

Naphthalene Inhalation Unit Risk Consultation

February 2017

The following guidance was developed in response to the Minnesota Pollution Control Agency's (MPCA) request that the Minnesota Department of Health (MDH) provide an opinion on the use of an Inhalation Unit Risk Value for naphthalene.

MDH has not derived new health-based values for naphthalene.

Background

Naphthalene is a commonly-occurring, volatile, polycyclic aromatic hydrocarbon, entering the environment from combustion processes, industrial uses, and consumer products (mothballs, cigarette smoke, etc.). Non-cancer air guidance Health-Based Values (HBV) were derived for naphthalene by MDH in 2004 for the acute ($200 \mu\text{g}/\text{m}^3$) and chronic ($9 \mu\text{g}/\text{m}^3$) durations. However, a cancer HBV has not been established. Possible carcinogenic concerns from inhalation of naphthalene have been an ongoing debate within the scientific community for nearly two decades (U. S. Environmental Protection Agency (EPA), 1998). The applicability of rodent respiratory (nasal/lung) tumors for deriving quantitative human health risk values is the critical outstanding issue.

The EPA's Integrated Risk Information System (IRIS) program evaluated naphthalene in 1998, 2004 (never completed), and is currently in the "Draft Development" stage for another update initiated in 2014. No estimate of naphthalene cancer potency, classified as a Group C carcinogen, has been published to date by EPA. EPA has also reviewed naphthalene toxicity for registration as a non-food use pesticide, and did not derive an inhalation unit risk (EPA, 2008). California's Office of Environmental Health Hazard Assessment (OEHHA) reviewed naphthalene in 2005 and updated this assessment in 2011, including an inhalation unit risk value based on nasal tumors occurring in male rats (OEHHA, 2005, 2011). The International Agency for Research on Cancer (IARC) has determined that naphthalene is 'possibly carcinogenic to humans' (Group 2B) based on evidence from animal studies, while noting that inadequate evidence exists for carcinogenicity in humans (IARC, 2002). IARC does not determine quantitative health risk values for any chemical. Finally, the National Toxicology Program (NTP) classifies naphthalene as 'reasonably anticipated to be a human carcinogen' and includes it in the Report on Carcinogens (NTP, 2016).

Naphthalene Inhalation and Cancer - Animal Studies

The NTP has conducted naphthalene inhalation cancer studies in mice and rats (NTP, 1992, 2000). Results from these studies indicated that nasal epithelial adenomas and neuroblastomas were clearly induced in male rats, while female rats also developed only nasal epithelial neuroblastoma. In mice, females developed lung alveolar/bronchiolar adenoma and carcinoma. Along with tumor induction, very high rates of tissue damage (cytotoxicity) were noted in the affected tissues.

The use of these animal studies to derive an inhalation unit risk value has been unsuccessful to date by EPA, noting the stark differences in rodent and human nasal physiology, metabolic capacity, the likely requirement for cyclical high dose cytotoxicity and cellular regeneration, and the applicability of linearity at low doses where cell killing would not occur. EPA's pesticide registration review notes that ongoing efforts to quantify chemical-specific interspecies extrapolation factors support considerably smaller uncertainty factors than default assumptions (EPA, 2008).

Human Epidemiological Studies

Despite the widespread exposure to naphthalene throughout the population both environmentally and residentially, high quality epidemiological investigations of possible health outcomes including cancer have not been conducted. A few case reports have been published where small groups exposed to naphthalene noted increased cancer development in either the larynx or gastrointestinal tract, but these reports are insufficient to demonstrate naphthalene carcinogenicity in humans (ATSDR, 2005 and NTP, 2016).

Recommendation for Inhalation Unit Risk (IUR) use

Emerging data suggest that humans would be significantly less susceptible than rodents based on physiology and enzymatic biotransformation (recently examined in Bailey et al., 2016).

MDH's recommendation at this time is to use the established chronic MDH HBV (9 µg/m³) for naphthalene to assess possible long-term health risks, which is expected to be protective of carcinogenicity, until EPA's IRIS program provides definitive quantitative IUR guidance. The presence of respiratory tract tumors in animals following naphthalene exposure by inhalation is sufficient to demonstrate carcinogenicity in these model systems, but the quantification of human cancer risk at low exposure levels based on these studies is a point of considerable debate. Use of the higher chronic MDH HBV compared to the available inhalation unit risk is considered sufficiently health protective until refinements to the quantitative cancer risk assessment are completed by EPA's IRIS program.

Resources Consulted During Review

Agency for Toxic Substances and Disease Registry (ATSDR). (2005). Toxicological Profile for Naphthalene 1–Methylnaphthalene and 2–Methylnaphthalene.

Bailey, L. A., Nascarella, M. A., Kerper, L. E., & Rhomberg, L. R. (2016). Hypothesis-based weight-of-evidence evaluation and risk assessment for naphthalene carcinogenesis. *Crit Rev Toxicol*,

46(1), 1-42. doi: 10.3109/10408444.2015.1061477

California Environmental Protection Agency - OEHHA. (2005). No Significant Risk Level (NSRL) for the Proposition 65 Carcinogen Naphthalene.

California Environmental Protection Agency - OEHHA. (2011). Technical Support Document for Cancer Potency Factors - Appendix B, Chemical-specific summaries of the information used to derive unit risk and cancer potency values.

International Agency for Research on Cancer (IARC). (2002). *Some traditional herbal medicines some mycotoxins naphthalene and styrene: Section on naphthalene*. In *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Retrieved from IARC Monographs on the Evaluation of Carcinogenic Risks to Humans.

National Toxicology Program (NTP). (1992). *Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91–20–3) in B6C3F1 Mice (Inhalation Studies)*. Retrieved from [Toxicology and Carcinogenesis Studies of Naphthalene \(PDF\) \(https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr410.pdf\)](https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr410.pdf).

National Toxicology Program (NTP). (2000). NTP Technical Report on the Toxicology and Carcinogenesis Studies of Naphthalene (CAS No. 91–20–3) in F344/N Rats (Inhalation Studies). *NTP–TR–500*.

National Toxicology Program (NTP). (2016). *Report on Carcinogens, Fourteenth Edition*. Retrieved from [14th Report on Carcinogens \(https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html\)](https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html).

U. S. Environmental Protection Agency - Office of Prevention, Pesticides and Toxic Substances. (2008). *Naphthalene: Phase 4 Amendment: Response to Comments in Reference to "Naphthalene: HED Chapter for the Reregistration Eligibility Decision Document (RED)"*. Retrieved from [Naphthalene Reregistration \(https://www.regulations.gov/docket?D=EPA-HQ-OPP-2008-0343\)](https://www.regulations.gov/docket?D=EPA-HQ-OPP-2008-0343).

U. S. Environmental Protection Agency. (1998). Toxicological Review of Naphthalene (CAS No. 91-20-3).

Minnesota Department of Health
ESA-EIA
625 Roberts St N
St. Paul, MN 55164
651-201-4899
health.risk@state.mn.us
www.health.state.mn.us

To obtain this information in a different format, call: 651-201-4899. Printed on recycled paper.