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Mobile-Source Air Toxics: A Critical Review of the Literature on Exposure and Health Effects

Naphthalene

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Naphthalene

INTRODUCTION

Naphthalene (CAS Registry Number 91-20-3; $C_{10}H_8$; molecular weight = 128) (Figure 19), also known as tar camphor, is a slightly water-soluble, two-ring aromatic hydrocarbon. A white, crystalline solid that readily changes from a solid to a gas at room temperature, it is used in moth repellents, lavatory scent discs, and soil fumigants and as a starting material in the manufacture of other organic compounds. Naphthalene is also found in light petroleum fractions and in residues from refineries. It is the most volatile member of the polycyclic aromatic hydrocarbons (PAHs), and inhalation is the principal pathway of exposure (Preuss et al. 2003).

BENCHMARK LITERATURE

The following evaluation of research literature on naphthalene is based on data and source tables listed in Appendices B–D (available on the HEI Web site) of this report. Additional information was obtained from reviews by the Agency for Toxic Substances and Disease Registry (ATSDR 2005e), the European Union Risk Assessment Report (European Chemicals Bureau 2003), the International Agency for Research on Cancer (IARC 2002), the National Toxicology Program (NTP 2005), the California Environmental Protection Agency (California EPA 2004), the EPA (1998d, 2000f; 2004c), the World Health Organization (WHO 2000b), and selected key articles.

EXPOSURE

SOURCES AND EMISSIONS

A thorough review of the sources of, and potential exposures of humans to, naphthalene is given in a toxicologic profile of the compound published by the ATSDR (2005e) and in a study by Preuss and colleagues (2003). Sources of airborne naphthalene include various industrial, domestic, mobile-combustion, and natural processes. Naphthalene is widely used in industry and is a traditional constituent of mothballs. It is a product of incomplete combustion from a variety of sources, including industrial plants, residential heating with fossil fuels, motor vehicles, air traffic, and forest fires. Naphthalene is a constituent of gasoline as well as diesel and jet fuels. Motor vehicles contribute to naphthalene emissions by way of incomplete combustion and evaporation from liquid fuel. Other important sources of exposure are tobacco smoke and the numerous consumer products that contain naphthalene.

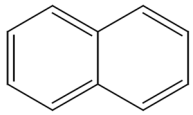

Figure 19. Structure of naphthalene.

The National Air Toxics Assessment (NATA) estimates indicate that on-road mobile-source emissions are responsible for approximately 20% of total naphthalene air emissions, with similar contributions in urban and rural areas. Non-road mobile-source emissions are estimated to contribute 6 to 7% of emissions (EPA 2006b). As with other PAHs, residential wood smoke is a major source of naphthalene emissions in areas with substantial wood-stove or fireplace use. Lu and colleagues (2005) reported data from Southern California showing that naphthalene concentrations were higher at urban sites with traffic sources nearby and that diurnal concentration patterns coincided with traffic patterns.

Naphthalene has been shown to react readily in the atmosphere with oxidant gases, such as nitrogen oxides and hydroxyl radicals (Reisen and Arey 2005). Concentrations of nitronaphthalenes, for example, can exceed those of naphthalene. The relative proportion of derivatives to the parent compound can vary depending on meteorology and the location of the mobile sources.

AMBIENT, OUTDOOR, AND INDOOR CONCENTRATIONS AND PERSONAL EXPOSURES

Ambient Air

The general public is exposed to naphthalene through inhalation of ambient and indoor air. Typical air concentrations for naphthalene are low—i.e., 1 $\mu g/m^3$ or less. The average daily intake of naphthalene from ambient air can

A glossary of terms appears on page 17; a list of abbreviations and other terms appears at the end of this report.

be estimated to be approximately 20 µg, based on a naphthalene concentration of 1 µg/m^3 in urban and suburban air and an inhalation rate of 20 m^3/day. Exposure has been estimated to range from 65 ng/kg body weight/day at the regional level to 0.25 mg/kg body weight/day at the local level in areas where naphthalene is emitted (for example, from releases associated with the manufacture of grinding wheels and mothballs) (European Chemicals Bureau 2003).

In the U.S., the NATA (EPA 2006b) estimated a national mean ambient naphthalene concentration of 0.07 µg/m^3. Estimated concentrations in urban areas (0.08 µg/m^3) were roughly four times higher than in rural areas (0.02 µg/m^3). Measured mean concentrations in urban and suburban areas agree well with these modeled estimates, with an overall mean of 0.08 µg/m^3 and individual-site means ranging from 0.01 to 0.4 µg/m^3 (EPA 2006b). Measurements in Southern California indicated slightly higher naphthalene concentrations (with site means ranging from 0.07 to 0.6 µg/m^3), while some measurements collected at urban sites in Arizona were even higher (with site means ranging from 0.01 to 0.9 µg/m^3 and individual measures as high as 2 µg/m^3 during episodes of summer photochemical air pollution) (Zielinska et al. 1998; Eiguren-Fernandez et al. 2004). Although summer episodes are associated with the highest concentrations, winter conditions (e.g., wood burning and surface inversions) can also result in high ambient concentrations. The measurements do not indicate strong seasonal variation in concentrations (Eiguren-Fernandez et al. 2004). Short-term urban in-vehicle concentrations (3- to 4-hour samples) as high as 3.8 µg/m^3 were measured in Detroit, but no concurrent fixed-site measurements were available for comparison (Batterman et al. 2002). Naphthalene is by far the most abundant vapor-phase PAH typically measured in ambient air, contributing, for example, 91% of the total (particle + vapor) PAH mass in measurements in Southern California (Eiguren-Fernandez et al. 2004).

Naphthalene can be converted in the atmosphere to naphthaquinones, a group of reaction products that are potent generators of reactive oxygen species and that are currently being investigated for their toxicity (Lu et al. 2005). Quinones and hydroquinones are described in more detail in the polycyclic organic matter (POM) section of this report.

Indoor Air

Although no recent studies of indoor naphthalene concentrations were found, studies from the early 1990s typically reported that average indoor air concentrations were less than 5 µg/m^3 (Lu et al. 2005) and that indoor concentrations were 5 to 10 times higher than those measured outdoors. Major indoor sources are tobacco smoke and moth repellents. It is likely that indoor concentrations have decreased in recent years because indoor smoking and the use of naphthalene in pesticides and mothballs have decreased (California EPA 2004).*

Personal Exposures

Consumers can be exposed to naphthalene through the use of moth repellents and tar shampoos and soaps as well as when damp-proofing homes. The European Union (European Chemicals Bureau 2003) estimated that the total daily intake from these exposures was 54.3 mg (0.77 mg/kg body weight/day). Infants, in particular, might have significant exposures to textiles (e.g., clothing and bedding) that have been in contact with naphthalene mothballs.

Although no personal-monitoring studies of naphthalene in the general community (non-workplace) were found, application of the regional human exposure (REHEX) model to Southern California indicated that indoor sources accounted for 40% of naphthalene exposure, in-vehicle exposure accounted for 4%, and environmental tobacco smoke accounted for 1 to 5%, depending on the season (Lu et al. 2005). Emissions estimates for California indicated that gasoline evaporation and engine exhaust accounted for 44% of total naphthalene emissions into ambient air; diesel exhaust was estimated to contribute another 9% of the total (Lu et al. 2005). Other major emissions sources, including asphalt and a large number of consumer products, contributed 15% of emissions.

AMBIENT CONCENTRATIONS IN OTHER COUNTRIES

Average ambient and indoor concentrations of naphthalene measured in several other countries are generally in the same range as those reported in the U.S. (reviewed in IARC 2002).

TOXICOLOGY

BIOCHEMISTRY AND METABOLISM

The metabolism of naphthalene and its respiratory toxicity have been studied extensively and reviewed (Buckpitt et al. 2002; Stohs et al. 2002) (Figure 20). The toxicity of naphthalene results from its reactive metabolites. The first step, oxidation via cytochrome P450 monooxygenases, produces an unstable 1,2-epoxide that can convert nonenzymatically to 1-naphthol. The epoxide can also be

* Naphthalene was not included in the survey of indoor exposures and is thus not listed in the indoor exposure table in Appendix D.

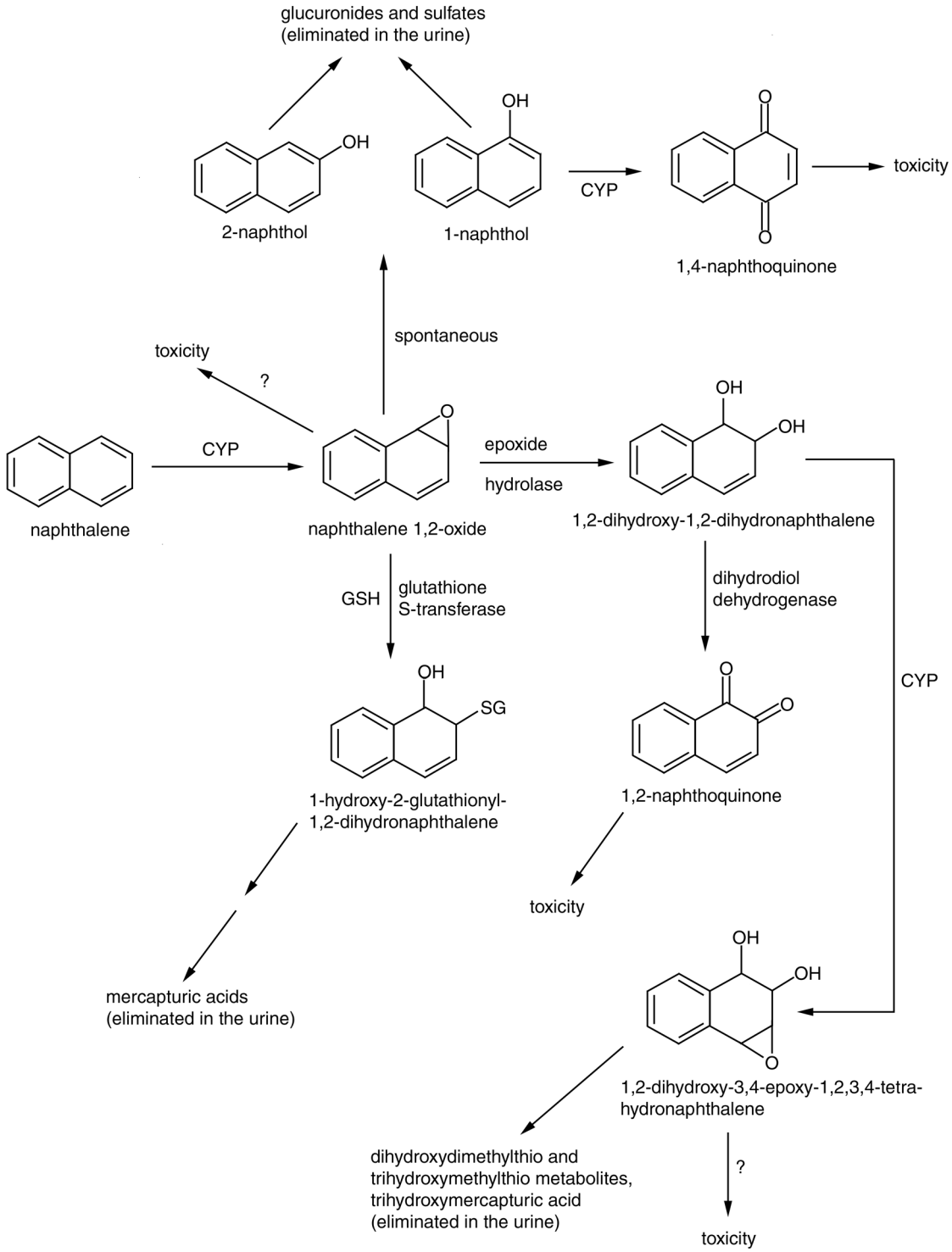

Figure 20. Metabolic pathway of naphthalene. CYP = cytochrome P450 enzymes; GSH = glutathione; SG = from glutathione. (From Agency for Toxic Substances and Disease Registry 2005e.)

converted via microsomal epoxide hydrolase to naphthalene dihydrodiol, via cytochrome P450 enzymes to naphthalene diepoxides, or via glutathione S-transferase to glutathione conjugates. The naphthol and the diol compounds can be further oxidized to form quinones, which, along with the epoxides, represent reactive toxic metabolites that can bind to macromolecules. Mice are the most sensitive (of the species tested) to the toxicity of inhaled naphthalene. They are also the most efficient at naphthalene oxidation. Humans and nonhuman primates are among the least efficient. Maximal rates of naphthalene metabolism measured in human lung microsomes are about 10 to 100 times lower than those in mice. These data suggest that the respiratory tract of humans is likely to be much less sensitive than that of mice to the toxicity of inhaled naphthalene (Figure 20).

In cellular systems from mice and rats, the enzyme CYP2F2 metabolizes naphthalene to 1R,2S-naphthalene oxide, which rearranges to 1-naphthol and forms the 1,2-dihydrodiol via epoxide hydrolase. Oxidation of 1-naphthol leads to 1,2- and 1,4-naphthoquinone. In nonciliated bronchiolar epithelial cells (Clara cells) isolated from the lungs of naphthalene-treated mice, covalent binding of 1,2-naphthoquinone to protein was reported. Treatment with the glutathione depletor diethylmaleate before naphthalene exposure decreased water-soluble naphthalene-metabolite formation by 48% yet increased naphthalene–protein adducts by 193% (Phimister et al. 2004). Recent studies (Baldwin et al. 2005) demonstrated a minimal pulmonary CYP2F2 expression in rats, indicating that CYP2F2 expression is the factor most clearly associated with susceptibility to naphthalene-induced pulmonary toxicity and might explain the limited susceptibility of rats.

In mice, glutathione depletion in Clara cells seems to be a determinant of the specific pulmonary toxicity of naphthalene. Plopper and colleagues (2001) have investigated early events in naphthalene-induced acute Clara-cell toxicity. Two hours after intraperitoneal injection of 200 mg/kg body weight naphthalene, they observed the highest glutathione depletion in the most susceptible distal bronchioles. Although severe glutathione depletion can lead to apoptosis and cell proliferation (Rahman et al. 1999), Phimister and colleagues (2005) concluded that, even though glutathione depletion might be responsible for certain aspects of naphthalene toxicity, it was not sufficient to cause cell death without additional stresses. Whereas these disruptive cellular changes seemed to be reversible after recovery of glutathione levels, they persisted after naphthalene exposure. Studies published recently by Lee and colleagues (2005) showed that the olfactory regions of the nasal septum and ethmoturbinates metabolize naphthalene at higher rates than the non-olfactory mucosa of the nasal septum. The regions of the nasal mucosa with high rates of naphthalene metabolism were the ones injured by inhaled or systemically administered naphthalene.

BIOMARKERS

Mercapturic acid and conjugates of naphthol in the urine have been used as biomarkers to indicate exposure to naphthalene.

NONCANCER HEALTH EFFECTS

Acute Effects

The toxicity of inhaled naphthalene has been shown to be greatest in the nasal cavity and in the Clara cells of the airways. These sites are also the location of high concentrations of cytochrome P450 enzymes, capable of oxidizing naphthalene to its reactive forms, and of the cellular systems with the highest rate of glutathione depletion (see above). Exposure of mice (but not rats) for 4 hours to concentrations as low as 10 mg/m^3 naphthalene resulted in detectable injury to Clara cells. Exposure of mice to the current 8-hour human occupational exposure standard (52 mg/m^3, time-weighted average [TWA]) resulted in substantial injury to epithelial cells in both the upper and lower respiratory tracts. In rats, after repeated exposures to 52 mg/m^3, non-neoplastic lesions were found in the olfactory and respiratory epithelia of the nose.

Interestingly, if naphthalene is administered to mice intraperitoneally, the injury site is still the epithelial cells of the respiratory tract. In mice exposed to cigarette smoke, recovery from naphthalene-induced injury to the bronchiolar epithelium was impaired. Clara cells of neonatal mice were more sensitive than those of adult mice to the cytotoxic effects of naphthalene. In rats and rabbits, repeated oral administration of naphthalene is known to cause cataract formation at doses of 700 mg/kg body weight/day and above.

There was no indication of hemolytic anemia in rodent studies. In isolated mouse Clara cells, 1,4-naphthoquinone and naphthalene 1,2-oxide were more toxic than naphthalene.

Reproductive and Developmental Effects

No studies of the effects of naphthalene exposure on the fertility of animals have been reported. Changes in the reproductive organs have not been detected in repeated-dose studies (including chronic-inhalation studies), and there are no available data on the effects of naphthalene exposure on reproductive function. In rats and rabbits exposed to naphthalene by gavage, signs of toxicity were observed in pregnant females (e.g., decreased body weight and lethargy) but not in fetuses. In mice exposed by

gavage, signs of toxicity were found both in pregnant females (increased mortality and reduced weight gain) and in fetuses (reduced number of live pups per litter).

GENOTOXICITY

The genotoxicity of naphthalene has recently been reviewed (Schreiner 2003).

In Vivo

In rats, inhalation of naphthalene caused oxidative stress and DNA damage in liver and brain tissue. Positive results were obtained for somatic mutations in *Drosophila melanogaster* and micronuclei in salamander-larvae erythrocytes. In mice given oral or intraperitoneal injections of naphthalene, negative results were obtained for micronuclei formation in bone marrow, and there was no induction of DNA single-strand breaks or unscheduled DNA synthesis in hepatocytes.

In Vitro

Naphthalene was not mutagenic in 16 bacterial assays and did not induce unscheduled DNA synthesis. In six cytogenetic assays, clastogenic effects (sister-chromatid exchanges and chromosomal aberrations) were seen in Chinese hamster ovary cells in the presence of metabolic activation. In human peripheral mononuclear leukocytes, the rate of sister-chromatid exchanges did not increase. Naphthalene induced chromosomal aberrations in mouse-embryo cultures and in micronuclei in human MCL-5 cells. It also induced DNA fragmentation in macrophages. Negative results were found in five cell-transformation assays, a gene-mutation assay in MCL-5 cells, three unscheduled-DNA-synthesis tests, and two alkaline-elution assays using primary rat hepatocytes. Because the cytogenetic effects were only seen at cytotoxic concentrations, they were considered to result from cytotoxicity rather than from gene mutations.

1,2-Naphthoquinone was mutagenic in *Salmonella typhimurium* without metabolic activation, formed N^7 adducts with deoxyguanosine, and caused DNA-strand scission in the presence of nicotinic adenine dinucleotide phosphate (NADPH) and copper via reactive oxygen species from an oxidation–reduction cycle. 1,4-Naphthoquinone induced chromosomal aberrations in Chinese hamster ovary and MCL-5 cells. Of other naphthalene metabolites tested, the 1,2-dihydrodiol and 1-naphthol were negative, and naphthoquinone was positive, for inducing sister-chromatid exchanges.

CANCER

Carcinogenicity studies have been completed in mice and rats by the NTP (1992, 2000). In mice, chronic-inhalation exposure to 0, 52, or 160 mg/m^3 naphthalene led to inflammation in the nose, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium, but not neoplasia. In rats, exposure to the same concentrations as well as a 314 mg/m^3 concentration led to a concentration-dependent increase in adenomas of the respiratory epithelium of the nose and neuroblastomas of the olfactory epithelium. Inflammation of the olfactory epithelium was observed at all concentrations. Because neuroblastomas are highly malignant and the cytochrome P450 isozymes that activate naphthalene in the nasal cavity of rodents are also present in humans, these neuroblastomas must be considered highly relevant. No liver tumors were induced by naphthalene in either mice or rats.

There are no adequate animal data available to assess the carcinogenic effects of oral or dermal exposure to naphthalene.

HUMAN HEALTH

BIOMARKERS

Biomarkers of Exposure

In Germany, a pilot study on naphthalene exposure in adults and children concluded that 1-naphthol and 2-naphthol concentrations in urine are accurate biomarkers for naphthalene exposure (Preuss et al. 2004). Naphthols could be detected in more than 90% of the urine samples. Concentrations of naphthols (the sum of 1-naphthol and 2-naphthol) were four times higher in adult smokers (median concentration, 37.6 µg/g creatinine) than in adult nonsmokers (8.2 µg/g creatinine). Compared with adults, children had slightly lower naphthol concentrations in urine (7.5 µg/g creatinine). Preliminary reference values proposed for the naphthols in urine (as means of the 95th percentile) were 41.2 µg/g creatinine (adult nonsmokers) and 23.5 µg/g creatinine (children). Chao and colleagues (2006) investigated the urinary excretion of 1- and 2-naphthol in workers exposed to naphthalene in jet fuel. Post-exposure urinary concentrations of both metabolites increased, although the concentrations of 2-naphthol were higher. The authors concluded that dermal exposure contributed significantly to urinary 2-naphthol concentrations, possibly because of naphthalene metabolism in the skin.

CANCER

Two case studies of cancer in humans exposed to naphthalene were reported. One describes four cases of laryngeal cancer (all in smokers) among workers in a naphthalene-purification plant in East Germany. The other describes 23 cases of colorectal carcinoma in people admitted to a hospital in Nigeria. The NTP (2005) and the IARC (2002) concurred that these studies provided inadequate evidence of naphthalene carcinogenicity in humans.

Naphthalene is metabolized to reactive intermediates. Of the species tested, mice are the most sensitive to inhaled naphthalene, and their metabolism is also the most efficient at naphthalene oxidation. Humans and nonhuman primates are among the least efficient at this oxidation. The data suggested that the respiratory tract of humans is likely to be much less sensitive to naphthalene than that of mice and rats. The higher rate of naphthalene metabolism in mice might lead to cytotoxic metabolites in the lung, causing increased cell turnover and tumors. The genotoxic effects of naphthalene are at present unclear. Although there is little evidence for the induction of gene mutations by naphthalene, there are indications of a clastogenic potential.

NONCANCER HEALTH EFFECTS

In humans, single or repeated exposures to naphthalene can cause severe hemolytic anemia. Hemolysis was observed in infants exposed to clothing and bedding that had been stored with naphthalene mothballs. However, no quantitative information on exposure concentrations was reported in these cases, and hence they cannot be used to establish a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL) for this effect on health.

No information is available on the reproductive or developmental effects of naphthalene exposure in humans. The occurrence of hemolytic anemia in the neonates of anemic, naphthalene-exposed mothers demonstrates that naphthalene or its metabolites can cross the placental barrier. Hemolytic anemia has also been reported in infants born to mothers who "sniffed" or ingested naphthalene (as mothballs) during pregnancy.

REGULATORY SUMMARY

Naphthalene is listed in the NTP's *11th Report on Carcinogens* as "reasonably anticipated to be a human carcinogen" (NTP 2005). The EPA (2004c) has classified it as Group C ("possible human carcinogen") and has assigned it an inhalation unit risk of 0.1 per mg/m^3, based on time-to-tumor modeling and a summed risk for adenomas of the respiratory epithelium and neuroblastomas of the olfactory epithelium in male rats (the most sensitive sex and species in the NTP studies). The equivalent air concentrations for naphthalene, based on 1×10^{-6} and 1×10^{-5} cancer-risk levels, are 0.01 μg/m^3 and 0.1 μg/m^3, respectively (EPA 2004c). At present, the new unit risk factor has not yet been incorporated in the Integrated Risk Information System (IRIS). The California EPA considers naphthalene a toxic air contaminant and a substance that causes cancer. It has calculated a unit risk of 0.034 per mg/m^3 (3.4×10^{-5} per μg/m^3), based on data for the incidence of adenoma of the nasal respiratory epithelium and neuroblastoma of the nasal olfactory epithelium in male rats (California EPA 2004). The IARC has concluded that there is inadequate evidence in humans and sufficient evidence in laboratory animals for the carcinogenicity of naphthalene and has thus classified it as Group 2B ("possibly carcinogenic to humans").

For noncancer effects, the EPA (1998d) set a reference concentration of 3 μg/m^3 (0.67 ppb), based on a LOAEL for hyperplasia in respiratory epithelia and metaplasia in olfactory epithelia of 9.3 mg/m^3 and an uncertainty factor of 3000. The California EPA adopted a chronic inhalation reference exposure level (REL) of 9 μg/m^3, based on an adjusted LOAEL of 9.4 mg/m^3 and an uncertainty factor of 1000 (California EPA 2004, 2005b). This REL was based on respiratory effects (nasal inflammation, hyperplasia of the respiratory epithelium, and metaplasia of the olfactory epithelium) in mice.

SUMMARY AND KEY CONCLUSIONS

EXPOSURE

Mobile sources are important contributors to ambient concentrations of naphthalene. But they are not the principal source of ambient emissions, nor are they major contributors to exposure. In some areas, wood combustion is the predominant source of emissions into ambient air, and environmental tobacco smoke, moth repellents, and other consumer products are major indoor sources. Given reduced exposures to environmental tobacco smoke and moth repellents in recent years, it is possible that ambient concentrations and mobile sources might become more important contributors to exposures than before. However, measurements to assess this possibility are not available at present.

TOXICITY

Animal studies have shown that exposure to naphthalene caused damage to the respiratory tract, including

chronic nasal inflammation, metaplasia of the olfactory epithelium, and hyperplasia of the respiratory epithelium. In mice, naphthalene causes damage to both ciliated and Clara cells of the bronchiolar epithelium. Its toxicity is associated with naphthalene metabolism by cytochrome P450 enzymes, which are concentrated in Clara cells and are present in higher amounts in cells of mice than of rats or humans. Naphthalene is correspondingly more cytotoxic in the respiratory tract of mice than rats. It also depletes the detoxifying tripeptide glutathione.

Genotoxicity tests of naphthalene are generally negative, although naphthalene's quinone metabolites are known to be genotoxic. Chronic exposures induced nasal adenomas and neuroblastomas in rats but not mice. Chronic inflammation in addition to glutathione depletion might be a key factor in the development of tumors in animals. However, the mechanisms of tumor induction are not yet fully understood. It is also not yet possible to characterize the roles of cytotoxicity and genotoxicity in tumor induction.

HUMAN HEALTH

Although there are no epidemiology studies of naphthalene, there are case reports that exposure to high concentrations of naphthalene can induce methemoglobinemia and hemolysis in humans; this is not seen in rodents. There is limited evidence from animal bioassays that naphthalene can cause cancer, but it is not clear how to extrapolate these results to humans. Both the NTP and the IARC concluded that the evidence for naphthalene carcinogenicity in humans is inadequate. Humans might be less sensitive than rodents to toxic and carcinogenic effects of naphthalene because humans are less efficient at naphthalene oxidation.

KEY CONCLUSIONS

1. To what extent are mobile sources an important source of naphthalene?

Mobile sources are important contributors to ambient concentrations of naphthalene but are not the principal source of ambient emissions, nor are they major contributors to exposure.

2. Does naphthalene affect human health?

Naphthalene can cause hemolytic anemia in the neonates of naphthalene-exposed mothers and in infants exposed to bedding or clothing treated with mothballs. Although there is evidence of toxicity in animal studies for both cancer and noncancer effects, humans might be less sensitive than rodents to these effects because humans are less efficient at naphthalene oxidation.

3. Does naphthalene affect human health at environmental concentrations?

In the U.S., the average ambient concentration of naphthalene is 0.08 $\mu g/m^3$. The highest mean concentrations (approximately 0.5 to 1 $\mu g/m^3$) are measured indoors. The highest ambient and indoor concentrations approach the reference concentration for chronic inhalation (29 $\mu g/m^3$), but the mean ambient concentration is one to two orders of magnitude below this benchmark. Thus there is probably no risk of noncancer health effects from environmental exposures. Given the uncertainty about the shape of the dose–response curve at low concentrations in animals and questions about the carcinogenicity of naphthalene in humans, the available evidence is not adequate to determine human cancer risk at this time.

RESEARCH GAPS AND RECOMMENDATIONS

Research recommendations for naphthalene include the following:

- Characterize naphthalene-exposure pathways, patterns of personal exposures to naphthalene and its atmospheric reaction products (including air toxics "hot spots"), and exposures of children and other susceptible populations.
- Undertake additional studies of the toxicokinetics of inhaled naphthalene (including, in particular, studies of the nasal compartments that metabolize naphthalene). Comparative studies of naphthalene's toxicokinetics in various species should also be undertaken in order to help decrease the uncertainty in extrapolating data from animals to humans.
- Undertake studies of the mechanisms of tumor induction by naphthalene and its atmospheric reaction products (e.g., naphthaquinones), including the roles of genotoxicity and cytotoxicity caused by reactive oxygen species.

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