation (McCann et al. 1975; Narbonne et al. 1987; Ho et al. 1981; Gatehouse 1980; Seixas et al. 1982; Kaden et al. 1979; Bos et al. 1988; Epler et al. 1979; Purchase et al. 1978)</p> <p>Negative: mutation at TK and HPRT loci; human MCL-5B-lymphoblastoid cells (Sasaki et al. 1997)</p> <p>Negative: <i>E. coli</i> K12 <i>envA</i>⁻ <i>uvrB</i>⁻, GY5027 <i>envA</i>⁻ <i>uvrB</i>⁻, GY40451 <i>amp</i>^R; prophage induction with activation (Ho and Ho 1981; Mamber et al. 1984)</p> <p>Negative: <i>E. coli</i> PQ37 (chromotest), SOS induction without activation (Mersch-Sundermann et al. 1993)</p> <p>Negative: <i>S. typhimurium</i> TA1535/pSK1002 (<i>umu</i> gene expression – SOS inducing activity) with and without activation (Nakamura et al. 1987)</p> <p>Negative: <i>E. coli</i> WP2/WP100 <i>uvrA</i>⁻ <i>recA</i>⁻ with activation (Mamber et al. 1984)</p> <p>Micronucleus formation: Positive: human MCL-5B-lymphoblastoid cells, without activation (Sasaki et al. 1997)</p> <p>Chromosomal aberrations: Positive: Chinese hamster ovary cells; with activation (Galloway et al. 1987; NTP 2000; NTP 1992a); preimplantation mouse embryo with and without activation (Gollahon et al. 1990) Negative: Chinese hamster ovary cells, without activation (Galloway et al. 1987; NTP 2000)</p> <p>Sister chromatid exchange:</p> |

| Endpoint | Lowest effect levels ¹ /Results |
|----------|--|
| | <p>Positive: Chinese hamster ovary cells, with and without activation (Galloway et al. 1987; NTP 2000; NTP 1992a) Negative: human lymphocytes, with and without activation (Tingle et al. 1993; Wilson et al. 1995)</p> <p>DNA strand breaks: Negative: alkaline elution; rat hepatocytes (Sina et al. 1983)</p> <p>Unscheduled DNA synthesis Negative: rat hepatocytes (Barfknecht et al. 1985)</p> <p>Protein adduct formation Positive: monkey lung without activation (Lin et al. 2006); mouse liver microsomes (Isbell et al. 2005)</p> <p>DNA fragmentation Positive: macrophage J774A.1 cells, without activation (Bagchi et al. 1998a)</p> <p>Cell transformation assay Negative: RLV-infected Fischer rat embryo cell; without activation (Freeman et al. 1973); BALB/3T3 cells, without activation (Rundell et al. 1983)</p> <p>T1 assay: Positive: bovine papillomavirus DNA-carrying C3H/10T1/2 cell line (T1) (Kowalski et al. 2001) [similar to Syrian hamster embryo test; identified in RTECS 2006]</p> |

¹ LD₅₀ = median lethal dose; LC₅₀ = median lethal concentration; LO(A)EL = Lowest-observed -(adverse)-effect level; LO(A)EC = Lowest-observed-(adverse)-effect concentration; NO(A)EL = No-observed-(adverse)-effect level; NO(A)EC = No-observed-(adverse)-effect concentration; LED = Lowest effective dose; HID = Highest ineffective dose

Appendix 3. Overview of reported human health effects of naphthalene

The European Commission (EURAR 2003) reported that there were no epidemiological studies on the human health effects of naphthalene, and the only human information available derives from a limited number of early case reports that provide no quantitative data on the levels or duration of exposure. Effects observed in humans after acute exposure to naphthalene are haemolytic anaemia and cataract formation. Most human toxicity is described by the International Agency for Research on Cancer (IARC 2002) as being of an accidental or suicidal nature, resulting from inhalation of fumes containing naphthalene or ingestion of mothballs. The European Commission also notes that exposure to naphthalene vapour may also result in dermal exposure (EURAR 2003). Some of these cases of haemolytic anaemia involved babies exposed to naphthalene through diapers, clothing and blankets treated with mothballs (Anziulewicz et al. 1959; Valaes et al. 1963). Additional case reports have been presented involving human transplacental exposure of the fetus after maternal ingestion of naphthalene, resulting in haemolytic anemia of the infant (Anziulewicz et al. 1959; Zinkham and Childs 1957, 1958). Within the human population, a subset of people may have increased susceptibility to the anaemic effects of naphthalene, due to a genetically inherited deficiency in an enzyme of the red blood cell, glucose-6-phosphate dehydrogenase (IARC 2002).