UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

April 18, 2008

MEMORANDUM

SUBJECT: **Naphthalene**: Phase 2 Amendment: Response to Registrant Submitted Error Only Comments In Reference to "Naphthalene: HED Chapter for the Reregistration Eligibility Decision Document (RED)"

PC Code: 055801
Decision No.: 374031
Petition No.: N/A
Risk Assessment Type: Single Chemical/No Aggregate
TXR No.: N/A
MRID No.: N/A

DP Barcode: 335941
Registration No.: N/A
Regulatory Action: Phase 2 (Error Correction)
Case No.: 0022

CAS No.: 91-20-03
40 CFR: N/A (Non-Food/Non-Feed)

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Attached is the Health Effect Division's (HED) Phase 2 amended risk assessment for the naphthalene RED. Error correction comments were submitted by Landis International on April 1, 2008 ("Registrant 30-day Response to Agency-Error corrections Preliminary Risk Assessment for the Reregistration Eligibility Decision for Naphthalene received March 3, 2008) and are incorporated in the attached amendment. This document supersedes the document "Naphthalene: HED Chapter of the Reregistration Eligibility Decision Document (RED). PC Code: 055801, DP#335946" dated February 28, 2008.

1.0 Executive Summary

Use Profile

Naphthalene is used as a moth repellant for the protection of wool clothing and as an animal repellant against nuisance vertebrate pests. Naphthalene is registered for uses in and around the home. In the home, it can be used to repel moths from clothing stored in enclosed areas or closed containers and as an indoor (attic) animal repellant. Outdoors, naphthalene may be used as an animal repellant and is applied as a narrow band around target areas to be protected (houses, wood piles, trash cans, flower beds, etc). Naphthalene is a non-food/non-feed pesticide.

Naphthalene is a white, crystalline solid which volatilizes to create a characteristic odor. In a sealed container, naphthalene vapors build up to levels toxic to both the adult and larval forms of many moths destructive to wool clothing. In addition, naphthalene's odor can be used to repel vertebrate animals.

Naphthalene products are formulated as mothballs, flakes, dusts, and granules and are labeled for application by hand. Re-treatments are recommended when product and odor dissipate. Even though this pesticide may be applied by hand, which could result in some dermal exposure, inhalation is the main route of exposure expected based on naphthalene's chemical nature and use pattern. Inhalation exposures may result from homeowners applying the pesticide, or to residents who inhabit homes that have been treated. Additionally, inhalation exposures can occur when an enclosed treated area, where the compound has been allowed to concentrate in the air, is temporarily accessed or opened. Oral exposures, on the other hand, are not as likely to occur. Since naphthalene is a non-food use pesticide, there are no dietary exposures expected from food. Dietary exposures via drinking water may be possible assuming the product is indeed entering drinking water sources as a result of outdoor home uses. There is also a possibility that a child may try to eat the applied product as it is encountered indoors or out. This scenario, however, can be considered episodic (a one time only incidental ingestion).

Hazard Characterization

Based on the use pattern, the standard toxicology database for naphthalene is complete for assessing dermal and oral exposure risks to humans. Although standard inhalation rodent toxicity studies are available, some mechanism studies have raised the issue of notable species differences (in regard to respiratory toxicity and metabolism) and the applicability of the rodent model as a default approach to estimate human risk following inhalation exposures. There is support from published studies and ongoing research on naphthalene that indicate that risk estimates, would be considerably less than those using default procedures when known species differences between rodents and humans (including humans) in metabolism and respiratory toxicity are factored into the estimates. The mechanism data are not yet complete and ongoing research, when completed, is expected to significantly refine the potential toxicity hazard associated with human exposure to naphthalene via inhalation. No new standard toxicology data are being required at this time.

Standared test guideline studies indicate that naphthalene is acutely toxic in the rat via the oral and inhalation routes of exposure. In the rabbit, it is a moderate acute dermal toxicant. It is a moderate skin and eye irritant in the rabbit. Naphthalene is not a dermal sensitizer in guinea pigs. In rats, critical effects of acute toxicity were hunched posture, shaking and reduced motor activities.

Cataracts have been observed in rabbits, rats and mice, but only at high dose levels (greater than or equal to 500 mg/kg/day). Cataracts have been noted in human case reports but exposure information is lacking and there are no well conducted epidemiology studies that have verified this effect.

Hemolytic anemia has also been reported in humans (acute oral or inhalation exposure) but information on exposure levels were lacking. Hemolytic anemia has not been observed in the laboratory animal studies.

Subchronic toxicity of naphthalene is manifested by body weight changes, organ weight changes and /or clinical signs of toxicity following gavage treatment to rats.

Naphthalene inhalation studies include nose-only, i.e., compound introduced directly to the nose (4-week, 13-week, and subchronic 90-day neurotoxicity) and chamber studies (2 year) in rodents, which involves whole body exposures. These studies indicate that naphthalene is a nasal toxicant in rodents at low experimental concentrations.

In a 90-day dermal toxicity study in the rat, effects were noted only at the high dose of 1000 mg/kg/day. Because effects were seen only at the limit dose, dermal toxicity is not likely a concern.

Based on an overall review of the database there was evidence of neurotoxicity at the port of entry (e.g., loss of olfactory neurons following inhalation exposure). Hunched posture and decreased motor activity following oral treatment were also reported, however, these effects were secondary to a high dose bolus gavage administration in the oral toxicity studies. Although decreased brain weights in female mice were reported in a published study (Shopp et al. 1984, this effect was not observed in male mice or rats of any sex, not supported by the NTP mouse oral study. No behavioral or neurohistopathological effects were noted in any available study that included these measurements.

There was no evidence of developmental toxicity in the rat or rabbit.

The toxicological (test guideline) database for naphthalene, a non-food use pesticide, is considered complete. Although there is no reproductive study on naphthalene, it is not required for this nonfood use pesticide. In the case of the risk assessment following oral exposure, an extra uncertainty factor of 10 has been applied to the chronic RfD to account for extrapolation from subchronic to chronic oral exposure, in addition to the 100-fold uncertainty factor applied to account for inter and intraspecies differences. The composite uncertainty factor of 1000-fold would address the lack of reproductive toxicity data.

The results of mutagenicity studies indicate that naphthalene was negative for gene mutations in bacteria, micronuclei induction in mice, DNA damage in primary rat hepatocytes, and mutation at the HGPRT or TK loci in human lymphoblastoid cells. The few positive results were limited to effects on sister chromatid induction and chromosomal aberrations in vitro in Chinese hamster ovary. Naphthalene undergoes extensive oxidative metabolism to form naphthoquinones, which are thought to generate reactive oxygen species. It is possible that the reactive oxygen species may result in DNA damage.

In chronic inhalation studies, carcinogenic effects have been observed in both rats and mice following inhalation exposure. In the rat study, nasal tumors included neuroblastomas of the olfactory epithelium and adenomas of the respiratory epithelium. Female mice exhibited increased incidences of alveolar/bronchiolar adenomas, and adenomas and carcinomas combined. The carcinogenic and noncarcinogenic potential of naphthalene is currently undergoing review by EPA Integrated Risk Information System (IRIS). Naphthalene has not been subjected to a full EPA/International Programme of Chemical Safety (IPCS) framework for the analysis of a cancer mode of action (MOA) and relevancy of animal MOA to human carcinogenicity.

A quantitative human health risk assessment has been performed for oral and dermal exposure routes. An inhalation quantitative cancer risk assessment or derivation of an inhalation reference concentration (RfC) for the nonfood pesticidal uses of naphthalene was not performed in this assessment. This is because HED has determined that it would not be accurate at this time to quantify human health risk estimates for non-cancer and cancer inhalation exposures to naphthalene using standard default procedures because of the notable differences in respiratory toxicity and metabolism between rodents and primates. As mentioned above, there is support from published studies and ongoing research on naphthalene that indicate that risk estimates, factoring in known species differences between rodents and humans (including humans) in metabolism and respiratory toxicity, would be considerably less than those using default procedures.

The primary adverse outcome reported in the available studies using rodents (rats and mice) exposed to naphthalene by the inhalation route is respiratory tract (nose and lung) tumors. Naphthalene clearly induced nasal tumors (adenomas and neuroblastomas) in rats. In mice, there was also some evidence of lung tumors in female mice, but this was less convincing than the tumor response in rats. The nasal tumors in rats was associated with cytotoxicity. Inflammation, degeneration, metaplasia, hyperplasia occur before nasal tumors. Cytotoxicity and regenerative proliferation is a plausible mode of action for naphthalene-induced respiratory effects. Studies are ongoing to further investigate this mode as well as the involvement of different CYP isoforms, different naphthalene metabolites, genotoxicity and reactive oxygen species.

There is available research indicating that metabolic activation by Cytochrome P-450 (CYP) to naphthalene-1,2-oxide is a required step for naphthalene's respiratory toxicity (unmetabolized naphthalene is not the cause of the cytotoxicity or tumors) and that there are notable species differences in respiratory effects and in the metabolism (i.e., stereoselectivity of metabolite

formation, CYP expression) of naphthalene between rodents and primates. Details on the metabolism of naphthalene are presented in Section 3.0. Mice are more sensitive to pulmonary toxicity from naphthalene, whereas the rat is more sensitive to nasal toxicity associated with naphthalene exposure. This apparent species difference to naphthalene toxicity may be related to species difference in metabolism, deposition and the anatomy of respiratory system. Available research to date indicates that the metabolism pathway in rodents is more active than in primates including humans (i.e., primates have a slower rate of formation of the active metabolite). Levels of CYP-associated metabolism of naphthalene in rodents are about 10-100X greater than measured in the lungs of nonhuman primate and humans (Buckpitt 2005). The low rates of naphthalene metabolism observed in human and monkey lung suggest that rodents do not accurately predict human pulmonary response to naphthalene (Baldwin 2004). Nasal CYP expression in monkeys is significantly lower than the rat (Baldwin 2004), and there is ongoing research to further examine aspects of nasal metabolism of naphthalene in rodents and primates.

Although rodents are most likely to be more susceptible to naphthalene's respiratory effects (cytotoxicity and tumors) than humans, the human relevance of the rodent respiratory tract tumors is not clear at this time. The issue of whether naphthalene poses a human health concern at ambient exposures will be informed to large degree by an explanation of the process by which naphthalene is absorbed, distributed, metabolized, and eliminated by the body (pharmacokinetics). The pharmacokinetic (PK) model that will quantify the species difference is not available now, but is forthcoming in approximately 2-3 years.

Because rodents are likely more susceptible to naphthalene's potential respiratory effects than humans, it would be inaccurate to quantify non-cancer and cancer inhalation risks in humans based on default methods which do not incorporate the critical metabolic and dosimetric differences between primates and rodents; to do so would likely result in inaccurate estimates of human risk. Studies have demonstrated that models that incorporate species differences in gas dosimetry (anatomical, physiological, biochemical and biophysical aspects) reveal that human nasal tissue dosimetry is significantly less susceptible to gas exposures than comparable rodent tissue (Andersen et al. 2000; Frederick et al. 1998; 2002). Thus, no quantification of either non-cancer or cancer inhalation risks to humans is provided in this assessment.

OPP considered a hierarchy of available information on naphthalene (metabolism, toxicity) and approaches (e.g., default RfC and cancer methodology, PBPK models) and considers the most scientifically reliable approach to be one that is more integrative of all the available information relating to dosimetry, species metabolic differences, pharmacokinetic and pharmacodynamic uncertainties, and one that incorporated critical research currently in progress on naphthalene. This integrative approach would provide a more accurate approach to characterize inhalation risk to naphthalene. OPP has characterized the inhalation toxicity hazards and then directly compared anticipated human exposure to naphthalene with 1) the doses found to result in no adverse effects in rodents (NOAELs) and 2) the doses found to result in toxic outcomes in rodents (LOAELs). That is, the levels (mg/m3) of naphthalene measured in a study simulating naphthalene-based mothball use inside a home (and ambient levels of naphthalene in homes where naphthalene-based mothballs may or may not have been used) were compared directly to the NOAELs and LOAELs identified in the rodent inhalation studies. This comparison is informational and provides a sense of the difference between expected ambient levels of

naphthalene that humans may be exposed to and the levels that cause no effect, as well as a toxic effect, in rodents.

The detailed characterization of the uncertainties associated with using rodent studies to estimate inhalation risk to humans is found in Section 3.5 of this document. The comparison of ambient naphthalene levels to NOAELs and LOAELs can be found in Section 5.4.1 and are also presented below in this Executive Summary [Residential Postapplication (Inhalation)].

Dietary Exposure

There are no agricultural or any food related pesticide uses of naphthalene. Therefore, no dietary exposure from food is expected. However, there is potential for drinking water exposure due to the outdoor uses of naphthalene. Using a screening modeling tool (FIRST), EFED calculated peak and annual average surface water Estimated Environmental Concentrations (EEC). These values represented the high-end use rate of naphthalene on ornamentals and were used to conduct unrefined acute and chronic dietary (water only) risk assessments using DEEM-FCID™.

The acute and chronic risk estimates were found to be well below the 100% Reference Dose (RfD) level of concern. Overall dietary exposure to naphthalene (pesticidal uses) via drinking water is expected to be insignificant.

Residential Exposure/Risk

Residential Handlers (Dermal)

HED has determined that there is potential for short-term exposure in residential settings during the application process for homeowners who purchase and use naphthalene-containing products. Applications of naphthalene can be made indoors and outdoors and are expected to be short-term in duration due to the intermittent nature of use associated with these products. HED anticipates both handler dermal and inhalation exposure during the application process; however, appropriate inhalation handler exposure data are not available to assess this scenario, therefore, only dermal exposure was assessed.

Margins of Exposure (MOEs) for residential handlers were calculated using standard assumptions and the results of an exposure study, "Estimation of Homeowner Exposure to LX1298-01 (Naphthalene) Resulting from Simulated Residential Use as an Insect Repellent," (MRID 43716501), in which dermal handler exposure data were derived from the monitoring of a person weighing out and placing mothballs in a closet and dresser at three different locations.

Residential handler MOEs (indoor and outdoor) were much greater than 100 and, therefore, not of concern to HED. Overall dermal exposure to handling naphthalene products, indoors and outdoors, is expected to be insignificant.

Residential Postapplication (Inhalation)

HED has determined that there is potential for adult and toddler inhalation exposure from naphthalene applications made indoors for moth treatments and animal repellency, and to a lesser extent, outdoors for animal repellency. While labels specify that treated indoor areas should be airtight to be effective, HED anticipates that naphthalene will volatilize and be inhaled by adults accessing treated areas (i.e., containers, dresser drawers, closets, etc.) and by adults and toddlers that inhabit treated areas exposed to ambient concentrations of naphthalene. Exposures from accessing treated areas are expected to be acute (approximately 15 minutes) in duration and exposures from inhabiting treated areas are short-(<1 month), intermediate- (1-6 months), and long-term (>6 months) in duration.

Since the data available to date indicate that rodents are more likely to be susceptible to the respiratory effects of naphthalene than humans, the use of rodents as a model without application of species scaling accounting for species differences in dosimetry and metabolism would likely result in inaccurate estimates of human risk. Therefore, rather than quantifying inhalation risks to humans, the levels of ambient naphthalene measured in the human exposure study were compared directly to the levels resulting in a 1) no adverse effects in the rodent studies (NOAELs) and 2) a toxic effect in rodents (LOAELs). This comparison provides a sense of the difference between actual naphthalene concentrations that a human may encounter and the doses which elicit either no adverse response or a toxic response in rodents.

Anticipated acute and short-term exposures were calculated using standard assumptions and the results of the aforementioned exposure study (MRID 43716501). Inhalation exposure data from the study apply to exposure durations ranging from 15 minutes (person accessing treated closets and dresser drawers) to 24 hours (average air concentration surrounding treated closets, dresser drawers, and beds). Anticipated acute and short-term exposures to naphthalene in residences are 20X and 30X below the rodent dose (NOAEL) resulting in no adverse effects, respectively. Anticipated acute and short-term exposures to naphthalene in residences are 60X and 80X below the rodent dose (LOAEL) resulting in respiratory toxicity (olfactory epithelium lesions), respectively.

Anticipated intermediate- and long-term exposures were also calculated using standard assumptions; however, because of the lack of a naphthalene-specific study of an appropriate duration, a different exposure study was used to assess these durations of exposure (Polycyclic Aromatic Hydrocarbon Exposure of Children in Low-Income Families, Chuang et al., 1999). This study was conducted to observe exposures to polycyclic aromatic hydrocarbons (PAHs), including naphthalene, inside of 24 homes from air, dust, soil, and food. This study is not specific to intermediate- or long-term exposure durations, nor does naphthalene necessarily originate from a mothball source; however, it has been identified as the best data source to account for naphthalene volatilization and dissipation over time. Due to the uncertainty associated with the use of an exposure study which is not specific to the duration assessed, HED selected the most conservative exposure value (i.e., maximum concentration observed) to represent intermediate- and long- term exposure levels. Based on the highest measured naphthalene levels from this study, intermediate-term exposures to naphthalene in residences are 540X below the rodent dose (NOAEL) resulting in no adverse health effects. [Note: a NOAEL was not identified in the chronic inhalation studies (rodents) for long-term exposure so that comparison has not been done]. Intermediate- and long-term exposures to naphthalene in

residences are 1000X and 5400X below the rodent dose (LOAEL) resulting in respiratory toxicity (olfactory epithelium lesions), respectively.

Generally, in the absence of information on kinetics/dynamics, it is assumed that humans may be 10 times more sensitive than animals (10X interspecies factor). The current research indicates that humans are less sensitive than rodents because of differences in rate of bioactivation of naphthalene as well as anatomical and physiological differences in the nose and respiratory tract. These critical differences between primates and rodents have not been accounted for in this assessment. Thus, with consideration of differences in dosimetry and species metabolism of naphthalene, the margins of exposure for human inhalation risk assessment are likely larger than the differences calculated here between the rodent NOAELs and LOAELs and the ambient naphthalene levels.

Studies determining the differences in nasal metabolism of naphthalene between rodents and primates are part of ongoing research. There are no data to indicate that humans have a slower rate of clearance, but if they did, then there would be a longer time for humans to produce the active metabolite. These issues are being addressed in current pharmacokinetic model research.

Residential Postapplication (Episodic Ingestion)

HED has determined there is potential that a toddler may ingest formulations used for indoor or outdoor treatments of naphthalene. In order to assess this exposure route, HED estimated the risk of a toddler ingesting a single mothball. In addition, HED estimated the amount of a single mothball that a toddler could ingest to result in a MOE = 100. While labels specify that indoor moth treatments be made in airtight containers, it is assumed that a toddler could potentially access these areas and ingest naphthalene products. Incident data indicate that ingestion of naphthalene by children primarily occurs by accessing products labeled for indoor use.

Toddler episodic ingestion of one naphthalene mothball results in a MOE < 100 (MOE=0.32) and, therefore, is of concern to HED. An oral dose of 0.5 mg/kg/day would be required to result in a MOE = 100. This dose is equivalent to toddler episodic (incidental) ingestion of 0.32% of one mothball (7.5 of 2350 total mg). While it is not expected that a toddler would intentionally ingest an entire mothball, that scenario cannot be completely discounted.

Aggregate Risk

An aggregate risk assessment for all expected routes of exposure was not performed as there is no common toxicity among all the routes of exposure. A short-term aggregate risk assessment could be performed by combining short-term incidental oral exposure and average/background dietary (in this case drinking water) exposures. However, a short-term aggregate risk assessment was not performed for naphthalene since the short-term incidental oral exposure risk estimate alone exceeds the level of concern and combining with other routes of exposure would only further exceed the level of concern.

Occupational Exposure/Risk

Naphthalene moth repellant products are not registered for occupational use and, therefore,

occupational exposure and risk is not anticipated and has not been assessed.

Epidemiology Studies

Three studies were submitted and reviewed by HED which explored the possible association between exposure to components of jet fuel, including naphthalene, and incident cancer among both private and military aerospace personnel. An additional recently published epidemiology study concerning the association between non-occupational exposure to naphthalene as a component of mothballs and non-Hodgkin's lymphoma (NHL) is also included in this review.

Three of the four studies utilized an ecologic exposure assessment method (indirect exposure method) and evaluated exposure to jet fuel in association with cancer. The question HED is addressing concerns exposure to naphthalene and adverse health outcomes. Given the non-specific exposure measure (jet fuel) and the potentially significant exposure misclassification reflected in these three studies, inference concerning the association between naphthalene exposure and incident cancer is severely limited based upon these studies alone. These studies are considered non-informative to the current naphthalene risk assessment and characterization.

The finding of a 2-fold increased risk of non-Hodgkins lymphoma among women in upstate New York in a study of non-occupational exposure to mothballs is suggestive of a possible association. However, as it is not known if the mothballs in this study were those containing naphthalene. This study does not contribute to the current naphthalene risk assessment and characterization.

Incident Reports

In order to complete the incident report for naphthalene (M. Hawkins and H. Allender, D336085), four databases were consulted for poisoning incident data. These include: OPP Incident Data System (IDS), Poison Control Centers (PCC), California Department of Pesticide Regulation, and National Institute of Occupational Safety and Health's Sentinel Event Notification System for Occupational Risks (NIOSH SENSOR). The summary findings from the incident report for the period 1993 to 2005 for naphthalene are:

- Naphthalene produces a higher proportion of acutely toxic incidents requiring medical attention when compared to the composite average of all other pesticides. There is a pattern of statistically significant results in cases seen in a health care facility. This pattern observed in the combined population (occupational, non-occupational, children) is largely due to the frequency and severity of pesticide poisoning among children less than 6 years;
- Exposure to children is much higher than a typical pesticide;
- Naphthalene PCC data show average results of about 11,647 exposures/year, 133 symptomatic cases/year, and 310 cases/year seen in a heath care facility;
- No apparent annual trend is evident in the 13 year-span of data collected; and
- NIOSH/SENSOR data indicate that indoor uses of naphthalene are responsible for a large number of cases.

- The large majority of incidents for children under 6 years of age were from ingestion of mothball products for indoor use.

Recommendations from the incident report for residential naphthalene use are as follows:

- In order to prevent exposures (oral) to children, actions restricting the access to the active ingredient should be taken. This could include packaging changes and other limitations to block children from coming into contact with the active ingredient.

The reported symptoms to naphthalene exposure include: neurological (headache, dizziness, and drowsiness/lethargy), gastrointestinal (nausea and vomiting), ocular (eye pain, irritation, and inflammation, and lacrimation), respiratory (upper respiratory pain, shortness of breath, coughing and choking).

Environmental Justice Considerations

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf).

As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas postapplication are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

Review of Human Research

This risk assessment relies in part on data from a study in which adult human subjects were intentionally exposed to a pesticide or other chemical. This study (Appendix B) has been determined to require a review of its ethical conduct, and has received that review. It was concluded that there are no regulatory barriers to EPA's reliance on this study in its actions under FIFRA (J. Carley, 4/24/07). Another study involving human subjects (Chuang et al., 1999) used in part in this assessment, does not meet the regulatory definition of research involving

intentional human exposure and is therefore not required to undergo ethical review. It was determined that "there are no regulatory, ethical, or policy barriers" to using this study in the naphthalene assessment (electronic communication, J. Carley to C. Eiden, 2/20/08).

2.0 Ingredient Profile

Naphthalene is used as a moth treatment for the protection of woolen clothing and as an animal repellant against nuisance vertebrate pests. All registered products of naphthalene are intended for residential uses only. The moth treatment use is registered for indoor only and is labeled for treatment of indoor storage areas (containers, drawers, and storage closets). The animal repellant use is labeled for indoor (attics and wall voids) and outdoor (around the perimeter of domestic dwellings, ornamental gardens, flower beds, lawns, or any area to be protected such as wood piles, utility houses, barns, and trash cans) use.

Naphthalene is a white, crystalline solid which volatilizes to create a characteristic odor. In a sealed container, naphthalene vapors build up to levels toxic to both the adult and larval forms of many moths destructive to wool clothing. In addition, naphthalene's odor can be used to repel vertebrate animals.

Naphthalene products for use within the home are formulated as mothballs or flakes, while outdoor products are formulated as dusts, flakes, and granules. Percent active ingredient of indoor-use products range from 99.7-100%, and from 7-99.9% for outdoor-use products.

Registered labels for indoor, moth treatment use recommend keeping the product in an airtight space for a minimum of seven days. Re-treatment is recommended when the mothballs have dissipated. Since moths are active all year, there is the potential for continual treatment indoors. One moth control label recommends re-treatment twice per year. Re-treatment for indoor/outdoor repellant uses are recommended as needed to maintain odor intensity. Hot weather, wind, and rain may diminish the effectiveness of the product and necessitate re-treatment.

Naphthalene treatments for indoor moth treatment use and indoor/outdoor repellant use are labeled for application by hand.

2.1 Summary of Registered Uses

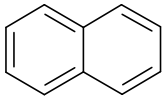
Table 2.1 . Summary of Registered Naphthalene Uses

Indoor Use				
Product	**Use Site**	**Formulation**	**% Active Ingredient**	**App. Rate for the Area to be Treated**
ENOZ® Old Fashioned Moth Balls (1475-74)	Indoor storage areas (containers and storage closets)	Moth Ball	99.95	1 ounce per 3 ft^3 - 0.25 lb ai / Average Garment Bag (12 ft^3) 0.33 lb ai / Large Trunk (15 ft^3) 1 lb ai / Small Closet (50 ft^3)
ENOZ® Old	Indoor storage areas	Flake	99.95	1 ounce per 3 ft^3 -

Fashioned Moth Flakes (1475-75)	(containers and storage closets)			0.25 lb ai / Average Garment Bag (12 ft^3) 0.33 lb ai / Large Trunk (15 ft^3) 1 lb ai / Small Closet (50 ft^3)
ENOZ® Cedar Pine Moth Balls (1475-120)	Indoor storage areas (containers and storage closets)	Moth Ball	99.85	1 ounce per 3 ft^3 - 0.25 lb ai / Average Garment Bag (12 ft^3) 0.33 lb ai / Large Trunk (15 ft^3) 1 lb ai / Small Closet (50 ft^3)
Chaperone Squirrel and Bat Repellant (2724-685)	Attics and wall voids and Indoor storage areas (containers and storage closets)	Flake	100	1 pound per 400 ft^3 1 ounce per 3 ft^3 - 0.25 lb ai / Average Garment Bag (12 ft^3) 0.33 lb ai / Large Trunk (15 ft^3) 1 lb ai / Small Closet (50 ft^3)
Dr. T's Rabbit, Squirrel, Bat & Bird Repellant (58630-2)	Attics and wall voids	Flake	99.95	1 pound per 400 ft^3
I-Ching Naphthalene Moth Balls (80305-1)	Indoor storage areas (containers and storage closets)	Moth Ball	99.9	1 ounce per 3 ft^3 - 0.25 lb ai / Average Garment Bag (12 ft^3) 0.33 lb ai / Large Trunk (15 ft^3) 1 lb ai / Small Closet (50 ft^3)
IMS Old Fashioned Moth Balls (81433-6)	Indoor storage areas (containers and storage closets)	Moth Ball	99.95	1.5 ounces per 3 ft^3 - 0.37 lb ai / Average Garment Bag (12 ft^3) 0.36 lb ai / Large Trunk (15 ft^3) 1.1 lb ai / Small Closet (50 ft^3)
Moth Avoid Brand Traditional Moth Balls (83424-2)	Indoor storage areas (containers and storage closets)	Moth Ball	99.7	1 ounce per 3 ft^3 - 0.25 lb ai / Average Garment Bag (12 ft^3) 0.33 lb ai / Large Trunk (15 ft^3) 1 lb ai / Small Closet (50 ft^3)
Outdoor Use				
F&B Rabbit and Dog Chaser (4-465)	Soil treatment on ornamental plants, paved areas	Dust	15	0.45 lb ai/ treated area (3 lb container) (assuming entire contents used to treat area)
ENOZ® Skat! (1475-146)	Around the perimeter of ornamental plants	Flake	99.45	2.5 lb ai/ treated area (2.5 lb container) (assuming entire contents used to treat area)
Dr. T's Snake-A-Way Snake Repellant (58630-1)	Around the perimeter of domestic dwellings (outdoors), wood piles, utility houses, barns, trash cans, flower beds, and gardens	Granule	7	0.28 lb ai/treated area (4 lb container) 2 lb ai/ treated area (28 lb container) (assuming entire contents used to treat area)
Dr. T's Rabbit,	Around the perimeter	Flake	99.95	4 lb ai/ treated area (4 lb container)

Squirrel, Bat & Bird Repellant (58630-2)	of ornamental plants			24 lb ai/ treated area (24 lb container) (assuming entire contents used to treat area)

2.2 Structure and Nomenclature

Table 2.2 Test Compound Nomenclature	
Chemical Structure	 Naphthalene
Empirical Formula	$C_{10}H_8$
Common Name	Naphthalene
IUPAC name	Naphthalene
CAS Name	Naphthalene
CAS Registry Number	91-20-3
Chemical Class	Fumigant insecticides

2.3 Physical and Chemical Properties

Table 2.3. Physiochemical Properties		
Parameter	Value	Reference
Molecular Weight	128.17	D322965, D. Rate, 12/20/05
Melting point/range	80.2°C	
pH	NA	
Density	1.162	
Water solubility	Water: 31 mg / L @25°C (insoluble)	
Solvent solubility	soluble in benzene, alcohol, ether, acetone	
Vapor pressure	0.085 mm Hg @ 25°C 1 mm Hg @ 53°C	
Dissociation constant, pKa	NA/NS	
Octanol/water partition coefficient, $\log P_{OW}$ (25°C)	Log Kow = 3.30	
UV/visible absorption spectrum	$\epsilon_{221} = 133000$ $\epsilon_{286} = 9300$ $\epsilon_{312} = 289$	

3.0 Hazard Characterization/Assessment

3.1 Hazard and Dose-Response Characterization

Database Summary

Based on the use pattern, the standard toxicology database for naphthalene is complete for assessing dermal and oral exposure risks to humans. Although standard inhalation rodent toxicity studies are available, some mechanism studies have raised the issue of notable species differences (in regard to respiratory toxicity and metabolism) and the applicability of the rodent model without appropriate dosimentric adjustments and scaling as a approach to estimate human risk. The mechanism data are not complete and ongoing research, when completed, is expected to refine the potential toxicity hazard associated with human exposure to naphthalene via inhalation. No additional test guideline data are being required at this time.

Sufficiency of studies/data

Based on the use pattern, the toxicology database for naphthalene is complete and adequate for dermal and oral risk assessment. Studies include the following:

- Acute Neurotoxicity: acute oral neurotoxicity study in the rat
- Subchronic Neurotoxicity: subchronic inhalation neurotoxicity study in the rat
- Developmental: National Toxicology Program (NTP) rabbit and rat developmental studies
- Subchronic oral: 90-day rat and mouse studies; published mouse study
- Subchronic inhalation: 13 week rat study; 90-day neurotoxicity in the rat study
- Chronic inhalation: NTP rat and mouse studies
- Mutagenicity: battery of mutagenicity assays
- Metabolism: several published studies
- Dermal Toxicity – 90-day dermal toxicity in the rat

Mode of action, metabolism, toxicokinetic data

The Registrant did not provide mode of action data. However, several published literature studies have addressed the role of cytochrome-P450-associated metabolic intermediates as the potential underlying mode of action of naphthalene-induced respiratory tract neoplastic and nonneoplastic lesions. Buckpitt et al. (2002) identified various metabolic intermediates of naphthalene, in particular, 1,2-naphthalene oxide, 1,2-naphthoquinone, and 1,4-naphthoquinone, that are involved in the formation of respiratory tract lesions in rodents. These metabolites are considered reactive and can covalently bind to various cellular proteins resulting in cellular damage.

A further mechanism for 1,2-naphthoquinone has also been suggested (Bolton et al. 2000). This mechanism involves the enzymatic and nonenzymatic redox cycling of the quinone with subsequent generation of reactive oxygen species (ROS) and lipid peroxidation, resulting in cellular damage.

Species susceptibility to naphthalene-mediated respiratory tract toxicity has been recognized (Buckpitt et al. 1992; 1995). With regard to lung toxicity, the mouse is considered more susceptible than the rat. This difference has been correlated to the higher rates of formation of the epoxide 1R,2S-naphthalne oxide in lung microsomes and isolated airways of mice compared to rats (Buckpitt et al. 1992; 1995). With regard to acute nasal injury to naphthalene, the rat is considered to be the most sensitive (Plopper et al. 1992). These data suggest differences in metabolism and toxicity and species susceptibility to naphthalene.

Toxicological Effects

Acute toxicity

Naphthalene is acutely toxic in the rat via the oral (Category III) and inhalation (Category II) routes of exposure. In the rabbit, it is a moderate acute dermal toxicant (Category III). It is a moderate (Category III) skin and eye irritant in the rabbit. Naphthalene is not a dermal sensitizer in guinea pigs.

Cataracts

Cataracts have been reported in several published studies (ATSDR 2005) on rabbits, rats and mice; however, these effects were noted at high oral doses (greater than or equal to 500 mg/kg/day). Cataracts have not been observed at lower oral doses in the NTP rat and mouse studies or in the published mouse study (Shopp et al 1984). Although there have been reports of humans exhibiting cataracts following oral, dermal or inhalation exposure, exposure levels were not identified and there are no well conducted epidemiology studies verifying these reports (ATSDR 2005).

Hemolytic Anemia

A number of reports have documented hemolytic anemia in humans following acute oral or inhalation exposure to naphthalene, however, information on dose levels were not available (ATSDR 2005). There was no evidence of hemolytic anemia in rats or mice (ATSDR 2005).

Subchronic oral

The primary effects observed in the subchronic rodent oral studies included body weight changes, organ weight changes and /or clinical signs of toxicity following gavage treatment at doses $\geq$ 200 mg/kg/day. These studies are discussed below.

The most sensitive effect noted in a subchronic (13-week) rat study (NTP 1980a) was decreased body weight gain. Body weight gain decrements exceeding 10% were observed in both males and females administered 200 or 400 mg/kg/day. At the highest dose level, clinical signs included lethargy, hunched posture, and roughened hair coats. High-dose rats also exhibited marginal decreases in hemoglobin and hematocrit levels. Males in this group also displayed a

moderate increase in neutrophils and decrease in lymphocytes. Minimal to moderate renal histological lesions (renal cortical focal lymphocytic infiltrate and focal tubular or cortical diffuse regeneration) were noted in male rats treated with 200 mg/kg/day and 400 mg/kg/day. There were no renal lesions in treated females, however, several females treated with 400 mg/kg displayed moderate lymphoid depletion of the thymus. No effects were observed at 100 mg/kg/day (NOAEL).

Clinical signs of toxicity, including rough hair coats and lethargy, were observed in male and female B6C3F1 mice exposed to 200 mg/kg/day (high dose) for 13 weeks (NTP 1980b). The signs were transient and noted only during weeks 3 and 4. No effects were observed at 100 mg/kg/day (NOAEL).

No clinical signs of toxicity were noted in a published 90-day study in CD-1 mice administered naphthalene at dose levels of naphthalene up to 133 mg/kg/day (Shopp et al. 1984). No immunological effects were detected following application of an immunotoxicity test battery. There were no biologically significant effects on mortality or body weights. Absolute weights of the brain, liver and spleen were statistically significantly decreased (>10%) in the high-dose females (133 mg/kg, the LOAEL). Relative spleen weights were significantly decreased by 24% in these females. However, no histological examinations were performed on organs to assess significance of organ weight changes. No effects were noted at 53 mg/kg/day (NOAEL).

Shopp et al. also presented results of a 14-day study on naphthalene in the same strain of mouse. Mortality was noted in the high-dose (267 mg/kg/day) males and females. Mean body weight in the high-dose males was significantly decreased by 13% (data were insufficient to calculate overall bodyweight gain decrement). Organ weight changes at the high dose included decreased absolute thymus weights (males), decreased absolute and relative spleen weights (females), and increased absolute and relative lung weights (females). However, histological examination of these organs was not performed to assess significance of organ weight alterations. No effects were seen at 53 mg/kg/day (NOAEL).

Nasal lesions (inhalation)

Naphthalene has been well-studied by the inhalation route of exposure, including nose-only (4-week, 13-week, and subchronic 90-day neurotoxicity) and chamber studies (2 year) in rodents. These studies indicate that naphthalene is a nasal toxicant at low concentrations, and that nasal lesions are the most sensitive endpoint via this route of exposure. Similar nasal lesions were noted in these studies.

Nasal nonneoplastic lesions noted in the 4-week (nose-only) inhalation study (MRID 42934901) in the rat included slight disorganization, rosette formation, basal cell hyperplasia, erosion, atrophy, and degenerate cells in the olfactory epithelium, loss of Bowman's glands, hypertrophy of respiratory epithelium, rosette formation in the septal organ of Masera and fusion of turbinates. Based on increased incidence and severity the LOAEL is 10 ppm and the NOAEL is 3 ppm.

Moderate degenerative changes in the olfactory epithelium, moderate to marked atrophy of olfactory epithelium, minimal to moderate erosion of olfactory epithelium, moderate hyperplasia of basal cells in olfactory epithelium, moderate rosette formation in olfactory epithelium, loss of Bowman's glands, hypertrophy of respiratory epithelium were noted in a 13-week (nose-only) inhalation study (MRID 42835901) in the rat following exposure to 10 or 60 ppm naphthalene. Similar findings were noted in rats at the low dose (2 ppm), but these changes were minimal. However, several of the low-dose rats exhibited some loss of Bowman's glands. The LOAEL is 2 ppm based on minimal nasal lesions and some loss of Bowman's gland. A NOAEL was not identified; however, a NOAEL of 1 ppm was identified in a similar inhalation study (MRID 44856401) conducted in the same laboratory (study discussed below). This similar study is a co-critical study and used to derive a NOAEL for nasal lesions following nose-only exposures.

The results of the 13-week study (MRID 42835901) were supported by a similarly conducted subchronic 90-day inhalation rat neurotoxicity study (MRID 44856401) in the same laboratory. Findings included slight hyperplasia of the respiratory/transitional epithelium in the rostral region, slight to moderate atrophy/disorganization of the olfactory epithelium, slight to moderate hyperplasia of the olfactory epithelium, slight rosettes of the olfactory epithelium, slight inflammatory exudate in the airway, moderate erosion/necrosis of the olfactory epithelium, and loss of Bowman's glands and olfactory nerve fibers in rats exposed to 10 or 60 ppm naphthalene. There were no apparent lesions of toxicological significance in rats treated with 1 ppm naphthalene (LOAEL = 10 ppm; the NOAEL = 1 ppm). There were no treatment-related effects on brain weight or neuropathology or clear evidence of direct behavior effects.

In a NTP chronic inhalation (chamber) study in the rat (NTP 2000) nasal lesions were observed at all concentration levels (10, 30, or 60 ppm) and included atypical (basal cell) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium; hyperplasia, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia of the respiratory epithelium; and glandular hyperplasia and squamous metaplasia. The severities of olfactory epithelial and glandular lesions increased with increasing exposure concentration. Survival in the exposed groups was similar to chamber controls. Mean body weight gains in the high-dose (60 ppm) males were significantly decreased throughout the study. The LOAEL is 10 ppm based on nasal lesions, and a NOAEL was not identified.

Nasal lesions were also observed in a NTP chronic inhalation chamber study (NTP 1992) in the mouse at all concentration levels (10 and 30 ppm) and consisted of increased incidence and severity of chronic inflammation, metaplasia of the olfactory epithelium, and hyperplasia of respiratory epithelium. There was also increased incidence and severity of chronic inflammation in the lung. The LOAEL is 10 ppm, and a NOAEL was not identified.

Dermal

In a 90-day dermal toxicity study in the rat (MRID 40021801), effects were noted only at the high dose of 1000 mg/kg/day. These effects included excoriated skin and papules in both sexes; atrophy of seminiferous tubules in the males; and nonneoplastic lesions in the cervical lymph node (hyperplasia), liver (hemosiderosis), thyroid (thyroglossal duct cysts), kidneys

(pyelonephritis), urinary bladder (hyperplasia) and skin (acanthosis, hyperkeratosis) in females. The NOAEL was 300 mg/kg/day. These results indicate that dermal toxicity is of low concern.

Neurotoxicity

Based on an overall review of the database (including acute oral neurotoxicity study and a subchronic inhalation neurotoxicity study; Section 3.3), there was evidence of neurotoxicity at the port of entry (i.e., loss of olfactory neurons following inhalation exposure). Although hunched posture and decreased motor activity following oral treatment were reported, these effects were secondarily to a high dose bolus gavage administration in the oral toxicity studies. There were no effects on brain weights or brain neurohistopathology in any of the NTP studies with naphthalene. Decreased brain weights in female mice were reported in a published study (Shopp et al. 1984), however, this effect was not observed in rats (either sex) or in male mice, and not supported by the NTP mouse oral study. No behavioral or neurohistopathological effects were noted in any study.

Mutagenicity

Three genetic toxicology studies, in accordance with pre-1991 FIFRA requirements, were submitted. Results show that naphthalene was negative for gene mutations in bacteria (Salmonella typhimurium), micronuclei induction in mice and DNA damage in primary rat hepatocytes. Accordingly, these studies satisfy the pre-1991 FIFRA requirements. Since that time, naphthalene was tested as part of the National Toxicology Program (NTP, 1992) for gene mutations in S. typhimurium, and was negative. NTP also found that naphthalene was positive for sister chromatid (SCE) induction and chromosomal aberrations in vitro in Chinese hamster ovary (CHO). Published literature showed that naphthalene was not mutagenic in bacteria (either Salmonella or Escherichia coli) or mammalian cells (human lymphoblastoid cells at the HGPRT or TK loci). With the exception of the positive in vitro chromosome aberration and SCE induction studies of NTP, naphthalene was not active at either endpoint in human lymphocytes.

Several studies in the open literature show that naphthalene undergoes extensive oxidative metabolism to form naphthoquinones, which are thought to generate ROS (superoxide anion radical, hydrogen peroxide, hydroxyl radical and o-semiquinone anion radicals) via redox cycling (Bolton, 2000). A number of investigators have reported evidence of naphthalene-induced oxidative damage by ROS (reviewed in Stohs, et al., 2002). See Section A.3.6. It is possible that the reactive oxygen species may result in DNA damage.

Developmental

No evidence of developmental toxicity was evident in the NTP developmental studies in the rat and rabbit. In the rat developmental study, the developmental NOAEL was 450 mg/kg/day (highest dose tested). In the NTP main developmental rabbit study, the maternal and developmental NOAELs were both 120 mg/kg/day (highest dose tested). In the NTP range-finding developmental rabbit study, the developmental NOAEL was 500 mg/kg/day.

Maternal toxicity (persistent clinical signs of lethargy, slow breathing, rooting behavior, and significant decreases in body weights/body weight gains and food and water consumption) was apparent in the developmental rat study (maternal LOAEL = 150 mg/kgday; maternal NOAEL = 50 mg/kg/day).

In the range-finding rabbit developmental study, mortality, decreased body weights and clinical signs (diarrhea, lethargy) were observed in maternal rabbits treated with doses ranging from 150 to 500 mg/kg/day.

Based on available data (rat developmental study, rabbit developmental study including a range-finder), there is no evidence of developmental toxicity. There are no residual uncertainties with regard to in utero toxicity; and the toxicological database for naphthalene is substantially complete for a non-food use pesticide. Although there are no reproductive toxicity studies, an extra uncertainty factor of 10 has been applied to exposure scenarios that are based on lifetime exposures to account for lack of reproductive toxicity and chronic toxicity studies.

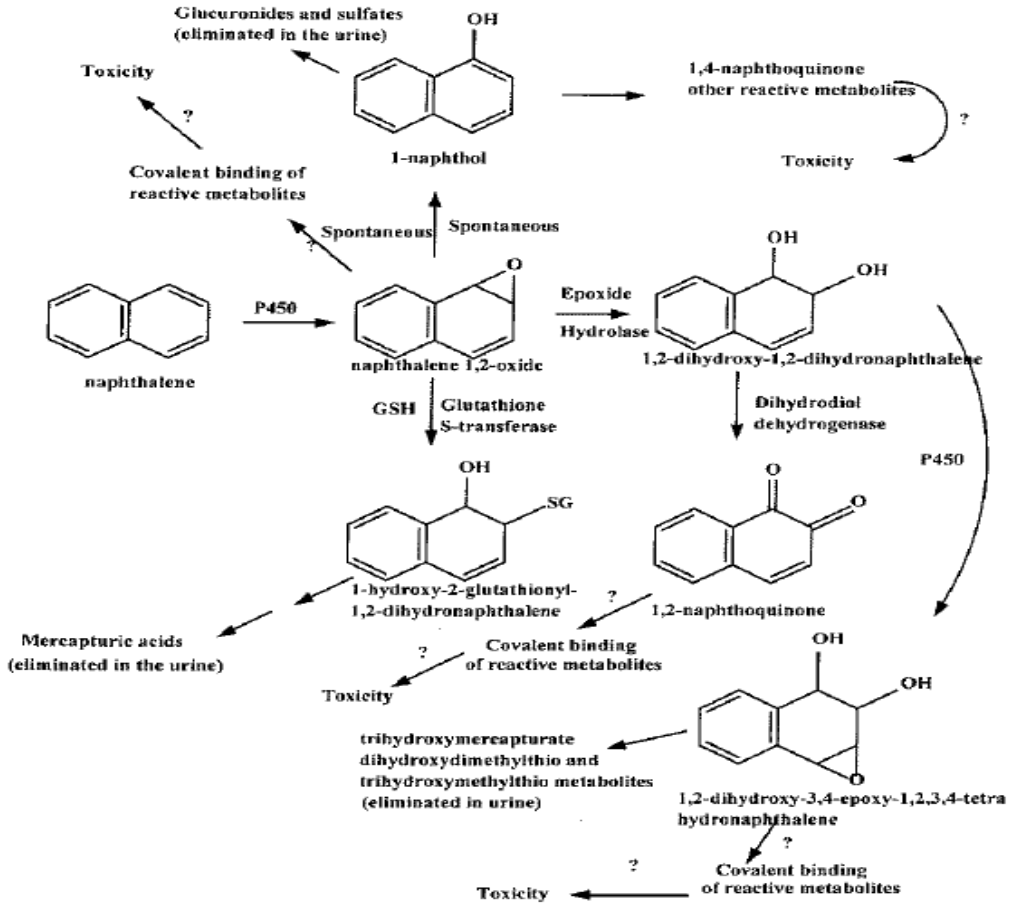
Dose-response

Inhalation (nose-only) toxicity studies on naphthalene have demonstrated increases in the incidence and severity of nasal lesions with dose, and time-to-effect dependence, that is, longer-term exposures result in effects at lower doses than short-term exposures. In the long-term exposure chamber studies, the LOAELs were 10 ppm; NOAELs were not identified. The subchronic inhalation neurotoxicity (nose-only) study established a NOAEL of 1 ppm. Dose-related body weight decrement was noted in the NTP subchronic oral rat study (NOAEL = 100 mg/kg/day). In the NTP subchronic mouse study, clinical signs were observed at the highest dose tested (LOAEL = 200 mg/kg/day; NOAEL = 100 mg/kg/day). Dose-related body weight decreases and clinical signs of toxicity were noted in the NTP developmental rat study (maternal NOAEL = 50 mg/kg/day). In the 90-day dermal toxicity study in the rat, effects (atrophy of seminferous tubules in males; various nonneoplastic lesions in females) were seen only at the limit dose of 1000 mg/kg/day. The NOAEL was 300 mg/kg/day. Therefore, dermal toxicity is of low concern.

3.2 Absorption, Distribution, Metabolism, Excretion (ADME)

Naphthalene undergoes oxidative metabolism by cytochrome P-450 oxygenases resulting in the epoxide 1,2-napthalene oxide (Buckpitt 2002). The epoxide can spontaneously hydrolyze to naphthols and then form glucuronic acid or sulfate conjugates. Alternatively, the epoxide can be conjugated with glutathione, as mediated by glutathione-S-transferase. Through several steps, the glutathionyl conjugates are converted to mercapturic acids. The epoxide can also be enzymatically hydrated by epoxide hydrolase to form 1,2-dihydorxy-1,2-dihydronaphthalene. The latter compound can then undergo further reactions (catechol reduction followed by oxidation) to form 1,2-naphthoquinone. Figure 1 below depicts the metabolism of naphthalene and its potential role in the toxicity of naphthalene as suggested by Buckpitt. Figure 1 is not meant to be a depiction of the mode of action of naphthalene.

FIGURE 1. Naphthalene Metabolism and Formation of Reactive Metabolites (Source: Buckpitt 2002)



3.3. Evidence of Neurotoxicity

In inhalation studies, there was evidence of neurotoxicity at the port of entry (i.e., loss of olfactory neurons). Although hunched posture and decreased motor activity following oral treatment were reported, these effects secondary to a high dose bolus gavage administration in the oral toxicity studies. There were no effects on brain weights or brain neurohistopathology in any of the NTP studies with naphthalene. Decreased brain weights in female mice were reported in a published study (Shopp et al. 1984), however, this effect was not observed in rats (either sex) or in male mice, and not supported by the NTP mouse oral study. No behavioral or neurohistopathological effects were noted in any study.

The potential neurotoxicity of naphthalene has also been examined in an acute oral neurotoxicity study in the rat and a subchronic inhalation neurotoxicity study in the rat. Neurotoxicity was noted in an acute oral neurotoxicity study in the rat. Effects observed on Day 1 in rats treated with ≥ 400 mg/kg included hunched posture (females), head shaking behavior (males and females), and decreased motor activity (males and females). High-dose (1200 mg/kg) females

exhibited elevated hind quarters and gait abnormalities. These effects were also noted at day 7. All treated males and females displayed increased urination and defecation on Days 7 and 14. No treatment-related effects were seen in landing footsplay or fore- and hind-limb grip strengths on any testing day. There was no difference in weight of the brain and pituitary between the control and treated groups. Gross and microscopic examinations of central and peripheral nervous tissue did not reveal any treatment-related effects. The LOAEL for neurotoxicity of naphthalene in rats was 400 mg/kg bw based on clinical signs. The NOAEL was not established. As mentioned above, these neurotoxic effects most likely occur secondarily to a high dose bolus gavage administration.

Lethargy and hunched posture were apparent in F344 rats administered 400 mg/kg/day naphthalene by gavage for 90 days (NTP 1980a). These neurotoxic effects most likely occur secondarily to a high dose bolus gavage administration. Lethargy and rough hair coat were observed in B6C3F1 mice given a gavage dose of 200 mg/kg/day naphthalene for 90 days (NTP 1980b); however, these signs were transient and occurred during week 3 and 4 of the study. No clinical signs were reported in a published 90-day CD-1 mouse study (Shopp et al. 1984).

Apparent loss of olfactory nerve fibers were noted in the (nose-only) neurotoxicity study in male and female rats exposed to 10 and 60 ppm naphthalene. As mentioned above, the nerve fiber loss most likely is related to the localized, irritative portal-of-entry effects of naphthalene. The continuous nose-only exposure is not a likely exposure scenario given the use pattern of naphthalene. In the NTP chronic (exposure chamber) inhalation study in the rat, neuroblastomas occurred in female rats exposed to 10, 30 or 60 ppm naphthalene, while in males these occurred at 30 or 60 ppm naphthalene.

3.3.1 Developmental Toxicity Studies

Well-conducted developmental oral toxicity studies in the rat (NTP 1991) and the rabbit (1992) were available. The data provided no indication of developmental toxicity in the rat or rabbit. or increased quantitative or qualitative susceptibility of rat or rabbit fetuses to in utero exposure to naphthalene. Developmental NOAELs are higher than maternal NOAELs.

In the rat developmental study, the maternal LOAEL was 150 mg/kgday based on persistent clinical signs of lethargy, slow breathing, rooting behavior, and significant decreases in body weights/body weight gains and food and water consumption. The maternal NOAEL was 50 mg/kg/day. The developmental NOAEL is 450 mg/kg/day (highest dose tested).

In the NTP developmental rabbit study, the maternal and developmental NOAELs were 120 mg/kg/day (highest dose tested).

3.3.2 Reproductive Toxicity Study

There are no reproductive toxicity studies on naphthalene, a non-food use pesticide.

3.3.3 Additional information from Literature Sources

Published literature on the metabolism and mechanism of action of naphthalene have been discussed in respective sections of this risk assessment.

3.3.4 Recommendation for a Developmental Neurotoxicity Study

As discussed in Section 3.3, neurotoxicity observed in several studies was related either to localized irritation on the nasal olfactory epithelium (portal of entry in the inhalation studies), or secondary to high dose bolus gavage administration in the oral toxicity studies. There were no effects on brain weights or brain neurohistopathology in any of the NTP studies with naphthalene. Decreased brain weights in female mice were reported in a published study (Shopp et al. 1984), however, this effect was not observed in male mice or in rats of either sex, and not supported by the NTP mouse oral study. No behavioral or neurohistopathological effects were noted in any study. Based on the rat developmental study, and the rabbit developmental (main and range-finding studies), there was no evidence of developmental toxicity in the rat or rabbit. A developmental neurotoxicity study is not required for naphthalene.

3.4 Hazard Identification and Toxicity Endpoint selection

Acute Reference Dose (aRfD) – Females age 13-49

No appropriate endpoint identified for this population.

Acute Reference Dose (aRfD) – General Population

Study Selected: Acute Oral Neurotoxicity Study - rat (OPPTS 870.6200a)

MRID No.: 44282801

Dose and Endpoint for Establishing aRfD: LOAEL = 400 mg/kg based on hunched posture in females, head shaking in males and females, and reduced motor activity in males and females. These clinical signs are considered to be secondary to bolus administration of a high dose of naphthalene. A NOAEL was not identified.

Comments on Study/Endpoint/Uncertainty Factors: The endpoint selected occurred following a single exposure and is relevant for all populations, including infants and children. The extrapolated NOAEL (40 mg/kg/day) is comparable to the NOAEL of 50 mg/kg/day identified in pregnant female rats (NTP developmental rat study). The data (Day 1) were not suitable for benchmark dose (BMD) analyses because of the lack of smooth dose response (i.e., either flat or near maximal response). An UF of 1000 was applied to account for a lack of a NOAEL (10x), inter-species extrapolation (10x) and intra-species variations (10x).

$$\textbf{Acute RfD} = \frac{\textbf{400 mg/kg/day (LOAEL)}}{\textbf{1000(UF)}} = \textbf{0.40 mg/kg/day}$$

Chronic Reference Dose

Study Selected: NTP 90-Day Study in the Rat (1980)
[Subchronic Toxicity Study: Naphthalene (C52904), Fischer 344 rats. Battelle's Columbus Laboratories, Columbus, OH. Report to the U.S. Department of Heath and Human Services, National Toxicology Program.]

MRID No.: n/a

Dose and Endpoint for Establishing the RfD: NOAEL = 100 mg/kg/day. LOAEL = 200 mg/kgday, based on decreased body weights/body weight gains.

Comments on Study/Endpoint/Uncertainty Factors: The endpoint is based on the most sensitive effect noted in the subchronic oral rat study. The study is supported by the NTP subchronic oral mouse study that indicated a clear NOAEL of 100 mg/kg/day. An UF of 1000 was applied to account for extrapolation from subchronic to chronic exposure and chronic toxicity studies (10x), inter-species extrapolation (10x) and intra-species variations (10x). This composite factor of 1000 was also address the lack of a reproductive toxicity study for this nonfood use pesticide.

$$\textbf{Chronic RfD} = \frac{\textbf{100 mg/kg/day (NOAEL)}}{\textbf{1000(UF)}} = \textbf{0.10 mg/kg/day}$$

Incidental Oral Exposure (Short-Term)

Study Selected: NTP Developmental Study in the Rat (NTP 1991):
[Final Report on the Developmental Toxicity of Naphthalene in Sprague-Dawley (CD) rats. U.S. Department of Heath and Human Services, National Toxicology Program.]

MRID No.: n/a

Dose and Endpoint for Risk Assessment: The incidental oral endpoint is based on maternal effects observed in a developmental rat study, and is the appropriate duration for short-term exposure scenarios. Maternal toxicity included persistent clinical signs of lethargy, slow breathing, rooting behavior, and significant decreases in body weights/body weight gains and decreased food and water consumption. The LOAEL is 150 mg/kg/day and the NOAEL is 50 mg/kg/day.

UF =100x (10x interspecies extrapolation, 10x intraspecies variability)

Comments on Study/Endpoint/Uncertainty Factors: The endpoints are considered relevant to children. The NOAEL of 50 mg/kg/day is also considered protective since it is based on the

pregnant female rat (treatment was from GD 6-15) which may be more sensitive than nonpregnant female rats and male rats after 90-day treatment. In this regard, a NOAEL of 100 was identified in both the NTP 13-week B6C3F1 mouse study and the NTP rat study. The results of a 14- and 90-day published study on CD-1 mice (Shopp et al. 1984) established a NOAEL of 53 mg/kg/day.

Dermal Absorption

There are no in vivo dermal absorption studies. However, a dermal absorption factor is not needed since there is an acceptable 90-day dermal toxicity study in the rat.

Dermal Exposure (Short-Term)

Study Selected: 90-Day Dermal Toxicity Study in the Rat

MRID No.: 40021801

Dose and Endpoint for Risk Assessment: The NOAEL of 300 mg/kg/day from a 90-day dermal toxicity study in the rat is selected for dermal risk assessment. The LOAEL of 1000 mg/kg/day is based on atrophy of seminiferous tubules in males, and nonneoplastic lesions in the cervical lymph node (hyperplasia), liver (hemosiderosis), thyroid (thyroglossal duct cysts), kidneys (pyelonephritis), urinary bladder (hyperplasia) and skin (acanthosis, hyperkeratosis) in females.

UF =100x (10x interspecies extrapolation, 10x intraspecies variability)

Comments on Study/Endpoint: Intermediate- and long-term dermal exposures are not anticipated. The dermal risk assessment for short-term exposure scenarios is conservative since it is based on a 90-day study.

Inhalation Exposure (All durations)

At this time, dose and endpoints have not been selected for the purposes of estimating human inhalation risk. See Section 3.5 below**.**

Recommendation for Aggregate Exposure Risk Assessments

Nasal lesions have been observed in the inhalation toxicity studies but not in the oral toxicity studies. Nasal lesions were the most sensitive endpoint in rodents. Body weight decrement was the most sensitive effect in subchronic oral rat study. There were clinical signs of toxicity at higher dose levels. Clinical signs of toxicity and body weight decrement were apparent in the NTP rat developmental study. Clinical signs of toxicity were noted in the subchronic oral B6C3F1 mouse study. There were no changes of toxicological significance in body weight gains in treated mice. Although not the most sensitive endpoint, body weight decrement was also noted in the inhalation toxicity studies (4-week nose only rat study; 13 week nose-only rat study; subchronic neurotoxicity rat study; and chronic exposure chamber rat NTP study) at ≥ 10 ppm

naphthalene. Body weight data in the NTP mouse study was presented only graphically. The 90-day dermal toxicity study in the rat revealed toxicity only at very high dose level (1000 mg/kg/day) that included atrophy of seminiferous tubules in males, and various nonneoplastic lesions in females (skin, lymph nodes, liver, thyroid, kidneys, urinary bladder and skin). There were no effects on body weights in the dermal study. Based on the available data, an aggregate exposure risk assessment is not supported as there is no common toxicity among all routes of exposure.

Classification of Carcinogenic Potential

In the NTP chronic studies, carcinogenic effects have been observed in both rats and mice following inhalation exposure.

In the rat, nasal tumors included neuroblastomas of the olfactory epithelium and adenomas of the respiratory epithelium. There was also an increase in the incidences of adenoma of the respiratory epithelium. The NTP concluded that "under the conditions of this 2-year inhalation study, there was clear evidence of carcinogenic activity of naphthalene in male and female F344/N rats based on increased incidences of respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose."

In the mouse study, male mice had statistically significant increased incidences of liver adenomas, and adenomas and carcinomas combined. Female mice exhibited increased incidences of alveolar/bronchiolar adenomas, and adenomas and carcinomas combined.
The NTP concluded that "under the conditions of this 2-year inhalation study, there was no evidence of carcinogenic activity' of naphthalene in male B6C3F1 mice exposed to 10 or 30 ppm. There was "some evidence of carcinogenic activity" of naphthalene in female B6C3F1 mice, based on increased incidences of pulmonary alveolar/bronchiolar adenomas.

The carcinogenic and noncarcinogenic potential of naphthalene is currently undergoing review by EPA Integrated Risk Information System (IRIS). Naphthalene has not been subjected to a full EPA/International Programme of Chemical Safety (IPCS) framework for the analysis of a cancer mode of action (MOA) and relevancy of animal MOA to human carcinogenicity.

3.5 Characterization of Inhalation Hazard

The primary adverse outcome reported in available studies (NTP cancer bioassay studies) using rodents (rats and mice) exposed to naphthalene throughout their lives by the inhalation route is respiratory tract (nose and lung) tumors. Naphthalene clearly induced nasal tumors in rats (both male and female). Specifically, adenomas of the nasal epithelium and olfactory epithelial neuroblastomas were observed. In mice, there was also some evidence of lung tumors in female mice only (all but one of the neoplasms observed in the female mice were benign), but this was less convincing than the tumor response in rats. The nasal tumors in rats appear to be secondary to cytotoxicity because cytotoxicity is found to occur first and morphologically may represent a precursor to the nasal tumors. Signs of cytotoxicity include: inflammation, degeneration, metaplasia, and hyperplasia. No significant systemic toxicities (effects distal to the site of

exposure, the nose) or tumors were observed following inhalation exposure in rats and mice. Cytotoxicity and regenerative proliferation is a plausible mode of action for naphthalene-induced respiratory effects. Studies are ongoing to further investigate this mode as well as the involvement of different CYP isoforms, different naphthalene metabolites, genotoxicity and reactive oxygen species.

Information on naphthalene and human cancer is extremely limited. Although reports are found in the literature, no conclusions can be drawn regarding the role, if any, of naphthalene in the induction of human cancer. For example, all the cases of laryngeal cancer occurring in workers involved in the purification of naphthalene involved smokers who were also exposed to other substances, including coal tar volatiles (ATSDR 2005; IARC 2002). However, evidence does indicate that cancers of the nasal passages are relatively rare in humans, with estimations of < 1 case/100,000 (Calderon-Garciduefias et al. 1999).

A large number of genotoxicity studies are available on naphthalene (reviewed by ASTDR, 2005, EC-JRC, 2003; IARC, 2002; IPCS, 1998). There is little evidence that naphthalene induces gene mutations. Some positive results are reported that suggest naphthalene is clastogenic (chromosome breaking) in vitro. In vivo chromosome assays were negative. The available data from short-term screening does not provide a compelling and convincing case that naphthalene is an in vivo genotoxin. There is some limited evidence suggesting that naphthalene generates reactive oxygen species, which may possibly lead to oxidation of DNA and DNA damage. Most of the experimental evidence suggests that the rodent tumor responses are driven by the metabolism of naphthalene to cytotoxic metabolites inducing cell injury and subsequent cell regeneration. As discussed below, the uncertainty of whether naphthalene poses a human cancer concern at ambient or environmental levels of exposure arises because of the potential species differences in rates of metabolism leading to its toxicity.

Critical research has been published indicating that metabolic activation is a required step for naphthalene's respiratory toxicity (unmetabolized naphthalene is not the cause of the cytotoxicity or tumors) and that there are notable species differences in the metabolism of naphthalene between rodents and primates (Buckpitt et al. 1992, 1995, 2002; Bogen et al. 2008). Available research to date indicates that the metabolism pathway in rodents is more active than in humans (i.e., humans have a slower rate of formation of the active metabolite) (Buckpitt et al. 1992, 1995, 2002; Bogen et al. 2008).

Although rodents are likely to be more susceptible to naphthalene's respiratory effects (cytotoxicity and tumors) than humans, the human relevance of the rodent respiratory tract tumors is not clear at this time. The issue of whether naphthalene poses a human health concern at ambient exposures will be informed to large degree by an explanation of the process by which naphthalene is absorbed, distributed, metabolized, and eliminated by the body (pharmacokinetics). The pharmacokinetic (PK) model that will quantify the species difference is not available now but is forthcoming in approximately 2-3 years.

Because rodents are likely to be more susceptible to naphthalene's potential respiratory effects than humans, there may not be a significant concern for respiratory toxicity in humans exposed at ambient levels. It would be inaccurate to quantify non-cancer and cancer risks in humans

based on default methods which do not incorporate the critical dosimetry and metabolic differences between primates and rodents. Thus, no quantification of either non-cancer or cancer inhalation risks will be provided in this assessment. Instead of dose-response modeling, this assessment 1) characterizes the uncertainties associated with species differences, and 2) estimates the typical human exposures to ambient naphthalene and directly compares these to the NOAELs and LOAELs identified in the rodent studies. This comparison is informational only and provides a sense of the difference between expected ambient levels of naphthalene that humans may be exposed to and the levels that cause no effect, as well as a toxic effect, in rodents.

The available data indicate that the production of tissue reactive metabolites, e.g., 1,2-naphthalene oxide, 1,2-naphthoquinone, 1,4-naphthoquinone, may be formed at a slower rate in the human than in the rat at the same parent compound concentration (Buckpitt et al. 1992, 1995, 2002; Bogen et al. 2008). These reactive metabolites are critically involved in the respiratory cytotoxicity and tumorigenic effects of naphthalene (Buckpitt et al. 1992, 1995, 2002; Bogen et al. 2008; Shultz et al. 2001). Target specificity of response (i.e., nasal tissue in rats; lungs in mice), is a reflection of the species differences in the metabolism of naphthalene and respiratory anatomy and airflow pattern (Lee et al. 2005; Buckpitt et al. 2002; Bogen et al. 2008). Species variation in metabolism can be explained by critical differences in the rate of formation of specific stereoisomeric metabolites, the levels of cytochrome P450 (specifically CYP2F has been studied), and catalytic activity of CYP2F. In regard to stereoselective pulmonary metabolism of naphthalene, higher rates of the specific enantiomeric epoxide (1R,2S-naphthalene oxide) were noted in mouse lung compared with rats (ATSDR 2005). Rat, hamster and monkey lungs preferentially formed the specific enantiomer 1S,2R-naphthalene oxide with lower rates of formation (ATSER 2005). The susceptibility of mouse lung to naphthalene is considered to be related to the higher rates of formation of 1R,2S-naphthalene oxide (ATSDR 2005). The preferential formation of 1S,2R-naphthalene oxide from microsomes prepared from human lymphoblastoid cells expressing recombinant human CYP2F1 suggests that humans may be less vulnerable than the mouse to pulmonary effects of naphthalene (ATSDR 2005).

In contrast to rodents, primates do not contain significant levels of CYP2F in the lung, and CYP2F levels in the nose are considerably lower (Baldwin et al. 2004). Primates exhibit a slower rate of pulmonary metabolism of naphthalene, about 100-fold lower than the mouse which has the highest activity (Buckpitt et al. 1992; Baldwin et al. 2004; Bogen et al. 2004). The differences in the rate of metabolism of naphthalene in nasal tissue may be related to differences in anatomy of nasal passages, CYP2F expression, and stereochemistry of naphthalene epoxidation between primates and rodents (Buckpitt et al. 1992).

Since the data available to date indicate that rodents are more susceptible to the respiratory toxicity of naphthalene, the use of rodents as a model without application of appropriate species scaling accounting for species differences in dosimetry and metabolism would most likely result in inaccurate estimates of human risk. Therefore, the current assessment provides, for informational purpose, a comparison of points of departure (LOAELs) from animal studies resulting in toxic outcomes in the rodents and typical ambient levels of naphthalene found in monitoring studies. A comparison was also made between the animal study dose in which no adverse effects were found (NOAELs) and ambient naphthalene levels.

Generally, in the absence of information on kinetics/dynamics, it is assumed that humans may be 10 times more sensitive than animals (10X interspecies factor). The current research indicates that humans may actually be less sensitive than rodents because of differences in rate of bioactivation of naphthalene as well as anatomical and physiological differences in the nose and respiratory tract. These critical differences between primates and rodents have not been accounted for in this assessment. Thus, with consideration of more appropriate species scaling and dosimetry, the margins of exposure for human inhalation risk assessments are likely to be larger than the differences calculated between the rodent NOAELs and LOAELs and the ambient naphthalene levels.

Although the margins of exposure are anticipated to be greater than the comparison exercise in this assessment, there are uncertainties in the database. For instance, CYP isoforms other than CYP2F (e.g., CYP2A, CYP2A13, CYP2J2 which have been detected in olfactory mucosa) and the potential role of these other CYP isoforms in naphthalene metabolism have not been studied (Ding and Kaminsky 2003). While CYP content in the nasal mucosa is high in many mammalian species, this apparently is not the case for humans (Ding and Kaminsky 2003). In addition, data on the kinetics of naphthalene metabolism in liver microsomes of humans reveal lower Vmax (maximum rate of bioactivation) rates and lower affinity of naphthalene for various CYP forms (including some of those detected in olfactory mucosa and other areas of the respiratory tract) compared to rodents, suggesting that rodents have a greater catalytic efficiency of naphthalene metabolism (Cho, Rose and Hodgson, 2006; Bogen et al. 2008). However, studies confirming that rodents have a greater catalytic efficiency of naphthalene bioactivation in nasal tissues compared to primates are still part of ongoing research. There are no data to indicate that humans have a slower rate of clearance, but if they did, then there would be a longer time for humans to produce the active metabolite. The metabolic rates of other CYPs and clearance is being addressed in the current PK model research, scheduled to be completed in 2-3 years.

3.6 Summary of Toxicological Doses and Endpoints for Naphthalene for Use in Human Risk Assessments

Table 3.6 Toxicological Doses and Endpoints for Naphthalene for Use in Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary All populations including infants and children	LOAEL = 400 mg/kg/day	UF_A= 10x UF_H = 10x UF_L= 10x	aRfD=0.4 mg/kg/day	**Acute Oral Neurotoxicity Study - Rat** NOAEL = not identified. LOAEL = 400 mg/kg/day based on hunched posture in females, head shaking in males and females, and reduced motor activity in males and females.

Table 3.6 Toxicological Doses and Endpoints for Naphthalene for Use in Human Health Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Chronic Dietary <u>All populations</u> including infants and children	NOAEL= 100 mg/kg/day	UF_A= 10x UF_H = 10x UF_S = 10x	cRfD = 0.1 mg/kg/day	**NTP Subchronic Rat Study** NOAEL = 100 mg/kg/day LOAEL = 200 mg/kg/day based on significant decreases in body weights/body weight gains.
Incidental Oral (Short-term; 1-30 days)	NOAEL= 50 mg/kg/day	UF_A= 10x UF_H= 10x	MOE= 100 (residential)	**NTP Developmental Rat Study** NOAEL = 50 mg/kg/day LOAEL= 150 mg/kg/day based on maternal effects – persistent clinical signs of lethargy, slow breathing, rooting behavior, and significant decreases in body weights/body weight gains and decreased food and water consumption.
Dermal (Short-Term; 1-30 days)	Dermal NOAEL= 300 mg/kg/day	UF_A= 10x UF_H= 10x	MOE= 100 (residential)	**90-Day Dermal Toxicity Study – Rat** NOAEL = 300 mg/kg/day LOAEL = 1000 mg/kg/day based on atrophy of seminiferous tubules in males, and nonneoplastic lesions in the cervical lymph node (hyperplasia), liver (hemosiderosis), thyroid thyroglossal duct cysts), kidneys (pyelonephritis), urinary bladder (hyperplasia) and skin (acanthosis, hyperkeratosis) in females.

Table 3.6 Toxicological Doses and Endpoints for Naphthalene for Use in Human Health Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Inhalation (Short-term; 1-30 days)	Inhalation **LOAEL** = 10 ppm or 52 mg/m^3 **NOAEL** = 3 ppm or 16 mg/m^3	N/A	N/A	**4-Week (Nose-Only) Inhalation – Rat** NOAEL = 3 ppm LOAEL = 10 ppm based increased incidence and severity of nasal lesions (slight disorganization, rosette formation, basal cell hyperplasia, erosion, atrophy, and degenerate cells in the olfactory epithelium; loss of bowman's glands; respiratory epithelium hypertrophy; rosette formation in the septal organ of Masera and fusion of the turbinates).
Inhalation (Intermediate-term; 1-6 months)	Inhalation **LOAEL** = 2 ppm or 10 mg/m^3 **NOAEL** = 1 ppm or 5.2 mg/m^3	N/A	N/A	**13-Week (nose-only) Inhalation Rat Study; Subchronic (nose-only) Neurotoxicity Rat Study** NOAEL = 1 ppm (Subchronic neurotoxicity study) NOAEL (13 week inhalation study) – not identified. LOAEL = 2 ppm (13 week inhalation study) based on increased incidence and severity of nasal lesions (degeneration, atrophy and hyperplasia of basal cells of the olfactory epithelium; rosette formation of olfactory epithelium; loss of Bowman's glands; hypertrophy of respiratory epithelium). LOAEL = 10 ppm (subchronic neurotoxicity study) based on atrophy/disorganization of the olfactory epithelium and hyperplasia of the respiratory and transitional epithelium.

Table 3.6 Toxicological Doses and Endpoints for Naphthalene for Use in Human Health Risk Assessments				
Exposure/ Scenario	Point of Departure	Uncertainty Factors	Level of Concern for Risk Assessment	Study and Toxicological Effects
Inhalation (Long-term; > 6 months)	Inhalation **LOAEL** = 10 ppm or 52 mg/m^3	N/A	N/A	**NTP ChronicToxicity and Carcinogenicity Studies in the Rat and Mouse** NOAEL = not identified LOAEL (rat study) = 10 ppm based on increased incidence and severity of atypical (basal cell) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium; hyperplasia, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia of the respiratory epithelium; and glandular hyperplasia and squamous metaplasia.

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). UF_L = use of a LOAEL to extrapolate a NOAEL. UF_S = use of a short-term study for long-term risk assessment. UF_{DB} = to account for the absence of key date (i.e., lack of a critical study). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

3.7 Endocrine disruption

EPA is required under the FFDCA, as amended by FQPA, to develop a screening program to determine whether certain substances (including all pesticide active and other ingredients) may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effects as the Administrator may designate. Following the recommendations of its Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), EPA determined that there was scientific basis for including, as part of the program, the androgen and thyroid hormone systems, in addition to the estrogen hormone system. EPA also adopted EDSTAC's recommendation that the Program include evaluations of potential effects in wildlife. For pesticide chemicals, EPA will use FIFRA and, to the extent that effects in wildlife may help determine whether a substance may have an effect in humans, FFDCA authority to require the wildlife evaluations. As the science develops and resources allow, screening of additional hormone systems may be added to the Endocrine Disruptor Screening Program (EDSP).

When the appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, naphthalene may be subjected to additional screening and/or testing to better characterize effects related to possible endocrine disruption.

4.0 Public Health and Pesticide Epidemiology Data

4.1 Epidemiology Studies

Three studies were submitted which explored the possible association between exposure to components of jet fuel, including naphthalene, and incident cancer among both private and military aerospace personnel. These three studies were reviewed by HED (C. Christensen, DP#339853, 5/31/07). An additional recently published epidemiology study concerning the association between non-occupational exposure to naphthalene as a component of mothballs and non-Hodgkin's lymphoma (NHL) is also included in this review.

HED Conclusions:

Three of the four studies presented here utilized an ecologic exposure assessment method (indirect exposure method) and evaluated exposure to jet fuel in association with cancer. The question HED is addressing concerns exposure to naphthalene and adverse health outcomes. Given the non-specific exposure measure (jet fuel) and the potentially significant exposure misclassification reflected in these three studies, inference concerning the association between naphthalene exposure and incident cancer is severely limited based upon these studies alone. These studies are considered non-informative to the current naphthalene risk assessment.

The finding of a 2-fold increased risk of NHL among women in upstate New York in a study of non-occupational exposure to mothballs, of which naphthalene is often a component, is suggestive of a possible association. However, as it is not known if the mothballs in this study were those containing naphthalene. This study does not contribute to the assessment and characterization of risks to naphthalene exposure.

4.2 Incident Data

Naphthalene poisoning incident data were reviewed from the following databases to identify potential patterns of the extent and severity of the health effects attributed to naphthalene exposure (M.Hawkins and H. Allender, DP#336085, 6/25/07):

1 - Cases reported in the Poison Control Center (PCC) Database from 1993 to 2005.
2 - Cases reported in the Incident Data System (Attachment 1) from 1999 to the present.
3 - Cases reported in the California Department of Pesticide Regulation from 1999 to 2004.
4 - Cases reported in the NIOSH system from 1998 to 2003.

1. Poison Control Center Data – 1993-2005

This section discusses results from the Poison Control Center's Toxic Exposure Surveillance System (TESS) from the years 1993 through 2005 and reflects data stratified by population: occupational, non-occupational, and children. The children class is five years of age or less; this definition includes children about to become six years old, or up to 72 months old. Cases involving exposures to multiple products and cases with unrelated medical outcome are excluded. Also excluded are intentional exposures, i.e., suicide attempts. There are no apparent

distinctions made for route of exposure (oral, dermal, inhalation).

The PCC data are summarized in such a way that the frequency of poisoning incidents for naphthalene are compared to the composite of all pesticides for which the PCC received a non-excluded incident report. The frequency of events are categorized by health severity category (i.e., all symptoms, moderate, and major) and by level of health care received. A comparative ratio provides a simple measure of the relative frequency of reported health effects by severity category. Knowledge of the ratios of symptoms for a single chemical (or a group of chemicals) provides a relative measure of the public health impact of the acute pesticide events. [See memo DP#336085, M.Hawkins and H. Allender, 6/25/07, for tables of comparison. Results are summarized below.]

Summary of PCC results

For the occupational class, the proportion who report symptoms among those who are followed and the proportion who are seen at a Health Care Facility (HCF) among those who are exposed are lower than the composite average. However, the occurrence of major symptoms and hospitalization in an ICU are greater than the composite average for those workers who are naphthalene exposed. [Note: occupational exposures for these data include pesticide poisoning events that take place at a workplace. An occupationally exposed individual in this dataset could be the applicator or a bystander; no distinction is made in the dataset.]

While the number of non-occupational naphthalene-exposed adults is 10-fold greater than the number exposed in the occupational environment, the frequency and severity of symptoms and/or health effects is lower than the all pesticide exposed composite average for this group.

The total number of children exposed to naphthalene reported to the PCC is 10-fold greater than among non-occupationally exposed adults. Clearly, exposure opportunities exist for non-occupational exposure to children. Among those who are exposed, nearly 1.5x the number of children are seen at a HCF as compared to the composite average. However, many fewer children who are exposed and followed by PCC staff reported symptoms as compared to the composite average. The magnitude of children exposed to naphthalene (15,572) suggests that children easily reach this chemical.

Naphthalene produces an average annual exposure for children of 1197 cases. The annual average exposure for a typical pesticide, affecting children, is 103 cases per year per pesticide. Comparing naphthalene with a typical pesticide, naphthalene produces about 11.6 times more exposures than a regular pesticide every year. In order to prevent exposure, measures restricting the access to the active ingredient should be taken. This could include special packaging and other limitations to block children from reaching the active ingredient.

Ratios for the entire population present lower percentages than the composite with the only exception of cases seen in a health care facility. With 21,417 exposures reported in 13 years, or annual average of 1647 cases per year, naphthalene produces a large number of cases compared to the average of 183 cases per year produced by a standard pesticide; this is about than 9 times the average of exposures produced by a typical pesticide. A reduction of exposure attributed to

naphthalene, especially in children, may represent a significant prevention opportunity to reduce further human incidents.

In total exposure, symptomatic cases, and cases treated in a HCF, naphthalene shows no trend by year in the 13 year-span of data collected. Calculations show an average of about 1647 exposures per year, 133 symptomatic cases per year, and 310 cases per year seen in a heath care facility.

Resulting from exposure to naphthalene, the health symptoms observed in the PCC database were concentrated in six areas, and within each area, the symptoms were:

1. Gastrointestinal: nausea, vomiting, and throat irritation
2. Neurological: headache, dizziness/vertigo, and drowsiness/lethargy
3. Respiratory: dyspnea, and cough/choke
4. Ocular: eye irritation/pain, and lacrimation
5. Dermal: edema, erythema/flushed, and irritation/pain
6. Miscellaneous: Other symptoms

2. Cases reported in the Incident Data System from 1999 to the present

IDS reported three cases:

Incident#1359-1: A pesticide incident occurred in 1994, when a neighbor, who lived below a woman's condominium, applied the product on the patio for moth control and not to repel cats which is a misuse of the product. Three individuals reported coughing and numbness in outer extremities that got progressively worse over the next several weeks. No further information on the disposition of the case was reported.

Incident#2368-1: A pesticide incident occurred in 1994, when a family's neighbor, which lived below, applied three boxes of the product as an animal repellent to her landscape. A woman, her husband, and her eleven year old son reported coughing and a headache. About ten days later, the woman reported numbness, tingling, and weakness in her extremities and face. The woman was treated by four neurologists and was diagnosed with peripheral neuropathy. No further information on the disposition of the case was reported.

Incident#7954-1: A pesticide incident occurred in 1998, when a woman's neighbors placed the product in the grassy around their common courtyard and grounds that are shared by the residents. The woman, who had a pre-existing respiratory condition, reported difficulty breathing whenever she opened her apartment door or windows or whenever she walked to her parking lot. No further information on the disposition of the case was reported.

3. California Pesticide Illness Surveillance Program Data 2000-2004

Detailed descriptions of four cases submitted to the California Pesticide Illness Surveillance Program (1999-2004) were reviewed. In two of these cases, naphthalene was used alone or was judged to be responsible for the health effects. In the first case, flakes that were on top of a container flew into a cashier's eyes and face when she picked up a broken package while she

checked out an individual in her line. The cashier reported eye irritation. In the second case, a social worker visited their client's apartment and noticed a mothball odor. The client had placed the mothballs in his apartment to eliminate cockroaches. The social worker reported coughing, watery eyes, throat irritation, and chest congestion.

4. NIOSH SENSOR

Out of 5,899 reported cases from 1998 to 2003, there are 15 cases reported in the SENSOR database involving naphthalene. Seven cases were reported in Texas, four in Washington State, three in Florida, and one in California; seven cases were males and seven were females with onecase of unknown gender. The average age of the cases was 46.2 years old with the youngest case being 22 years old and the oldest case being 76 years old. Two cases in Texas relate to an apartment complex that applied snake repellant granules to attics. Other two cases in Texas also relate to another apartment complex that spread mothballs in attics to repel pigeons, odor was overwhelming and people fell sick. In addition, in Texas a chemistry teacher was conducting and experiment with mothballs in a test tube; student dropped test tube in sink and the teacher reported herself to HCF; no medical treatment was provided. Two cases in Florida suspect that naphthalene in mothballs used at their home was causing ill symptoms. The most common symptoms were classified in the following five areas:

Nervous/Sensory symptoms: Headache and dizziness
Gastrointestinal: Nausea and vomiting
Ocular symptoms: Eye pain/irritation/inflammation, lacrimation, and conjunctivitis
Respiratory symptoms: Upper respiratory pain/irritation and dyspnea/shortness of breath
Miscellaneous symptoms: Acidosis, Alkalosis, and anion gap increase

Study Summary

The summary findings for the period 1993 to 2005 for naphthalene, mainly for PCC data are:

- Naphthalene produces a higher proportion of acutely toxic incidents requiring medical attention when compared to the composite average of all other pesticides. There is a pattern of statistically significant results in cases seen in a health care facility. This pattern observed in the combined population (occupational, non-occupational, children) is largely due to the frequency and severity of pesticide poisoning among children less than six years old.
- Exposure to children is much higher than a typical pesticide.
- Naphthalene PCC data show average results of about 11647 exposures/year, 133 symptomatic cases/year, and 310 cases/year seen in a heath care facility.
- No apparent annual trend is evident in the 13 year-span of data collected.
- For children under six years old, the large majority of exposures were from ingestion of mothball products marketed for use in the home.

5.0 Exposure Characterization/Assessment

5.1 Dietary Exposure/Risk Pathway

5.1.1 Food Exposure/Risk Pathway

None, since there are no food uses.

5.1.2 Water Exposure/Risk Pathway

Environmental Fate and Effects Division's (EFED) has performed a drinking water exposure assessment for naphthalene (M. Corbin, DP#339118, 4/25/07; amended under DP#351119). No acceptable environmental fate data have been submitted to support the registration of naphthalene. Several environmental fate studies (aerobic soil and aqueous photolysis) were submitted but deemed to be unacceptable for risk assessment purposes due to poor material balances, inadequate sample intervals, and issues with volatile trapping and therefore have not been used in this assessment. A single overview of open literature data (MRID 45346801) provided supplemental data on the adsorption/desorption and aerobic soil metabolism properties of naphthalene.

For sorption a total of 13 open literature studies were submitted and summarized and indicated that the solubility of naphthalene ranged from 30 to 31.7 mg/L and that the Koc ranged from 200 to 1470 for a variety of soils from North America, Europe and China. The study author concluded from this review that naphthalene was bound relatively rapidly to soils with a sustained desorption over days to weeks. For biodegradation a total of 15 open literature studies were submitted and reviewed and found that naphthalene degraded with aerobic soil metabolism half lives between 3.5 and 40 days with no appreciable degradation under anaerobic conditions. Possible degradation processes affecting naphthalene (and PAH's in general) include volatilization, photo-oxidation, bioaccumulation, adsorption, leaching, and microbial degradation.

A number of degradates were identified in the various open literature studies. The study author proposed a degradation pathway for naphthalene which ultimately resulted in catechol. Transitional degradates included cis-1,2-dihydroxy-1,2-dihydronaphthalene, 1,2-dihydroxy-naphthalene, 2-hydroxchromene-2-carboxylate (HCCA), trans-o-hydroxy-benzylidenpyruvate (tHBPA), salicyladehyde, and salicylate. However, there is no environmental fate data for these degradates and therefore, exposure estimates are for parent only.

Aquatic Exposure Modeling

Typically, EFED relies on an integrated approach for conducting exposure assessments that relies on an analysis of both monitoring data and modeling. In the case of naphthalene, no

monitoring data that specifically targets this use pattern are available. Therefore, this assessment relies solely on modeling.

EFED has conducted a Tier I aquatic exposure assessment relying on FIRST. FIRST (*F*QPA *I*ndex *R*eservoir *S*creening *T*ool, version 1) is a program to calculate acute as well as longer-term estimated environmental concentration (EEC) values. It considers reduction in dissolved pesticide concentration due to adsorption of pesticide to soil or sediment, incorporation, degradation in soil before washoff to a water body, direct deposition of spray drift into the water body, and degradation of the pesticide within the water body.

Given the limited use of this compound and the fact that it is applied to in a band around ornamentals, planting beds and gardens as a repellent, an adjustment to the modeled EEC was made assuming 4.1% of a typical residential lot would be treated (see DP#339118 for calculations). The resultant FIRST EEC has been adjusted by this factor. Input parameters and for the FIRST modeling are presented in the table below.

Table 5.1.2.1 Summary of FIRST environmental fate data used for aquatic exposure inputs for naphthalene

Fate Property	Value	MRID (or source)
Solubility in Water	31 mg/L	Product Chemistry
Photolysis in Water	stable	Assumed
Aerobic Soil Metabolism Half-lives	32.6 days (90th % of 9 values)	MRID 45346801
Hydrolysis	stable	Assumed
Aerobic Aquatic Metabolism (water column)	65.2 days	Twice the aerobic soil metabolism rate constant
Koc	131	MRID 45346801
Application Efficiency	100 % for granular[1]	default value
Spray Drift Fraction	0 % for granular	default value

Two scenarios were modeled to represent a high naphthalene use scenario and at low use scenarios. The high use scenario was modeled at 10.8 lbs/acre with six applications per year, while the low use scenario was modeled at 0.56 lbs/acre with six applications per year. The application method was modeled as ground application with a granular formulation.

Table 5.1.2.2 Results of FIRST Modeling for Naphthalene Use on Ornamentals*

Use Site	Application Rate (lbs/acre)	Number of Applications (interval)	Peak EEC (ppb)	Annual Average EEC (ppb)

Table 5.1.2.2 Results of FIRST Modeling for Naphthalene Use on Ornamentals*				
Use Site	**Application Rate (lbs/acre)**	**Number of Applications (interval)**	**Peak EEC (ppb)**	**Annual Average EEC (ppb)**
Ornamentals for rabbit & dog repellent	10.8	6 (2 months)	43.4	6.5
Ornamentals for snake repellent	0.56	6 (2 months)	2.2	0.3

Unaccounted for in this exposure assessment is the fact that naphthalene is volatile. No product chemistry data were available but an estimate of the vapor pressure was made using EpiSuite. EpiSuite reported an experimentally derived value for vapor pressure of 8.5 $x10^{-2}$ mm Hg (which is consistent with the registrant reported value of 10.5 Pa, or 7.8 x 10^{-2} mm Hg) and a Henry's Law Constant of 0.00044 atm-m^3/mol suggesting that naphthalene is volatile. Given the potential volatility of this compound and the fact that the Tier I model used to estimate exposure does not account for volatility as a route of dissipation it is likely that the exposure estimates derived above are over-predictions of potential exposure. It is unclear from the open literature data whether degradation in the studies reported accounted for the fraction lost due to volatility or not.

Finally, Sci-Grow modeling was conducted for both use scenarios to provide an estimate of the potential loading of naphthalene to groundwater. Sci-Grow modeling relied on similar model inputs with the exception of aerobic soil metabolism which uses the average half life of 14 days. The results are summarized in Table II.3.

Table 5.1.2.3 Results of Sci-Grow modeling for naphthalene used on ornamentals at the high and low application rates			
Use Site	**Application Rate (lbs/acre)**	**Number of Applications (interval)**	**Annual Average EEC (ppb)**
Ornamentals for rabbit & dog repellent	10.8	6 (2 months)	4.5
Ornamentals for snake repellent	0.56	6 (2 months)	0.2

5.2 Dietary Exposure Estimates

There are no agricultural or any food related pesticide uses of naphthalene, therefore, no dietary exposure from food is expected. However, there is a potential for drinking water exposure due to the outdoor uses of naphthalene.

Acute and Chronic Dietary Assessments

Unrefined acute and chronic screening-level drinking water assessments were conducted for naphthalene using the version 2.03 Dietary Exposure Evaluation Model (DEEM-FCID™) which uses food consumption data from the U.S. Department of Agriculture's Continuing Surveys of Food Intakes by Individuals (CSFII) from 1994-1996 and 1998.

The acute and chronic screening-level drinking water assessments are conservative evaluations of dietary exposure to naphthalene. They are made using the Environmental Fate and Effects Division (EFED) determination of Estimated Environmental Concentrations (EECs) in water (M. Corbin, DP#339118, 4/25/07; amended under DP#351119). Using a screening modeling tool (FIRST), EFED calculated peak and annual average surface water Estimated Environmental Concentrations (EEC) of 43.4 ppb and 6.5 ppb, respectively. These values represented the high-end use rate of naphthalene on ornamentals.

The acute screening-level drinking water assessments using the DEEM-FCID™ Model were reported at the 95th percentile of exposure for the general U.S. population and all of its subgroups. It is based exclusively on the peak EEC of 43.4 ppb for all direct and indirect water sources. Risk estimates were all found to be well below the 100% acute Reference Dose (aRfD) threshold level of concern. The acute exposure for naphthalene was estimated to be 0.0023 mg/kg/day at 0.6% of the aRfD for the general U.S. population. In comparison, acute exposure for the most highly exposed population subgroup, all infants, was estimated to be 0.0080 mg/kg/day at 2.1% of the aRfD.

In conjunction, the chronic screening-level drinking water assessment is another conservative evaluation based exclusively on the annual average EEC of 6.5 ppb for all direct and indirect water sources. Risk estimates were all found to be well below the 100% chronic Reference Dose (cRfD) threshold level of concern. The chronic exposure for naphthalene was estimated to be 0.0001 mg/kg/day at 0.1% of the cRfD for the general U.S. population. In comparison, chronic exposure for the most highly exposed population subgroup, all infants, was estimated to be 0.0004 mg/kg/day at 0.4% of the cRFD.

Additional Drinking Water Characterization

As previously noted, a drinking water assessment for naphthalene was carried out by EFED for its use as a pest repellant outdoors around the home. This screening level assessment relied on modeling analyses to calculate EECs for drinking water. Given the potential volatility of this compound and the fact that the Tier I model used to estimate exposure does not account for volatility as a route of dissipation it is likely that the EECs are overestimated. Additionally, the dietary (water only) assessment used only the high end EECs from a maximum use rate and the resulting risk estimates, while not of concern, can be considered upper bound. Although a number of potential water degradates have been identified, the drinking water assessment is only for the parent compound naphthalene. There were no data on the environmental fate of the degradates, or on the toxicity of the degradates in relation to the parent. However, given the overall conservative nature of the water assessment it is unlikely that risks from exposure to

naphthalene in drinking water were underestimated.

Available water monitoring data, while non-targeted, indicate that naphthalene was infrequently detected in water supplies, and those detects were usually well below the Health Reference Level (HRL) of 140 ppb. EPA's Office of Water has concluded that the regulation of naphthalene in drinking water is unlikely to represent a meaningful opportunity for health risk reduction (USEPA, Office of Water Reprt: EPA 815-R-03-014, July 2003). While it is not known if detects in ambient water are from pesticide or industrial uses, it should be noted that about 190,000 lbs of naphthalene a year is used for outdoor pest control compared to more than 1.8 billion lbs naphthalene used for the US jet fuel market (3/28/07 Naphthalene SMART meeting).

Table 5.2.1 Summary of Screening –Level Drinking Water Exposure and Risk for Naphthalene

Population Subgroup	Acute Dietary[1] (95th Percentile)		Chronic Dietary[2]	
	Dietary Exposure (mg/kg/day)	% aRfD	Dietary Exposure (mg/kg/day)	% cRfD
General U.S. Population	0.002267	0.6	0.000137	0.1
All Infants	**0.008548**	**2.1**	**0.000449**	**0.4**
Children 1-2 years old	0.003557	0.9	0.000203	0.2
Children 3-5 years old	0.003250	0.8	0.000190	0.2
Children 6-12 years old	0.002262	0.6	0.000131	0.1
Youth 13-19 years old	0.001839	0.5	0.000099	0.1
Adults 20-49 years old	0.002101	0.5	0.000128	0.1
Adults 50+ years old	0.001897	0.5	0.000135	0.1
Females 13-49 years old	0.002112	0.5	0.000127	0.1

[1] Acute dietary analysis derived from a 0.40 mg/kg/day aRfD.
[2] Chronic dietary analysis derived from a 0.10 mg/kg/day cRfD.

5.3 Residential (Non-Occupational) Exposure/Risk Characterization

HED has determined that there is a potential for exposure in residential settings during the application process for homeowners who purchase and use pesticide products containing naphthalene. There is also a potential for postapplication exposure from inhabiting indoor areas previously treated with naphthalene (inhalation), as well as, incidental toddler ingestion of formulations used for indoor/outdoor treatments.

A quantitative exposure assessment was performed for homeowners applying naphthalene in the residential environment and for toddler incidental ingestion of naphthalene used for indoor/outdoor treatments. Human health risk estimates were not calculated for postapplication inhalation scenarios because of the uncertainties associated with extrapolating animal (rodent) data to humans as discussed previously in this document. Rather than quantifying inhalation risks to humans, the levels of ambient naphthalene measured in the human exposure study were compared directly to the levels resulting in a 1) no adverse effects in the rodent studies (NOAELs) and 2) a toxic effect in rodents (LOAELs). This comparison provides a sense of the difference between actual naphthalene concentrations that a human may encounter and the doses which elicit either no adverse response or a toxic response in rodents.

5.3.1 Residential Handler Exposure and Risks

The Agency uses the term "handlers" to describe those individuals who are involved in the pesticide application process. The Agency believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Job requirements (e.g., the amount of chemical to be used in an application), the method of application, and the target being treated can cause exposure levels to differ in a manner specific to each application event.

HED has determined that there is potential for exposure in residential settings during the application process for homeowners who purchase and use naphthalene-containing products. According to label instructions, homeowners must physically place naphthalene formulations into indoor storage areas and around the perimeter of outdoor areas to be protected. HED anticipates handler dermal and inhalation exposure during the application process. However, appropriate inhalation exposure data are not available to assess this handler scenario, therefore, only dermal exposure was assessed.

Applications of naphthalene are expected to be short-term in nature because the products are typically applied only intermittently and usually on a seasonal basis, i.e. when storing winter clothes or when outdoor pests are active. As a result, no intermediate-term or long-term assessments were assessed for handlers.

Residential Handler Scenarios, Data Sources and Assumptions

<u>Scenarios</u>

1. Hand application of naphthalene formulations for indoor moth treatments
2. Hand application of naphthalene formulations for indoor/outdoor animal repellent treatments

<u>Data Sources</u>

Exposure data for residential handler and residential postapplication were taken from the exposure study, "Estimation of Homeowner Exposure to LX1298-01 (Naphthalene) Resulting

from Simulated Residential Use as an Insect Repellent (MRID 43716501)." Dermal handler exposure data was derived from the result of monitoring a person weighing out and placing mothballs in a closet and dresser at three different locations.

Assumptions Regarding Residential Applicators

- Homeowner handlers are expected to complete all tasks associated with the use of a pesticide product (e.g., application);
- The maximum application rate of 14.4 lb ai/ treated area was used for indoor moth treatment risk calculations, assuming that 3 closets (600 ft^3) and 3 dresser drawers (90 ft^3) are treated at 0.0625 lb ai/ 3 ft^3;
- The maximum application rate of 24 lb ai/ treated area was used for outdoor repellant treatment risk calculation, assuming the entire contents of a 24 lb container is used for treatment at 99.95% ai;
- A body weight of 70kg was assumed because the endpoint is not gender specific;
- Dermal absorption is assumed to be 100%, which is representative of a conservative assumption of risk; and
- Areas for chemical used in the risk assessment are based on Agency guidance specific to residential use patterns.

Residential Handler Exposure and Risk Estimates

The Margin of Exposures (MOEs) are > 100 and the risks are below EPA's level of concern for both dermal exposure scenarios for homeowner handlers.

Table 5.3.1 Naphthalene Noncancer Risks Attributable to Homeowner Handler Exposures

Exposure Scenario	Total Applied (lb ai)	Daily Exposure (mg/ lb ai)	MOE (LOC = 100)
1 - Apply Moth Treatment by Hand	14.4	0.053	28000
2 – Apply Animal Repellant Treatment by Hand	24	0.053	17000

5.4 Residential Postapplication Exposure and Risks

The Agency uses the term "postapplication" to describe exposures to individuals that occur as a result of working in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). HED has determined that there is potential for adult inhalation exposure from accessing treated areas (such as containers and closets) and adult and toddler inhalation exposure from inhabiting homes previously treated with naphthalene. Additionally, there is a potential for oral exposures to toddlers from the episodic (incidental) ingestion of formulations used for indoor/outdoor animal repellency.

5.4.1 Residential Postapplication Inhalation Exposure and Risk

As previously described, naphthalene applications may be made indoors. While labels specify that treated indoor areas (i.e., containers, dresser drawers, and storage closets) should be airtight to be effective, HED anticipates that naphthalene will volatilize and be inhaled by adults accessing treated areas (acute exposure). Additionally, adults and toddlers that inhabit treated areas may be exposed to ambient concentrations of naphthalene (short-, intermediate-, and long-term exposures).

Since the data available to date indicate that rodents are more susceptible to the respiratory toxicity of naphthalene, the use of rodents as a model without the appropriate species scaling accounting for species differences in dosimetry would very likely result in an inaccurate estimation of human risk from inhalation exposures. Therefore, rather than quantifying inhalation risks to humans, the levels of ambient naphthalene measured in the human exposure study were compared directly to the levels resulting in a toxic effect in the rodent studies (LOAELs). This comparison provides a sense of the difference between actual naphthalene concentrations that a human may encounter and the doses which elicit a toxic response in rodents.

In lieu of an appropriate inhalation study for comparison to anticipated acute (15 minute) exposures, HED used the available short-term (≥1 day) inhalation endpoint. The pairing of an acute inhalation exposure with a short-term toxicity endpoint can be considered conservative. HED used endpoints from short-, intermediate-, and long-term rodent inhalation toxicity studies for comparison to ambient naphthalene levels expected from those exposure durations.

Residential Postapplication Inhalation Exposure and Risk Estimates

Scenarios

Adult:

1. Acute inhalation from accessing treated areas

Adult/Toddler:

2. Short-/intermediate-/long-term inhalation from inhabiting treated area

Data Sources

Exposure data for residential postapplication inhalation was taken from the exposure study, "Estimation of Homeowner Exposure to LX1298-01 (Naphthalene) Resulting from Simulated Residential Use as an Insect Repellent (MRID 43716501)." Inhalation exposure data was derived for accessing treated areas (15-minute duration) from the results of air sampling of an individual accessing a treated drawer and closet, and performing household tasks (i.e., dusting, sitting in a chair, etc) in a treated room. Inhalation exposure data was also derived for inhabiting a treated area from the results of indoor air sampling in enclosed rooms in 3 different locations. Air samples were collected continuously (in 8-hour intervals) for 3 consecutive days from devices surrounding treated closets, dresser drawers, and beds. [A summary of the exposure

study data is provided in DP#335944, W. Britton (note: see amended version DP#351120 dated 4/10/08).]

HED determined that the exposure data used to assess acute and short-term exposure to indoor postapplication inhalation exposure to naphthalene from mothball sources was not appropriate to assess intermediate- and long-term exposure durations. As described previously, naphthalene volatilizes into the treated area and it is assumed that adults and toddlers who inhabit these areas are potentially exposed. Based upon label application timing recommendations for moth control, it is likely that re-treatment could occur, at a minimum, once every 1-6 months. The continued volatilization and dissipation of naphthalene over time results in a reduced concentration of the chemical and, likewise, reduced potential for inhalation exposure. Therefore, the exposure data used for the acute and short-term duration overestimates the concentration of naphthalene available for inhalation over longer term durations. HED was unable to locate any exposure data sources which assessed intermediate- and long-term exposure levels to naphthalene from 'mothball' sources. Exposure data was located, however, from a study which observed indoor ambient concentrations of naphthalene in 24 homes **(**J. Chuang et al. Polycyclic Aromatic Hydrocarbon Exposure of Children in Low-Income Families. Journal of Exposure Analysis and Environmental Epidemiology. (1999) 2, pp. 85-98**).** This study is not specific to intermediate- or long-term exposure durations, nor does naphthalene necessarily originate from a mothball source; however, it has been identified as the best data source to account for naphthalene volatilization and dissipation over time. Due to the uncertainty associated with the use of an exposure study which is not specific to the duration assessed, HED selected the most conservative exposure value (i.e., maximum concentration observed) to represent intermediate- and long- term exposure levels. [A summary of the exposure study data is provided in DP#335944, W. Britton (note: see amended version DP#351120 dated 4/10/08).]

Assumptions Regarding Postapplication Inhalation

- HED assumes that an individual could access treated areas (i.e., containers, dresser drawers, and storage closets) for an exposure duration of 15 minutes; and
- HED assumes that an individual could be exposed continually within their home (i.e., 24 hours per day) for short-/intermediate-/long-term duration.

Residential Postapplication Inhalation Exposure and Risk Estimates

A comparison was performed between both the NOAELs and LOAELs from rodents studies and human exposure studies. For acute- and short-term exposure scenarios, the results of an exposure study, "Estimation of Homeowner Exposure to LX1298-01 (Naphthalene) Resulting from Simulated Residential Use as an Insect Repellent (MRID 43716501)" were used. The 15 minute (acute) and 24 hour (short-term) samples resulted in average concentrations of 0.85 and 0.66 mg/m^3 of naphthalene, respectively. These values were compared directly to the rodent NOAEL (16 mg/m^3) and LOAEL (52 mg/m^3) selected for acute and short-term exposure durations.

Anticipated acute and short-term exposures to naphthalene in residences are 20X and 30X below the rodent dose (NOAEL) resulting in no adverse effects, respectively. Anticipated acute and

short-term exposures to naphthalene in residences are 60X and 80X below the rodent dose (LOAEL) resulting in respiratory toxicity (olfactory epithelium lesions), respectively.

For intermediate- and long-term durations, the results of an exposure study, "Polycyclic Aromatic Hydrocarbon Exposure of Children in Low-Income Families (Chuang et al., 1999) were utilized." The indoor ambient samples which pertain to the air concentrations of naphthalene resulted in a maximum level of 0.0097 mg/m^3. This exposure value was directly compared to the rodent NOAEL (5.2 mg/m^3) and LOAEL (10 mg/m^3) selected for intermediate-term durations and to the LOAEL (52 mg/m^3) selected for long-term exposure. A long-term NOAEL was not identified in the rodent chronic inhalation study.

Anticipated intermediate-term exposures to naphthalene in residences are 540X below the rodent dose (NOAEL) resulting in no adverse health effects. Intermediate- and long-term exposures to naphthalene in residences are 1000X and 5400X below the rodent dose (LOAEL) resulting in respiratory toxicity (olfactory epithelium lesions), respectively.

5.4.2 Residential Postapplication Episodic Ingestion Exposure and Risk

As previously described, naphthalene applications are made indoors for moth treatments and indoors/outdoors for animal repellency. HED anticipates that toddlers could come in contact with naphthalene formulations inside a treated home or in treated outdoor areas. While labels specify that indoor moth treatments be made in airtight containers, it is assumed that a toddler could potentially access these areas and ingest naphthalene products. Outdoor applications of naphthalene are labeled for use around the perimeter of areas to be protected. While a toddler could potentially access outdoor treated areas, naphthalene incident reports indicate that a large majority of incidents for children under six years old are from ingestion of indoor products. In order to assess postapplication episodic (incidental) ingestion of naphthalene, a potential dose was derived from the assumption of a toddler ingesting one mothball. HED also estimated the amount of the mothball that could be ingested by a toddler to result in a MOE = 100.

Inhalation and episodic (incidental) ingestion routes of exposure were not combined for toddlers in order to differentiate the occurrence of a discrete accidental event (assessed to give a worst-case estimate of risk) from the expected daily exposure via the inhalation route. It would not be appropriate to combine episodic exposure for comparison to a short-(or longer) term endpoint.

Scenarios

Toddler

1. Episodic (incidental) ingestion of naphthalene formulation from indoor/outdoor exposure

Data Sources

The residential indoor/outdoor postapplication episodic (incidental) ingestion exposure risk calculations are presented in this section. Noncancer risks were calculated using the approach described in the Standard Operating Procedures (SOPs) for Residential Exposure Assessments,

Section: 2.3.1, Postapplication – Incidental Nondietary Ingestion. SOPs were used to derive the potential dose rate of a toddler ingesting one mothball, which was then compared to the incidental oral endpoint to calculate an MOE. In addition, HED estimated the amount of a single mothball that a toddler could ingest to result in an MOE = 100. (See DP#335944, Appendix A for algorithms.)

Assumptions Regarding Toddler Episodic Ingestion

- One mothball weighs 2.35 grams (or 2350 mg) and the maximum labeled percent active ingredient is 99.95%;
- For the purposes of this risk assessment, HED is assuming that a child is only ingesting one mothball; and
- 3 year old toddlers are expected to weigh 15 kg.

Episodic Ingestion Risk Estimate

Toddler episodic (incidental) ingestion of one naphthalene mothball results in an MOE < 100 and, therefore, is of concern to HED. An oral dose of 0.5 mg/kg/day would be required to result in an MOE = 100. This dose is equivalent to toddler incidental ingestion of 0.32% of one mothball (7.5 of 2350 mg).

6.0 Aggregate Risk Assessments and Risk Characterization

An aggregate risk assessment for all expected routes of exposure was not performed as there is no common sensitive endpoint among all routes of exposure. Generally, a short-term aggregate risk assessment may be performed by combining short-term incidental oral exposure and average/background dietary (in this case drinking water) exposures. A short-term aggregate risk assessment was not performed for naphthalene since the short-term incidental oral exposure risk estimate alone exceeds the level of concern and combining with other routes of exposure would further exceed the level of concern.

7.0 Cumulative Risk Characterization/Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to naphthalene and any other substances and naphthalene does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that naphthalene has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

8.0 Occupational Exposure/Risk Pathway

Naphthalene products are not registered for occupational use and, therefore, occupational exposure and risk is not anticipated and has not been assessed.

9.0 Data Needs

Residential

HED recommends that the registrant conduct an exposure study to determine levels of naphthalene in indoor air resulting from simulated residential mothball use over intermediate- and long-term durations. Intermediate- and long-term residential indoor postapplication exposure and risk was estimated using surrogate data from an exposure study which was conducted to determine indoor ambient levels of naphthalene. Since the surrogate exposure study was not duration- or use-specific, it may potentially underestimate naphthalene exposure and risk. An appropriate study is required to confirm that the estimation of residential postapplication inhalation exposure is protective of human health.

Toxicology

No new data are currently being required. There is ongoing naphthalene research to address toxicology issues including:

- More accurate assessment of species differences in metabolism and clearance of naphthalene.
- Cell proliferation data to provide linkage to cytotoxicity.
- DNA adduct and mutagenicity studies in relevant target tissues in vivo to confirm lack of direct DNA mutagenicity.
  PbPK model under development (2-3 years rough estimate) to better support the mode of action, and to characterize species differences in metabolism, and address involvement of multiples enzymes and clearance in humans versus rodents. The PBPK model will also provide a more accurate determination of a human equivalent dose to be used in inhalation risk assessment.

Appendix A: Toxicology

A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for a food use for naphthalene are in Table A.1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

TABLE A.1 Test		Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rodent)	yes	yes
870.3150	Oral Subchronic (nonrodent)	yes	yes
870.3200	21/28-Day Dermal	yes	yes
870.3250	90-Day Dermal	no	---
870.3465	90-Day Inhalation	no	---
870.3700a	Developmental Toxicity (rodent)	yes	yes
870.3700b	Developmental Toxicity (nonrodent)	yes	yes
870.3800	Reproduction	no	---
870.4100a	Chronic Toxicity (rodent)	yes	yes
870.4100b	Chronic Toxicity (nonrodent)	yes	yes
870.4200a	Oncogenicity (rat)	yes	yes
870.4200b	Oncogenicity (mouse)	yes	yes
870.4300	Chronic/Oncogenicity	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Other Genotoxic Effects	yes	yes
870.6100a	Acute Delayed Neurotox. (hen)	no	---
870.6100b	90-Day Neurotoxicity (hen)	no	---
870.6200a	Acute Neurotox. Screening Battery (rat)	no	yes
870.6200b	Chronic Neurotox. Screening Battery (rat)	no	yes
870.6300	Develop. Neuro	no	---
870.7485	General Metabolism	yes	yes
870.7600	Dermal Penetration	no	yes

A.2 Toxicity Profiles

Table A.2.a Acute Toxicity of Naphthalene.				
GDLN	**Study Type**	**MRID**	**Results**	**Tox Category**
870.1100	Acute Oral - rat	257224	LD_{50}: 2649 mg/kg (♂+♀)	III
870.1200	Acute Dermal	257229	LD_{50} >2000 mg/kg (♂+♀)	III
870.1300	Acute Inhalation	257902	LC_{50} > 0.4 mg/L (77.7 ppm) (♂+♀)	II
870.2400	Primary Eye Irritation	257228	Slight-moderate irritation	III
870.2500	Primary Skin Irritation	257227	Moderate irritation	III
870.2600	Dermal Sensitization	00148173	Nonsensitizer – guinea pig	N/A

Table A.2.b Subchronic, Chronic and Other Toxicity.	
Guideline No./Study Type	**Doses tested and Results**
Nonguideline 90-Day oral toxicity – rat NTP 1980a	Doses: 0, 25, 50, 100, 200, or 400 mg/kg/day NOAEL = 100 mg/kg/day (males/females) LOAEL = 200 mg/kg/day (males/females) based on decreased body weight gain. Renal lesions in males at 200 mg/kg (minimal cortical focal lymphocytic infiltrate; focal tubular regeneration) and 400 mg/kg (cortical diffuse tubular degeneration). At 400 mg/kg/day, clinical signs (lethargy, hunched posture) and roughened hair coat in both sexes. 2/10 females at 400 mg/kg displayed moderate lymphoid depletion of thymus.
Nonguideline 90-Day oral toxicity – B6C3F1 Mouse NTP 1980b	Doses: 0, 12.5, 25, 50, 100 or 200 mg/kg/day NOAEL = 100 mg/kg/day (males/females) LOAEL = 200 mg/kg/day based on transient clinical signs (rough hair and lethargy) at weeks 3 and 4.
Nonguideline 90-Day oral toxicity – CD1 Mouse Shopp et al. 1984	Doses: 5.3, 53 or 133 mg/kg/day NOAEL = 53 mg/kg/day mg/kg/day Possible LOAEL = 133 mg/kg/day based on >10% decreases in absolute weights of the brain, liver and spleen in females and decreased relative spleen weights in females. However, no histopathological examinations were performed. Decreassed absolute and relative spleen weights also noted in females after 14 day treatment with 267 mg/kg naphthalene, but no histological examinations were performed. Mortality observed at 267 mg/kg/day. Immunotoxicity assays were negative.

Table A.2.b Subchronic, Chronic and Other Toxicity.	
Guideline No./Study Type	**Doses tested and Results**
870.3250 90-Day dermal toxicity – rat MRID 40021801 Acceptable guideline	Doses: 0, 100, 300, or 1000 mg/kg/day NOAEL = 300 mg/kg/day (males/females) LOAEL = 1000 mg/kg/day based on atrophy of seminiferous tubules in males; non-neoplastic lesions in cervical lymph node, liver, thyroid, kidneys, urinary bladder and skin in females. Both sexes also displayed excoriated skin and papules.
870.3700a Prenatal developmental – rat NTP 1991	Doses: 0, 50, 150 or 450 mg/kg/day **Maternal** NOAEL = 50 mg/kg/day LOAEL = 150 mg/kg/day based on persistent clinical signs of lethargy, slow breathing, rooting behavior, and significant decreases in body weights/body weight gains and food and water consumption. **Developmental** NOAEL = 450 mg/kg/day LOAEL = not identified
870.3700b Prenatal developmental – rabbit NTP 1992	Doses: 0, 20, 80, or 120 mg/kg/day **Maternal** NOAEL = 120 mg/kg/day LOAEL = not identified **Developmental** NOAEL = 120 mg/kg/day LOAEL = not identified
870.6200a Acute Neurotoxicity (Oral) Study – rat MRID 44282801 Acceptable Guideline	Doses: 0, 400, 800, or 1200 mg/kg/day NOAEL = not identified LOAEL = 400 mg/kg based on clinical signs (piloerecton, fast respiration, hunch posture), reduced motor activity, lower body temperature, and head shaking and increased urination and defecation in the open field.
870.6200a Subchronic Neurotoxicity (inhalation) Study – rat MRID 44856401 Acceptable Guideline	Concentrations: 0, 1, 10, or 60 ppm NOAEL = 1ppm LOAEL = 10 ppm (males/females) based on nasal lesions (loss of olfactory nerve fibers, loss of bowman's glands, olfactory epithelium atrophy/disorganization, olfactory epithelium erosion/necrosis, olfactory epithelium hyperplasia, olfactory epithelium inflammatory exudate in airway, olfactory epithelium rosettes, respiratory epithelium hyperplasia.
Nonguideline 4-Week Inhalation – rat MRID 42934901 Acceptable nonguideline	Concentrations: 0, 1, 3, 10, 30 or 77 ppm. 6hrs/day; 5 d/wk. NOAEL = 3 ppm LOAEL = 10 ppm (males/females) based on increased incidence and severity of nasal lesions (slight disorganization, rosette formation, basal cell hyperplasia, erosion, atrophy, and degenerate cells in the olfactory epithelium; loss of bowman's glands; respiratory epithelium hypertrophy; rosette formation in the septal organ of Masera and fusion of the turbinates).

Table A.2.b Subchronic, Chronic and Other Toxicity.	
Guideline No./Study Type	**Doses tested and Results**
870.3465 90-day inhalation – rat MRID 42835901 Acceptable guideline	0, 2, 10 or 60 ppm . 6hrs/day; 5 d/wk. NOAEL = not identified LOAEL = 2 ppm based on increased incidence and severity of nasal lesions (degeneration, atrophy and hyperplasia of basal cells of the olfactory epithelium; rosette formation of olfactory epithelium; loss of Bowman's glands; hypertrophy of respiratory epithelium).
Nonguideline Chronic toxicity/carcinogenicity (chamber) Inhalation – rat NTP 2000 Acceptable nonguideline	Concentrations: 0, 10, 30, or 60 ppm. 6hrs/day; 5 d/wk. NOAEL = not identified. LOAEL = 10 ppm, based on increased incidence and severity of atypical (basal cell) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium; hyperplasia, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia of the respiratory epithelium; and glandular hyperplasia and squamous metaplasia.
Nonguideline Chronic toxicity/carcinogenicity (chamber) Inhalation – mouse NTP 1992 Acceptable nonguideline	Concentrations: 0, 10, or 30 ppm. 6hrs/day; 5 d/wk. NOAEL = not identified. LOAEL = 10 ppm increased incidence and severity of chronic inflammation, metaplasia of the olfactory epithelium, and hyperplasia of respiratory epithelium. There was also increased incidence and severity of chronic inflammation in the lung.
870.5265 Gene mutation in *S. typhimurium* MRID 42071602 Acceptable	Naphthalene (99.9%) was not mutagenic in S. typhimurium strains TA98, TA100, TA1535, TA1537 or TA1538 up to cytotoxic concentrations (300 μg/plate ± S9)
870.5265 Gene mutation in *S. typhimurium* NTP 2000	Naphthalene was negative in S. typhimurium strains TA98, TA100, TA1535, TA1537 or TA1538 up to cytotoxic concentrations (100 μg/plate ± S9) in two separate trials using the pre-incubation modification to the standard assay and S9 derived from hamster and Aroclor 1254-induced rat livers.
870.5375 CHO chromosome aberration NTP 2000	Structural aberrations (types not reported) were observed only in the presence of S9 activation, over a concentration range of 30 to 67.5 μg/mL. Based on cell cycle data from the SCE assay, the harvest time was extended to 20.5 hours to allow accumulation of a sufficient number of metaphases to score and to demonstrate a clastogenic effect in the CHO chromosome aberration assay.

Table A.2.b Subchronic, Chronic and Other Toxicity.	
Guideline No./Study Type	**Doses tested and Results**
870.5375 CHO Sister Chromatid Exchange NTP 2000	Naphthalene induced significant and concentration-related increases in SCEs in CHO cells within a concentration range of 27 to 90 μg/mL ± S9).
870.5395 *In vivo* mouse bone marrow micronucleus MRID 42071603 Acceptable	Naphthalene was negative for micronuclei induction in the bone marrow of CD-1 male and female mice up to the maximum tolerated dose (250 mg/kg) administered by intraperitoneal injection.
870. 5550 UDS assay MRID 42071604 Acceptable	Naphthalene did not induce UDS in primary rat hepatocytes up to insoluble (≥ 166 μg/mL) and cytotoxic (≥ 50 μg/mL) concentrations.
Nonguideline In Vitro Dermal penetration – rat Acceptable nonguideline	Based on an exposure time of 10 minutes, the short-term in vitro penetration rate was calculated to be 142.6 μg equiv/cm^2/h. Based on an exposure time of 60 minutes, the short-term penetration rate was calculated to be 25.0 μg equiv/cm^2/h.

A.3 Executive Summaries

A.3.1 Subchronic Toxicity

- **90-Day Oral Toxicity – Rat**

EXECUTIVE SUMMARY: Rats were administered by gavage to groups of 10 male and 10 female Fischer 344 rats at dose levels of 0, 25, 50, 100, 200, or 400 mg/kg/day, for 5 days/week for 13 weeks (NTP 1980a). Body weight gains decrements exceeding 10% was observed in both males and females administered 200 or 400 mg/kg/day. At the highest dose level, clinical signs included lethargy, hunched posture, and roughened hair coats. High-dose males and females also exhibited marginal decreases in hemoglobin and hematocrit levels. Males in this group also displayed a moderate increase in neutrophils and decrease in lymphocytes. Minimal renal cortical focal lymphocytic infiltrate (1 of 10 males) and minimal renal focal tubular regeneration (1 of 10 males) were noted in male rats treated with 200 mg/kg. One male rat treated with 400 mg/kg naphthalene exhibited moderate renal cortical diffuse tubular degeneration. There were

no renal lesions in treated females, however, 2 of 10 females treated with 400 mg/kg displayed moderate lymphoid depletion of the thymus.

The LOAEL = 200 mg/kg/day based on significant body weight decrement. The NOAEL = 100 mg/kg/day.

- **90-Day Oral Toxicity – Mouse**

EXECUTIVE SUMMARY: In this study, groups of 10 male and 10 female B6C3F1 were administered 0, 12.5, 25, 50, 100 or 200 mg/kg naphthalene by gavage 5 days/week for 13 weeks (NTP 1980b). Vehicle controls received corn oil. Animals were observed for clinical signs of toxicity. Body weight and food consumption were frequently monitored. Hematology, clinical chemistry, and complete necropsy and histology were performed. In the high-dose males and females, rough hair coats and lethargy were noted at weeks 3 or 4. There were no other effects of biological significance.

The LOAEL is 200 mg/kg/day based on transient clinical signs of toxicity (rough hair coat and lethary). The NOAEL is 100 mg/kg/day.

- **90-Day Inhalation – Rat**

EXECUTIVE SUMMARY: In this study, Sprague-Dawley rats, 10/sex/group, were exposed to naphthalene vapor (purity: 99.9%) for 13 consecutive weeks(MRID 42835901). Concentrations were 0, 2, 10 or 60 ppm. The parameters monitored included: clinical observations, body weights, food consumption, hematology, clinical chemistry, ophthalmoscopy, necropsy, organ weights, and histology.

Moderate degenerative changes in the olfactory epithelium, moderate to marked atrophy of olfactory epithelium, minimal to moderate erosion of olfactory epithelium, moderate hyperplasia of basal cells in olfactory epithelium, moderate rosette formation in olfactory epithelium, loss of Bowman's glands, hypertrophy of respiratory epithelium were noted in rats following exposure to 10 or 60 ppm naphthalene. Similar findings were noted in rats at the low dose (2 ppm), but these changes were minimal. However, several of the low-dose rats exhibited some loss of Bowman's glands. Significant body weight decrements (≥ 10%) were observed throughout the study in males and females exposed to 10 or 60 ppm.

The LOAEL is 2 ppm based on nasal lesions and a NOAEL was not identified.

- **90-Day Dermal Toxicity – Rat**

EXECUTIVE SUMMARY: Groups of 10 – 20 male and female Sprague-Dawley rats were exposed to naphthalene via the dermal route at 0, 100, 300, and 1000 mg/kg/day. The test material was applied as a neat solid under occlusion for 6 hours/day, 5 days/week for 13 weeks. Rats (10/group) were sacrificed after 13 weeks of treatment, except for additional animals

(10/group) from each of the control and high-dose groups that were observed for 4 weeks during a recovery phase. Following each exposure, the treatment area was wiped clean, and the wrap and the test material discarded. Animals were inspected for clinical signs, mortality, changes in body weights, food consumption, ophthalmology, hematology and clinical chemistry, organ weights, urinalysis, gross necropsy and histopathology.

There were no effects on mortality, food consumption, body weights, hematology, clinical chemistry, urinalysis, and organ weights. At 1000 mg/kg/day, there was excoriated skin and papules in both sexes; atrophy of seminiferous tubules in the males; and nonneoplastic lesions in the cervical lymph node (hyperplasia), liver (hemosiderosis), thyroid (thyroglossal duct cysts), kidneys (pyelonephritis), urinary bladder (hyperplasia) and skin (acanthosis, hyperkeratosis) in females.

The LOAEL is 1000 mg/kg/day based on atrophy of seminiferous tubules in males and various nonneoplastic lesions in females. The NOAEL was 300 mg/kg/day.

A.3.2 Prenatal Developmental Toxicity

- **Prenatal Developmental Toxicity Study – Rat**

EXECUTIVE SUMMARY: In the developmental toxicity study in Sprague-Dawley CD rats, naphthalene was administered in corn oil by gavage to 25-26 pregnant rats/dose group during gestation days 6 – 15. Dose levels were 0, 50, 150 or 450 mg/kg/day. Dams and fetuses were examined for signs of toxicity and teratogenicity.

Clear evidence of maternal toxicity was noted in the mid- and high-dose groups. Maternal toxicity consisted of persistent clinical signs of lethargy, slow breathing, rooting behavior, and significant decreases in body weights/body weight gains and food and water consumption. In regard to body weight decrement, the mid-dose group exhibited a 31% reduction in weight gain compared to controls, while the high-dose group displayed a 53% reduction. Post-treatment weight gain remained below control values. There were no treatment-related mortalities.

There were no biologically significant effects of naphthalene on number of corpora lutea per dam, % resorptions or fetal deaths/litter, % litters with resorptions or deaths, number of live fetuses/litter, average fetus body weight/litter, % malformed fetuses/litter, % litters with malformations (external, visceral, skeletal) and % fetuses with variations/litter.

The maternal LOAEL is 150 mg/kgday based on persistent clinical signs of lethargy, slow breathing, rooting behavior, and significant decreases in body weights/body weight gains and food and water consumption. The maternal NOAEL is 50 mg/kg/day.

The developmental NOAEL is 450 mg/kg/day (highest dose tested).

- **Prenatal Developmental Toxicity Study – Rabbit**

EXECUTIVE SUMMARY: In the NTP developmental rabbit study, naphthalene was administered in corn oil by gavage at dose levels of 0, 20, 80, or 120 mg/kg/day to pregnant rabbits during gestation days 6 – 19. Maternal clinical signs, body weights, and food consumption were monitored on gestation days 0 – 30. Fetuses were removed from dams on gestation day 30, and then subjected to examination for any treatment-related alterations on growth, viability, and morphological development.

There were no effects of naphthalene treatment on survival, maternal body weights (including corrected gestational weight gain), and food consumption.

Naphthalene was not fetotoxic. Average live litter size and average fetal body were similar between control and treated groups. There was no effect of treatment on the incidence of external, visceral, or skeletal malformations. Similarly, the incidence of variations or defects on a fetal or litter basis was unaffected by treatment.

The maternal and developmental NOAELs are 120 mg/kg/day (highest dose tested).

A.3.3 Reproductive Toxicity

No reproductive toxicity studies are available.

A.3.4 Chronic Toxicity - See A.3.5 for Combined Chronic/Carcinogenicity NTP Inhalation Studies in the Rat and Mouse.

A.3.5 Carcinogenicity

- **Combined Chronic/Carcinogenicity Study – Rat**

EXECUTIVE SUMMARY: In this study, groups of 49 male and 49 female F344/N rats were exposed to naphthalene by inhalation at concentrations of 0, 10, 30, or 60 ppm for 6 hours plus T90 (12 minutes) per day, 5 days per week for 105 weeks (NTP 2000). Additional groups of nine male and nine female rats were exposed to 10, 30, or 60 ppm for up to 18 months for evaluation of toxicokinetic parameters.

Survival in the exposed groups was similar to chamber controls. Decreased mean body weight was observed at the highest dose level in males throughout the study (89-91% of control). Mean body weight gains in the high-dose group males were decreased by 10.5% (weeks 1-13), 10.9% (weeks 14-52) and 8.6% (weeks 53-104).

Nasal lesions were observed at all concentrations levels and included atypical (basal cell) hyperplasia, atrophy, chronic inflammation, and hyaline degeneration of the olfactory epithelium; hyperplasia, squamous metaplasia, hyaline degeneration, and goblet cell hyperplasia of the respiratory epithelium; and glandular hyperplasia and squamous metaplasia. The severities of olfactory epithelial and glandular lesions increased with increasing exposure concentration.

Nasal tumors included neuroblastomas of the olfactory epithelium and adenomas of the respiratory epithelium. Neuroblastomas of the olfactory epithelium occurred in males exposed to 30 or 60 ppm and in all exposed groups of females. The incidences of neuroblastoma occurred with positive trends in males ($p<0.05$) and females ($p<0.01$), and the incidence in females exposed to 60 ppm was significantly greater ($p<0.01$) than that in the chamber controls. Neuroblastomas have not been observed in male or female chamber control rats in the NTP database for animals fed NIH-07 feed in 2-year inhalation studies or in the more recent, smaller database for control rats fed NTP-2000 feed.

The incidences of adenoma of the respiratory epithelium occurred with a positive trend in male rats and were significantly increased in all exposed groups; the incidences in female rats exposed to 30 or 60 ppm were also increased, but not significantly. Nasal adenomas have not been observed in male or female chamber control rats in the NTP database for animals fed NIH-07 feed in 2-year inhalation studies or in the more recent, smaller database for control rats fed NTP-2000 feed.

The NTP concluded that "under the conditions of this 2-year inhalation study, there was clear evidence of carcinogenic activity of naphthalene in male and female F344/N rats based on increased incidences of respiratory epithelial adenoma and olfactory epithelial neuroblastoma of the nose. In male and female rats, exposure to naphthalene caused significant increases in the incidences of non-neoplastic lesions of the nose."

The LOAEL is 10 ppm based on nasal lesions, and a NOAEL was not identified.

- **Combined Chronic/Carcinogenicity Study – Mouse**

EXECUTIVE SUMMARY: In this inhalation chamber study, groups of 75 mice per sex were allocated to dose levels of 0 and 10 ppm, and 150 mice per sex to the 30 ppm group (NTP 1992). Nasal lesions were observed in all concentration levels and consisted of increased incidence and severity of chronic inflammation, metaplasia of the olfactory epithelium, and hyperplasia of respiratory epithelium. There was also increased incidence and severity of chronic inflammation in the lung.

Male mice had statistically significant pair-wise comparisons of the 10 ppm dose group with the controls for liver adenomas, and adenomas and carcinomas combined, both at $p < 0.01$. Only those animals with gross lesions were examined microscopically for the liver in the 10 ppm dose group, therefore, the statistical significance of the liver at this dose group is skewed. There were no statistically significant trends for liver or lung tumors in the males and no pair-wise statistical significance in the lung. The statistical analyses of the tumors in male mice were based upon Peto's Prevalence Test since there were statistically significant survival disparities among the dose groups.

Female mice had statistically significant trends, and statistically significant pair-wise comparisons of the 30 ppm dose group with the controls, for alveolar/bronchiolar adenomas, and

adenomas and carcinomas combined, all at $p < 0.01$. The statistical analyses of the tumors in female mice were based upon Peto's Prevalence Test since there were statistically significant survival disparities among the dose groups.

The NTP concluded that "under the conditions of this 2-year inhalation study, there was "no evidence of carcinogenic activity" of naphthalene in male B6C3F1 mice exposed to 10 or 30 ppm. There was "some evidence of carcinogenic activity" of naphthalene in female B6C3F1 mice, based on increased incidences of pulmonary alveolar/bronchiolar adenomas.

The LOAEL is 10 ppm, and a NOAEL was not identified.

A.3.6 Mutagenicity

Gene Mutations

Naphthalene (99.9%) was not mutagenic in S. typhimurium strains TA98, TA100, TA1535, TA1537 or TA1538 up to cytotoxic concentrations (300 µg/plate +/-S9) (MRID 42071602).

In the NTP microbial gene mutation assay, naphthalene was negative in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 up to a cytotoxic concentration (100 µg/plate +/-S9) in two separate trials using the pre-incubation modification to the standard assay and S9 derived from hamster and Aroclor 1254-induced rat livers.

Chromosome Aberrations

Based on the cell cycle data from the SCE assay (see below) showing cell cycle delay (indicative of cytotoxicity), an extended harvest time of 20.5 hours was used in the NTP study to allow accumulation of a sufficient number of metaphases to score and to demonstrate a clastogenic effect in the CHO chromosome aberration assay. The positive response was observed only in the presence of S9 activation, over a concentration range of 30 to 67.5 µg/mL. The types of structural aberrations were not reported.

In a mouse micronucleus assay (MRID 42071603), naphthalene (99.9%) was negative for micronuclei induction in the bone marrow of CD-1 male and female mice up to the maximum tolerated dose (250 mg/kg) administered by intraperitoneal injection. At this dose, reduced body tone, abnormal gait and lacrimation were seen in conjunction with cytotoxic effects on the target organ (i.e., reduced polychromatic to normochromatic erythrocytes at all sacrifice times).

Other Genotoxic Tests

In an in vitro unscheduled DNA synthesis (UDS) assay (MRID 42071604), naphthalene (99.9%) did not induce UDS in primary rat hepatocytes up to insoluble (≥ 166 µg/mL) and cytotoxic (≥ 50 µg/mL) concentrations.

In the NTP SCE assay, naphthalene induced significant and concentration-related increases in SCEs in CHO cells within a concentration range of 27 to 90 µg/mL +/-S9.

Evidence of Oxidative Stress

Several studies in the open literature show that naphthalene undergoes extensive oxidative metabolism to form naphthoquinones, which are thought to generate ROS (superoxide anion radical, hydrogen peroxide, hydroxyl radical and *o*-semiquinone anion radicals) via redox cycling (Bolton, 2000). A number of investigators have reported evidence of naphthalene-induced oxidative damage by ROS (reviewed in Stohs, et al., 2002).

Vuchetich et al., (1996) provided evidence of naphthalene-induced oxidative stress in Sprague-Dawley rats following an acute oral dose (1100 mg/kg) as shown by increased brain and hepatic lipid peroxidation, glutathione depletion, increased single strand breaks and alterations in membrane viscosity. Significant brain and hepatic lipid peroxidation was observed in rats administered (oral) naphthalene up to 120 days at 110 mg/kg/day (Bagchi et al., 1998) and at doses up to 750 mg/kg for 9 weeks (Germansky and Jamall, 1988). Increases in brain and hepatic DNA fragmentation were also observed in C57BL/6 24 hours after administration of naphthalene at 158 mg/kg (0.5 LD_{50}) (Bagchi et al., 2000). A concentration-dependent increase in lipid peroxidation and DNA fragmentation was demonstrated *in vitro* in J774A.1 macrophage cells (Bagchi et al, 1998). Similarly, *in vitro* treatment of J774A.1 cells with naphthalene resulted in a concentration-dependent increase in superoxide anion ($O_2^{\cdot -}$) and hydroxyl radical (OH) production.

In vivo evidence of increased superoxide anion production was also observed in hepatic and brain tissues in mice (C57BL/6NTac) treated with naphthalene (Bagchi et al., 2000). As previously mentioned, the naphthalene metabolite 1,2-naphthoquinone was positive for mutation in *S. typhimurium* TA104, a tester strain sensitive to oxidative damage (Flowers-Geary, et al., 1996). Overall, the evidence suggests that the oxidative metabolism of naphthalene leads to the production of ROS which may result in oxidative-stress induced cytotoxicity.

Other Published Literature

Using a modified CREST in vitro micronucleus assay, Saskai et al. (1997) reported that naphthalene (30 µg/ml) induced chromosome breakage-type micronuclei and naphthalene metabolite 1,4-naphthoquinone (0.10 µg/ml) induced chromosome loss-type micronuclei in metabolically competent human lymphoblastoid cells (MCL-5). However, in vivo studies showed no induction of micronuclei using either the oral or intraperitoneal (ip) route in mouse bone marrow cells. Similarly, naphthalene was negative for in vivo UDS in rat hepatocytes and failed to induce morphologic cell transformation in five different cell lines including Fischer rat embryo, Syrian baby hamster, BALB/c, BALB/c 3T3 or human diploid WI-38 cells.

In another study, naphthalene did not induce neoplastic transformation in partially hepectomized F344 rats receiving single oral gavage administrations of 100 mg/kg. However, Bagchi et al. (1998, 2000 and 2002), reported that naphthalene caused DNA fragmentation in brain and liver tissue of C57BL/6NTac dosed once with 158 mg/kg (0.5x LD_{50}), in Sprague-Dawley rats

administered an oral dose of 110 mg/kg/day for 120 days and in p53-deficient mice (C57BL6/6TSG-p53) after single oral doses of 0.01x, 0.10x or 0.5x LD_{50}. In these assays, DNA fragmentation was accompanied by increased lipid peroxidation in the harvested tissues. It was, therefore, speculated that, the results were unclear as to whether the DNA damage was "due to direct effects of naphthalene metabolites or reactive oxygen species (ROS) or was secondary to cell death induced at an extranuclear site." No genetic toxicology studies were found for sensitive target organs (lung or nasal epithelial tissues).

A.3.7 Neurotoxicity

870.6200a Acute Neurotoxicity Screening Battery – Oral route

EXECUTIVE SUMMARY - In an acute neurotoxicity study (MRID 44282801*)*, groups of fasted, 5-7 week-old CD rats (10/sex/dose) were given a single oral dose of naphthalene (99.9% a.i., batch/lot # 235/50320) in corn oil at doses of 0, 400, 800, or 1200 mg/kg bw and observed for 14 days. Neurobehavioral assessment (functional observational battery and motor activity testing was performed on all animals pre-treatment, on Day 1 at estimated time of peak effect (i.e. 2 hours after dosing) and Days 7 and 14 of the observation period. Cholinesterase activity was not determined. Motor activity of all animals was measured for one hour, at 6-minute intervals, immediately after the completion of the Functional Observation Battery (FOB). At study termination, 5 animals/sex/group were euthanized and perfused *in situ* for neuropathological examination. Of the perfused animals, 5/animals/sex from the control and high dose groups were subjected to histopathological evaluation of brain and spinal cord. In addition, peripheral nervous system tissues from all animals sacrificed were examined. All animals survived to study termination. Clinical signs from daily cage-side observation were similar to findings in the FOB (see below).

Absolute body weight was slightly decreased in high dose males on Day 7 and 14 (12% and 9%, respectively) compared to controls. A dose-related decrease in body weight gain was noted in all treated animals compared to controls. The most pronounced effect on weight gain was during the first four days of the study when the low-, mid-, and high-dose groups gained 30%, 57%, and 80%, respectively, less than controls in males and 23%, 40%, and 57%, respectively, less in females. Recovery was subsequently seen in all treated groups. Food consumption in females was unaffected by treatment. Food consumption among treated males was reduced on the day of administration (37%, 52% and 67% in low-, mid- and high-dose groups, respectively).

During the FOB tests, findings in the home cage on Day 1 included hunched posture in females, (0/10 controls, 3/10 low-dose, 2/10 mid-dose and 4/10 high-dose), decreased reactivity during removal from cage in all mid- and high-dose males, and instances of limp body tone in females in the mid- and high-dose groups (3/10 and 5/10, respectively, compared to 0/10 controls and 1/10 low-dose rats) with 4/10 high-dose females being limp during handling. Treatment-related effects seen in the open field were gait abnormalities in high-dose females (9/10), and head shaking behavior in males and females from low-, mid- and high-dose groups (2/10, 4/10 and 6/10 in males and 5/10, 6/10 and 7/10 in females, respectively). On Day 7, hunched posture (1/10, 3/10, 5/10 and 6/10) was seen in females at all dose levels with decreased reactivity during removal from cage in both sexes (6/10, 9/10, 9/10 and 10/10 in males; 4/10, 8/10, 9/10 and 10/10

in females at control, low-, mid- and high-dose groups, respectively) and an increased incidence of piloerection in high-dose males (8/10) and all treated females (5/10, 3/10 and 5/10 at low-, mid- and high-dose, respectively). Urination and defecation frequencies were higher in all treated groups of males and females compared to those of controls. By Day 14 in both males and females there was increased urination in all dose groups and defecation in mid- and high-dose groups. Body temperature of the treated female groups was 35.2-36.8°C compared with 38.4°C for the controls on Day 1, 38.1-38.2°C compared with 38.6°C for controls on Day 7 and 38.0-38.2°C compared with 38.5°C for controls on Day 14.

No treatment-related effects were seen in landing footsplay or fore- and hind-limb grip strengths on any testing day.

On Day 1, a marked decrease in motor activity was noted in both sexes in all treatment groups. Low and high beam counts for the treated groups were 63-75% and 78-88%, respectively, less than controls for males and 74-78% and 90-94%, respectively, less than controls for females. On Day 7, motor activity was significantly reduced compared to controls in all treatment groups with low and high beam breaks 38-62% and 49-61%, respectively, less than controls for males and 54-60% and 58-67%, respectively, less than control levels for females. Motor activity on Day 14 was lower compared to that of the controls although to a lesser extent than on day 7 with low and high beam breaks 27-43% and 36-50%, respectively, less than control levels for males and 23-40% and 41-42%, respectively, less for females.

There was no difference in weight of the brain and pituitary between the control and treated groups. Gross and microscopic examinations of central and peripheral nervous tissue did not reveal any treatment-related effects.

The LOAEL for neurotoxicity of naphthalene in rats was 400 mg/kg bw based on clinical signs (piloerection, fast respiration, hunch posture), reduced motor activity, lower body temperature, and head shaking and increased urination and defecation in the open field. The NOAEL was not established.

870.6200b Subchronic Neurotoxicity Screening Battery – Inhalation route

EXECUTIVE SUMMARY - In this subchronic inhalation neurotoxicity study (MRID 44856401) naphthalene was administered to 10 CD rats/sex/group as a vapor by dynamic nose-only exposure at target concentrations of 0, 1, 10, or 60 ppm for 6 hours per day, 5 days/week for a total of 13 weeks. Overall mean analytical concentrations were 0, 0.99, 10.0, and 62.8 ppm. Neurobehavioral assessment (functional observational battery and motor activity testing) was performed on all animals pre-test and at the end of Weeks 4, 8, and 13. At study termination, the animals were euthanized and perfused *in situ*. The first 5 males and 5 females per group were used for neuropathological examination (control and high-concentration, only) and microscopic evaluation of the nasal passages (all treatment groups).

There were no deaths during the study. One female from each of the mid- and high-concentration groups appeared slightly emaciated during Week 12. Five/10 and 6/10 mid- and

high-concentration females and 1/10 mid-concentration males had brown staining of the ventral surface during Weeks 10-14 with two females from each group also showing brown staining of the dorsal surface. At 10 and 60 ppm, mean cumulative body weight gain was significantly decreased in both sexes compared to controls (males: -22% and -34%, respectively; females: -26% and -34%; $p<0.01$). Absolute body weight was also decreased in these same groups compared to their respective controls, with high-concentration males weighing 12-18% less during Weeks 4-13, mid-concentration males weighing 9-11% less during Weeks 8-13, high-concentration females weighing 10-14% less during Weeks 4-13, and mid-concentration females weighing 9-12% less during Weeks 3-13. Mean weekly food consumption was decreased in high-concentration males during Weeks 3-13 (12-16% less than that of controls) and in mid- and high-concentration females during Weeks 2-13 (10-15% and 10-19% less than controls, respectively). High-concentration females spent significantly less total time in locomotor activity at Week 13 (-38%; $p<0.01$).

A number of treatment-related microscopic lesions of the nasal passages were seen. Minimal or slight hyperplasia of the respiratory/transitional epithelium in the rostral region was noted in all treated animals (vs. no controls), and atrophy/disorganization of the olfactory epithelium was seen at all exposure levels in both sexes (in ascending dose order, males: 0/5,1/5, 3/5, 5/5 and females 0/5, 2/5, 5/5, 5/5). Apparent loss of Bowman's glands and olfactory nerve fibers was noted in all animals of both sexes at 10 and 60 ppm. Other lesions included erosion/necrosis of the olfactory epithelium (males: 0/5, 0/5, 0/5, 2/5; females: 0/5, 1/5, 5/5, 4/5), hyperplasia of the olfactory epithelium (males: 0/5, 0/5, 0/5, 5/5; females; 0/5, 0/5, 5/5, 4/5), inflammatory exudate in the airway (males: 0/5, 0/5, 2/5, 3/5; females: 0/5, 0/5, 5/5, 5/5), and rosettes of the olfactory epithelium (males: 0/5, 0/5, 1/5, 5/5; females: 0/5, 0/5, 2/5, 3/5). There were no treatment related effects on brain weight or neuropathology.

The LOAEL was 10 ppm based on atrophy/disorganization of the olfactory epithelium and hyperplasia of the respiratory and transitional epithelium. The NOAEL is 1 ppm.

Appendix B: Review of Human Research

Studies reviewed for ethical conduct:

No MRID - PHED Surrogate Exposure Guide

MRID 43716501
Waggoner, T. (1994) Estimation of Homeowner Exposure to LX1298-01 (Naphthalene) Resulting from Simulated Residential Use as an Insect Repellent. Unpublished study prepared by Landis International, Inc. and Pharmaco LSR Inc. under Project No. 93-9083. 100 p.