March 21, 2003

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C.W. Jameson, Ph.D.
National Toxicology Program
NIEHS
P.O. Box 12233
79 Alexandar Drive
Research Triangle Park, NC 27709

Dear Dr. Jameson:

AMEC Earth & Environmental respectfully submits the attached comments on NTP's proposal to list naphthalene as "reasonably anticipated to cause cancer in humans" in the eleventh edition of *Report on Carcinogens.* The comments were also e-mailed to you today. Since the comments were transmitted on March 21, 2003, AMEC asks that NTP consider them in making its final decision to list nominated chemicals.

If you have any questions on the comments, please call me at 978-692-9090.

Sincerely,

Signature

Brian Magee, Ph.D.
Vice President
Principal Toxicologist

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COMMENTS ON PROPOSAL TO LIST NAPHTHALENE IN THE REPORT ON CARCINOGENS, ELEVENTH EDITION

SUBMITTED TO:

C. W. JAMESON, PH.D.

NATIONAL TOXICOLOGY PROGRAM

March 21, 2003

AMEC EARTH & ENVIRONMENTAL
WESTFORD, MASSACHUSETTS

EXECUTIVE SUMMARY

The National Toxicology Program (NTP) has proposed to list naphthalene in the Eleventh Edition of the *Report on Carcinogens* as "reasonably anticipated to cause cancer in humans". In order to be listed as "reasonably anticipated to cause cancer in humans", a compound must meet several criteria.

Either there must be "limited evidence of carcinogenicity from studies in humans which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not be adequately excluded," or there must be "sufficient evidence of carcinogenicity from studies in experimental animals which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors." If the listing is based on "sufficient evidence" in animals, certain other criteria must also be met. Specifically, the animal data must be "in multiple species or at multiple tissue sites; by multiple routes of exposure; or to an unusual degree with regard to incidence, site, or type of tumor or age at onset."

Lastly, even if a chemical does not have sufficient evidence of carcinogenicity in animals, NTP can list the chemical as "reasonably anticipated to cause cancer in humans" based on other considerations concerning structure and mechanism.

NTP listing criteria require that all conclusions be made based on scientific judgment with consideration of dose response, metabolism, pharmacokinetics, and other relevant information. NTP specifically states: "substances for which there is evidence of carcinogenicity in laboratory animals are not considered 'reasonably anticipated to cause cancer in humans' where there are compelling data indicating that the agent acts through mechanisms which do not operate in humans."

AMEC strongly recommends that NTP not list naphthalene as "reasonably anticipated to cause cancer in humans" because the NTP's listing criteria are not met for naphthalene. First, there is no "limited evidence of carcinogenicity from studies in humans" reported in the literature. The only human studies that have been discussed by NTP are survey studies in which the author himself stated: "All my patients were smokers of more than 10 cigarettes per day or 2 to 8 packets of tobacco per week...cigarette smoke is regarded as a causal factor in the genesis of laryngeal cancer (Wolf, 1976)." Also, the author stated: "The histological findings did not reveal any particular features suggestive of occupational cancer (Wolf, 1976)." As noted elsewhere in these comments, the vast literature on the health status of thousands of workers in numerous industries who were exposed to naphthalene-containing mixtures reveals no indication that naphthalene exposure was responsible for any nasal tumors, as were seen in rats in the NTP bioassay. Clearly, there is not "limited evidence of carcinogenicity from studies in humans."

Second, there is not "sufficient evidence of carcinogenicity from studies in experimental animals" because the NTP criteria are not met. Specifically, the evidence of carcinogenicity is only in one species, not multiple species; the evidence is at one tissue site, not multiple tissue sites; the evidence is from one route of exposure, not multiple

routes of exposure; and finally the evidence does not show that tumors were seen in the rats to an unusual degree.

More importantly NTP specifically states that "substances for which there is evidence of carcinogenicity in laboratory animals are not considered 'reasonably anticipated to cause cancer in humans' where there are compelling data indicating that the agent acts through mechanisms which do not operate in humans." Because of the differences in the nasal anatomy and physiology of the rat and the human and because of the differences in toxifying and detoxifying metabolism in these two species, the mechanism of action in the rat is not relevant to the human. This fact alone would require NTP to conclude that naphthalene does not meet the criteria for listing.

These comments demonstrate that the empirical evidence showing a lack of nasal tumorigenic response in humans is entirely consistent with the scientific arguments regarding the lack of relevance of the mechanism of action of high dose naphthalene exposure in rats to the human situation. The comments show that if the rat mechanism of action were relevant, then nasal tumors should be prevalent in the human population. Since nasal tumors are very rare in the human population, then it must be concluded that the rat mechanism of action is, in fact, irrelevant to the human. Thus, there are "compelling data indicating that the agent acts through mechanisms which do not operate in humans."

Clearly, the NTP Executive Committee Working Group for the Report on Carcinogens is aware of the relevance issue. The report of the second review committee (GR2) stated: "An argument was made that the rarity of the nasal tumors in rats as well as the unusual occurrence of tumors at this site in humans suggested this response was of questionable relevance for humans." AMEC notes that the committee was tied in its vote and did not recommend naphthalene's listing. Accordingly, AMEC recommends that naphthalene be remanded for further study and not be listed as "reasonably anticipated to cause cancer in humans."

I. RELEVANCE OF THE NTP RAT CANCER STUDY TO THE EVALUATION OF HUMAN HEALTH

In December of 2000, the NTP released the results of a standard chronic carcinogenesis bioassay in which male and female cohorts of F344/N rats were exposed to 10, 30 and 60 ppm naphthalene via inhalation (TR 500). Table 1 presents the major findings for non-carcinogenic lesions for rats in all dose groups (male and female combined); the results of a similar (TR 410) study in mice are also presented for comparison of similar pathology categories and dosing scheme. The vast majority of animals had signs of severe irritation, as evidenced by the number of animals exhibiting inflammation, metaplasia, hyperplasia, and atrophy of the olfactory epithelium. The report notes that "some or all of the non-neoplastic lesions observed in this study are commonly observed in NTP inhalation studies with chemicals of an irritant nature and appear to be adaptive responses".

Table 1.
Incidence of Key Non-carcinogenic Lesions in Mice and Rats[1]
(NTP TR410 and 500)

		Exposure Concentration			
		0 ppm	10 ppm	30 ppm	60 ppm
MICE	Nasal (olfactory) inflammation	3/139	34/134	108/270	n/a
	Olfactory epithelial metaplasia	0/139	131/134	269/270	n/a
	Respiratory epithelial hyperplasia	0/139	131/134	269/270	n/a

		Exposure Concentration			
		0 ppm	10 ppm	30 ppm	60 ppm
RATS	Nasal (olfactory) inflammation	0/98	96/98	95/97	93/97
	Olfactory epithelial hyperplasia	0/98	96/98	93/97	89/97
	Respiratory epithelial hyperplasia	3/98	39/98	51/97	52/97
	Olfactory epithelial atrophy	3/98	98/98	97/97	94/97

[1]Males and females combined.

Table 2 presents the results of the observations of animals exhibiting malignant tumors. Male rats showed a dose-related increase in respiratory adenomas, but not olfactory neuroblastomas, whereas female rats showed a dose-related increase in the incidence of neuroblastomas, but not adenomas. An argument is later presented that suggests that, as in the mouse model, naphthalene may act like other model compounds that are metabolized to reactive intermediates by cytochrome P-450 enzymes (like the phosphodiesterase inhibitor RP 73401), being metabolically activated via specialized cells lining the respiratory tract, such as the Clara cells in lung or sustentacular cells in olfactory epithelium. It is then stated that "the carcinogenic effect of naphthalene observed in the nose of F344/N rats in the current study contrasts with the lack of carcinogenic effect of naphthalene observed in the earlier study with rats (strain unspecified) (Schmahl, 1955)".

This presents a logical dilemma because one would expect that if the mechanism of naphthalene toxicity and/or carcinogenicity is, as in the mouse, metabolic activation via specialized cells in the lung and upper respiratory tract (O'Brian *et al.*, 1989; Plopper *et al.*, 1992), then one would expect a toxic or carcinogenic response that is remote from the site of administration, whether that be intraperitoneal (as in the mouse) or orally by gavage. This is also in light of the fact that rats, before the study was initiated, were deemed "less sensitive to naphthalene toxicity than mice", apparently based on some of the historical studies that were categorized as "inadequate" for assessing respiratory insult. The results of this TR 500 study, however, showed that the rats had a similar steady-state concentration of naphthalene in the lung and that they responded the same as mice at all dose levels. Unlike mice, the male rats responded with a significant dose-

related increase in the incidence of nasal adenomas. The rats also saw a dose-related increase in the incidence of olfactory neuroblastomas, but only in the females.

Table 2.
Incidence of Key Carcinogenic Lesions in F344/N Rats (TR 500)

	Exposure Concentration			
MALE	0 ppm	10 ppm	30 ppm	60 ppm
Olfactory epithelial neuroblastoma	0/49	0/49	4/48	3/48
Respiratory epithelial adenoma	0/49	6/49	8/48	15/48

	Exposure Concentration			
FEMALE	0 ppm	10 ppm	30 ppm	60 ppm
Olfactory epithelial neuroblastoma	0/49	2/49	3/49	12/49
Respiratory epithelial adenoma	0/49	0/49	4/49	2/49

Neuroblastomas are of no direct relevance with regard to the long-term carcinogenic risk of naphthalene to humans because a) they are exceedingly rare in the human population (a recent literature review suggests 1 case per 1 million people per year) and occur in a bimodal age distribution (teenagers and 6th decade of life), suggesting no correlation with known lifetime exposure to this compound (e.g., cigarettes, fossil fuel combustion) and b) dose ranges and exposure levels that induced these tumors cannot be separated from the promotional effect of the *chronic and severe irritation* observed in the pathological data presented in the TR500 rat study. In short, given the widespread use of naphthalene within the human population since the advent of the industrial revolution, one would expect a much higher incidence of olfactory neuroblastomas, at least within the population that is exposed to levels close to that seen in this study (e.g., manufacturers of mothballs and grinding wheels). In virtually all of the epidemiological studies conducted on industrial workers exposed to elevated levels of naphthalene in the workplace (see Section II), there is never any mention, nor is there any specific report, of an increase in the incidence of nasal cancers. Indeed, a recent gathering of 29 experts from 15 countries concluded that "no relevant data were available to the Working Group on the carcinogenicity of naphthalene in humans (IARC, 2002)." Given the fact that naphthalene has been in such widespread use for such a long period of time, both domestically and industrially, one would expect to see either recorded or anecdotal evidence of nasal tumors in humans (similar, for example, to myelogenous effects seen on the bone marrow and blood following exposure to benzene).

Based on data presented in the SEER Cancer Statistics Review (http://seer.cancer.gov), the incidence of malignant tumors of the "nose, nasal cavity and middle ear" is 0.7 per 100,000 population. Given that there are currently 280 million people in the United States, one would expect approximately 1,960 new cases of nasal cancer per year for all tumor types observed in this general anatomical category (nasal cavities, middle ear, and accessory organs). A recent review of the incidence of olfactory neuroblastoma (Anavi et al., 1989) estimates that these rare types of tumors constitute 2 - 5% of the

total intranasal malignant tumors. Therefore, of these 1,960 cases, one would expect no more than 100 new cases of olfactory neuroblastoma per year (an incidence rate of 0.7 x 0.05 per 100,000, or 0.035 per 100,000).

A similar argument can be made for the degree of naphthalene exposure versus the potential to induce nasal adenomas. The high doses used in the TR 500 study most likely saturated all of the key cytochrome P-450 enzymatic pathways required for normal metabolism of the compound, as verified in the discussion by the TR 500 authors and the reviewers of the study. Several reviewers were concerned that "the role of inflammation in genesis of these lesions needs to be considered" and that a "discussion of biological relevance to human health risk is warranted".

Naphthalene does not appear to be a genotoxic agent, which should also affect the NTP's decision regarding the relevance of the rat bioassay data to humans. Naphthalene and its metabolites do not show genotoxicity when tested in standard bacterial mutagenicity assays *in vitro.* Some cytotoxicity is observed when tested in mammalian cell lines (CHO, human lymphoblasts), but the evidence that this compound may act by a genetic mechanism is very weak. A recent comprehensive review of the genetic toxicology of this compound concluded that the "results of standard genetic toxicity assays suggest that naphthalene is not likely to be genotoxic *in vivo*" and that "the absence of naphthalene-induced gene mutation and the presence of cytotoxicity and some chromosomal events *in vitro* are consistent with a threshold-related mechanism of tumor induction, driven by cytotoxicity and cell regeneration, followed by genetic events....or by accumulation of naphthalene at specific target sites to allow *in situ* formation of a genotoxic metabolite to trigger or enhance spontaneous tumor development" (Schreiner, 2003).

This author presented the results of five previously unpublished studies. Two were Ames bacterial assays *in vitro*, one was an *in vitro* unscheduled DNA synthesis assay, one was an *in vivo* mouse micronucleus assay, and the last was an *in vivo* unscheduled DNA synthesis assay. All five assays were negative which adds to the database that NTP considered in its Report on Carcinogens Background Documents for Naphthalene (August, 2002) and increases the strength of the conclusion that naphthalene is not genotoxic. In fact, the EU (2003) concludes: "Overall, the balance of evidence indicates that naphthalene is not genotoxic." AMEC recommends that NTP take into consideration the new data from Schreiner (2003).

There are no studies in the scientific literature that demonstrate that naphthalene is carcinogenic to humans. The recent European Union Risk Assessment Report on Naphthalene (EU, 2003) states that the only literature on human carcinogenicity are two papers by Wolf (1976; 1978) that discuss four reported laryngeal cancers in workers engaged in the purification of naphthalene. EU (2003) concluded that "Overall, no conclusion can be drawn from these reports regarding the role, if any, of naphthalene in the production of these cancers." This is because "it is clear from the reports that all of the cases were smokers and were exposed to other substances...."

In conclusion, NTP should not list naphthalene as "reasonably anticipated to cause cancer in humans." Mouse lung adenomas as seen in NTP's TR 410 study are not

relevant to human health because of the known species-specific metabolism that occurs in the mouse causing the mechanism of action in the mouse not to be relevant to humans. The rat nasal tumors are not be relevant to humans because: (a) rats are obligate nose breathers and have nasal turbinates that are unique; (b) rat nasal tumors appear to be the consequence of chronic tissue damage, and (c) a specific naphthalene metabolite is found in significant amounts in rat and nasal olfactory epithelium that may be unique to these species. Overall, the European Union (EU, 2003) evaluated the NTP bioassay data and concluded that it was not appropriate to list naphthalene as a carcinogenic hazard to humans based on the available information.

II. EVALUATION OF EPIDEMIOLOGICAL LITERATURE ON WORKER GROUPS EXPOSED TO NAPHTHALENE

A. BACKGROUND

Naphthalene is a component of coal tar, coal tar creosote and coal tar pitch. In addition to the many exposures that the general population experiences, many thousands of workers in a large number of industries have been exposed to naphthalene for their entire working lifetimes. The world literature on human health effects associated with exposures in industry contains no evidence that exposures to naphthalene in these products can or does cause nasal tumors.

Coal tar is a mixture that is derived from coal that is used as a product in commerce. It is also used as a starting material for the manufacture of various other mixtures, including coal tar creosote. Thus, workers can be exposed to coal tar at ambient temperatures. They can also be exposed to coal tar at elevated temperatures, such as during the distillation of coal tar or during the hot application of coal tar as roofing material or paving material. If the coal tar is heated, certain volatile chemicals, such as naphthalene, are emitted. However, the concentrations of each of the volatile constituents emitted from coal tar will differ from the concentrations of the same volatiles emitted from heated creosote or heated coal tar pitch. The naphthalene content of coal tar is significant. Wright et al. (1985) reported that coal tar contained 11% naphthalene. IARC (1985) reported that coal tars contain naphthalene at concentrations that range from 1-10%.

According to the Hazardous Substances Data Base, coal tar creosote is a mixture derived from coal tar by distillation in the range of 200-250 degrees Celsius. According to the American Wood Preservers' Association, the standard for P1/P13-95 creosote preservative requires that the mixture distills within the following ranges:

	Not Less than	Not More Than
Up to 210 degrees C	-	2.0%
Up to 235 degrees C	-	12.0%
Up to 270 degrees C	10.0	40.0%
Up to 315 degrees C	40.0	65.0%
Up to 355 degrees C	65.0	77.0%

Thus, most of the components of the mixture must distill between 270 and 355 degrees C. Workers who are exposed during the manufacture of creosote could therefore be exposed to a mixture that is 270 degrees or more for some period of time. However, workers who are employed in the wood treating industry could be exposed to creosote solutions only at the temperatures employed in the treatment cylinders, which cannot exceed 99 degrees C according to American Wood Preservers' Association standards. Similarly, people who work with creosoted timbers might be exposed to this mixture, but the mixture would be at the ambient temperature, not an elevated temperature. In all cases, there would be exposure to naphthalene, but the levels would differ depending on the particulars of the exposure. The naphthalene content of creosote is reported by IARC (1985) to vary from 1-18%. Nylund et al. (1992) reported naphthalene content for four types of creosote, with concentrations ranging from 9%-17%. Lorenz and Gjovik (1972) report a concentration of naphthalene of 3% in a sample of creosote. Sundstrom et al. (1984) also reports 3% for the naphthalene content of creosote.

Coal tar pitch is the residue that remains after distillation of coal tar. Thus, it is a solid after it has cooled, and there are no exposures to volatile compounds at ambient temperatures. However, coal tar pitch is also used in various high temperature manufacturing operations, such as the production of aluminum, where it is heated to extremely high temperatures. The coal tar pitch volatiles that are emitted during these processes are specific to the mixture (coal tar pitch) and the temperatures involved (over 1000 degrees C). Machado et al. (1993) measured the naphthalene content of coal tar pitch and found 1.2%. The naphthalene content of pitch is low, but the use of coal tar pitch in very high temperature applications can cause the volatilization of the remaining naphthalene. Thus, workers in the industries that use pitch at high temperatures have exposures to naphthalene. Machado et al. (1993) found that the naphthalene content of coal tar pitch fume was 0.2%.

Coke oven emissions or emissions from coal gasification processes are entirely different mixtures than the ones already discussed. In these industrial processes, coal is heated to extremely high temperatures, and many different chemicals are released from the coal and from the chemical reactions that take place within the hot gases. These complex mixtures have little relationship to the gases that are emitted from the heating at lower temperatures of mixtures such as coal tar creosote. However, naphthalene exposures do occur from coking operations.

Thus, toxicological evaluations of the many different mixtures that have their genesis in coal chemistry must focus on the specific mixture and the conditions of exposure. Studies of coke oven workers, aluminum reduction workers, creosote workers, coal tar distillation workers, roofers, and others are all unique. However, these workers are all exposed to naphthalene to varying degrees. As noted below, there is no evidence from the many studies of such workers that naphthalene exposure causes nasal tumors.

B. SUMMARY OF LITERATURE

AMEC has evaluated the large number of studies (see Tables 3-5 below) that address the health effects of exposures to complex mixtures containing naphthalene and has found only two references that report the presence of nasal tumors. No studies were

found regarding workers exposed only to pure naphthalene. All studies involved complex mixtures. Because nasal tumors are rare in humans, it is very likely that the presence of such tumors would have been reported in all of these studies had they been seen. It should be noted that creosote vapors, coal tar volatiles, coal tar pitch volatiles, diesel exhaust, asphalt fumes, roofing fumes, and other complex mixtures are extremely complex and also contain high molecular weight PAHs that are classified as potential human carcinogens. Thus, naphthalene is only one chemical to which people are exposed when they are exposed to these mixtures. However, naphthalene exposure is not insignificant in such settings, and it is instructive to note that nasal tumors are only mentioned twice in the vast literature on the health effects of these complex mixtures. Following this voluminous search of the literature addressing the human health effects of workers exposed to naphthalene-containing mixtures, AMEC concludes that the induction of nasal tumors in rats exposed to extremely high levels of naphthalene vapor is not relevant to human health.

1. OVERVIEW SUMMARY OF LITERATURE ON CREOSOTE, COAL TAR, AND COAL TAR PITCH

The following tables (Tables 3-5) summarize literature evaluated for nasal tumors regarding creosote, coal tar and coal tar pitch. None of the studies and reports listed in the tables presents any cases of nasal tumors, despite the fact that exposures to naphthalene would have been high enough in many cases to have caused them if the data from the NTP rat study were relevant to the prediction of human carcinogenic response. AMEC notes that none of these studies were designed to specifically study nasal tumors and most of these studies were not broadly designed to study all forms of cancer in these workers. In fact, many studies only report data on benign skin tumors. However, they are presented to show that workers exposed to naphthalene-containing complex mixtures have been intensively studied for over one hundred years. If a rare cancer such as nasal cancer were caused by naphthalene, it most certainly would have been seen over the years and been reported in some of these studies.

TABLE 3
HUMAN HEALTH STUDIES
COAL TAR CREOSOTE

AUTHOR	DATE	COUNTRY
Ball	1885	UK
Mackenzie	1898	UK
Legge	1912	UK
Legge	1913	UK
O'Donovan	1920	UK
Cookson	1924	UK
Hamilton	1925	US
Bridge and Henry	1928	UK
Wood	1929	US
Bridge	1930,1931	UK
Henry et al.	1931	UK
Henry	1947	UK
Hueper	1948	US
Hueper	1950	UK, Germany, France
Lenson	1956	US
Cote et al.	1973, 1976	US
Garrett	1975	US
Markel et al.	1977	US
NIOSH	1977	US
Dusich et al.	1980	US
Axelson & Kling	1983	Sweden
Willeitner & Dieter	1984	Germany
Flodin et al.	1987	Sweden
Cordier et al.	1988	France
Dean et al.	1988	US
Persson et al.	1989	Sweden
Steineck et al.	1989, 1990	Sweden
Karlehagen et al.	1992	Sweden
Nokso-Koivisto & Pukkala	1994	Finland
Siemiatycki et al.	1994	Canada
Tynes et al.	1994	Norway

TABLE 4
HUMAN HEALTH STUDIES
COAL TAR

AUTHOR	DATE	COUNTRY	STUDY TYPE	COAL TAR TYPE	CO-EXPOSURES
Volkmann	1875	Germany	Case study	Unspecified	
Manouvriez	1876	France	Case study	Unspecified	
Tillmanns	1880	Germany	Case study	Brown Coal	Paraffin
Ball	1885	UK	Case study	Unspecified	
Butlin	1892	UK	Case study	Unspecified	Asphalt
Liebe	1892	Germany	Case study	Unspecified	
Lueke & Cleveland	1907	US	Case study	Unspecified	Pitch
Schamberg	1910	US	Case study	Unspecified	
O'Donovan	1920	UK	Case study	Gas Works	
O'Donovan	1920	UK	Case study	Gas Works	Pitch
Southam & Wilson	1922	UK	Case study	Unspecified	Paraffin
Legge	1922	UK	Survey	Primarily Gas Works	
Courmont	1924	France	Case study	Gas Works	Pitch
Courmont	1924	France	Case study	Coke Oven	
Dejong et al.	1924	France	Case study	Unspecified Pharmaceutical	
Kennaway	1925	UK	Survey	Unspecified Tar	
Lazzarini	1928	Italy	Case study	Unspecified	
O'Donovan	1929	UK	Case study	Unspecified	
Heller	1930	US	Case study	Gas Works	Gas Works Pitch
Heller	1930	US	Case study	Coke Oven	Coke Oven Pitch
Heller	1930	US	Case study	Unspecified	Unspecified Coal Tar Pitch
Heller	1930	US	Case study	Coke oven	
Bridge	1930	UK	Survey	Tar Distilleries	Pitch
Bridge	1930	UK	Survey	Gas Works	Pitch
Haagensen	1931	US	Case study	Unspecified	
Henry et al.	1931	UK	Survey	Unspecified	Pitch, Others
Goulden & Stallard	1933	UK	Case study	Unspecified	Pitch
Shambaugh	1935	US	Case study	Horizontal Retort	
Henry & Irvine	1936	UK	Survey	Unspecified	Pitch
Henry & Irvine	1936	UK	Survey	Coke oven	
Henry & Irvine	1936	UK	Survey	Gas works	
Hueper	1942	Germany	Case study	German Tar	
Hueper	1942	US	Case study	Unspecified	Coal Tar Pitch Volatiles
Henry	1947	UK	Survey	Unspecified	
Henry	1947	UK	Survey	Unspecified	Pitch
Henry	1947	UK	Survey	Unspecified	Pitch and Tar Products

TABLE 4
HUMAN HEALTH STUDIES
COAL TAR

AUTHOR	DATE	COUNTRY	STUDY TYPE	COAL TAR TYPE	CO-EXPOSURES
Dean	1948	US	Case study	Unspecified	
Hodgson	1948	UK	Case study	Pharmaceutical	
Hueper	1948	US	Review article	Unspecified	Pitch
Ross	1948	UK	Case study	Primarily Gas works	Pitch
Ross	1948	UK	Survey	Primarily Gas Works	
Ross	1948	UK	Survey	Primarily Gas Works	Pitch
Fisher	1952	UK	Epidemiology	Horizontal retort	
Rosmanith	1953	Russia	Case study	Unspecified	
Alexander & Macrosson	1954	UK	Case study	Unspecified Pharmaceuetical	
Rook et al.	1955	UK	Case study	Unspecified Pharmaceutical	Other Pharmaceuticals
Carli	1958	NA	Case study	Unspecified Pharmaceutical	
Mackenna	1959	UK	Review article	Pharmaceutical	
Phair and Sterling	1961	US	Epidemiology	High Temperature Horizontal Coke Oven	Pitch
Muller & Kierland	1964	US	Epidemiology	Pharmaceutical	UV
Spink et al.	1964	UK	Case Study	Unspecified	Mineral Oil
Doll R. et al.	1965	UK	Survey	Gasworks	
Perry et al.	1968	US	Epidemiology	Pharmaceutical	UV
Doig et al.	1970	UK	Case Study	Unspecified	
Doig et al.	1970	UK	Survey	Unspecified	Coal Tar Pitch
Doll et al.	1972	UK	Survey	Gasworks	
Lee et al.	1972	UK	Case study	Unspecified	
Spitzer et al	1975	Canada	Epidemiology	Unspecified	UV
Durkin et al.	1978	US	Case study	Pharmaceutical	UV, Steroids
Epstein	1979	US	Review article	Pharmaceutical	UV
Maughan et al.	1980	US	Epidemiology	Pharmaceutical	UV
Stern et al.	1980	US	Epidemiology	Pharmaceutical	PUVA
Annamalai et al.	1981	India	Case study	Unspecified. Pharmaceutical	X-ray
Bickers	1981	US	Review	Pharmaceutical	Various
Muller et al.	1981	US	Epidemiology	Pharmaceutical	UV
Pittlekow et al.	1981	US	Epidemiology	Pharmaceutical	UV
Alderson & Clarke	1983	UK	Epidemiology	Pharmaceutical	UV + others
Menter & Cram	1983	US	Epidemiology	Pharmaceutical	UV
Waldron et al.	1984	UK	Survey	Unspecified	Pitch
Jones et al.	1985	UK	Epidemiology	Unspecified, pharmaceutical	
Jones et al.	1985	UK	Epidemiology	Pharmaceutical	
Lin & Moses	1985	Canada	Survey	Pharmaceutical	UV
Maclaren et al.	1986	Scotland	Epidemiology	Unspecified	

TABLE 4
HUMAN HEALTH STUDIES
COAL TAR

AUTHOR	DATE	COUNTRY	STUDY TYPE	COAL TAR TYPE	CO-EXPOSURES
Moy et al.	1986	US	Case study	Pharmaceutical	UV
Maclaren & Hurley	1987	UK	Epidemiology	Unspecified	
Jensen et al.	1988	Denmark	Epidemiology	Unspecified	Asphalt
Maizlish et al.	1988	US	Epidemiology	Unspecified.	Asphalt fumes
Torinuki & Tagami	1988	US	Epidemiology	Pharmaceutical	UV
McGarry & Robertson	1989	UK	Case study	Unspecified Pharmaceutical	Vioform hydrocortisone
Bender et al.	1989	US	Epidemiology	Unspecified	
Ahrens et al.	1991	Germany	Epidemiology	Unspecified	Diesel, oil, gasoline, bitumen
Bhate et al.	1993	UK	Epidemiology	Pharmaceutical	PUVA, As, Others
Lindelof & Sigurgeirsson	1993	Sweden	Epidemiology	Pharmaceutical	PUVA, methotrexate
Partanan & Boffetta	1994	France, Finland	Epidemiology	Unspecified	Bitumen, Asphalt
Siemiatycki et al.	1994	CANADA	Epidemiology	Unspecified	Coal Tar Pitch
Stern & Laird	1994	US	Epidemiology	Unspecified, pharmaceutical	PUVA, methotrexate, As, UV
Stern	1995	US	Epidemiology	Pharmaceutical	PUVA, other
Gallagher et al.	1996	Canada	Epidemiology	Unspecified	Various
Maier et al.	1996	Austria	Epidemiology	Unspecified, Pharmaceutical	PUVA, As, x-rays, UVB, methotrexate
Consultants In Epidemiology & Occupational Health	1997	US	Epidemiology	Coke Oven	
Swaen & Slangen	1997	Netherlands	Epidemiology	Unspecified	
Letzel & Drexel	1998	Germany	Epidemiology	Unspecified	
Stern et al.	1998	US	Epidemiology	Pharmaceutical	PUVA

TABLE 5
HUMAN HEALTH STUDIES
COAL TAR PITCH

AUTHOR	DATE	COUNTRY	PITCH TYPE	CO-EXPOSURES
Butlin	1892	UK	Unspecified	Asphalt
Lueke & Cleveland	1907	US	Unspecified	Coal Tar
O'Donovan	1920	UK	Gas Works Pitch	
O'Donovan	1920	UK	Gas Works Pitch	Coal Tar
Legge	1922	UK	Patent-fuel pitch, Gas works pitch	Coal Tar
Kennaway	1924(b)	UK	Patent-fuel pitch, Gas works pitch	Coal Tar
Courmont	1924	FRANCE	Unspecified	Unspecified Tar
Kennaway	1925	UK	Unspecified	
Wood	1929	UK	Gas Works and Coke Oven	Coal Tar
O'Donovan	1929	UK	Gas Works Pitch	Coal Tar
Teutschlaender	1929	GERMANY	Unspecified	
Bridge	1930	UK	Patent fuel pitch	
Bridge	1930	UK	Tar distilleries	Coal Tar
Bridge	1930	UK	Gas works pitch	Gas Works Coal Tar
Heller	1930	US	Coke Oven	
Heller	1930	US	Gas Works Pitch	Gas Works Coal Tar
Heller	1930	US	Coke Oven Pitch	Coke Oven Tar
Heller	1930	US	Unspecified Pitch	Unspecified Coal Tar
Henry et al.	1931	UK	Unspecified	Coal tar and Coal Tar Products
Goulden & Stallard	1933	UK	Unspecified Pitch	Unspecified Coal Tar
Henry & Irvine	1936	UK	Unspecified	Unspecified Coal Tar
Kennaway & Kennaway	1936	UK	Gas Works and Coke Oven	Coke Oven Emissions, Coal Gas, Coal Tar and Others
Hueper	1942	US	Unspecified	Unspecified Coal Tar
Henry	1947	UK	Unspecified	
Henry	1947	UK	Unspecified	Coal Tar
Henry	1947	UK	Unspecified	Coal Tar and Tar Products
Kennaway & Kennaway	1947	UK	Gas Works and Coke Oven	Coke Oven Emissions, Coal Gas, Coal Tar and Others
Witternitz	1947	UK	Unspecified	Coal Tar
Ross	1948	UK	Primarily Gas Works	
Ross	1948	UK	Primarily Gas Works	Coal Tar

TABLE 5
HUMAN HEALTH STUDIES
COAL TAR PITCH

Dean	1948	US	Unspecified	
Hueper	1948	US	Unspecified	Coal tar
Cruickshank & Gourevitch	1952	UK	Unspecified	
Patch	1954	UK	Unspecified	Bitumen, asbestos slate
Phair & Sterling	1961	US	High Temperature Horizontal Coke Oven	Coal Tar
Doig et al.	1970	UK	Unspecified	
Doig et al.	1970	UK	Unspecified	Coal Tar Pitch
Hodgson & Whiteley	1970	UK	Unspecified	
Hammond et al.	1976	US	Unspecified	Asphalt
Birmingham et al.	1978	US	Unspecified	
Everall & Dowd	1978	UK	Unspecified	
Jarvis	1980	UK	Unspecified	
McLaughlin et al.	1983	US	Unspecified	Petroleum or coal tar
Wang et al.	1983	US	Unspecified	Mineral Oil, Abrasives
Waldron et al.	1984	UK	Unspecified	Unspecified coal tar
Moulin et al.	1989	FRANCE	Unspecified	Petroleum Coke
Sharp et al.	1989	CANADA	Unspecified	Unspecified tar, Organic Solvents and Others
Siemiatycki et al	1994	CANADA	Unspecified	Coal Tar
Gallagher et al.	1996	CANADA	Unspecified	Unspecified tar and tar products

2. SUMMARY OF TWO PAPERS THAT MENTION NASAL TUMORS

Of all the literature involving workers who were exposed to naphthalene-containing complex mixtures that was evaluated by AMEC, only two studies reported nasal tumors, and only one study reported an increase in nasal tumors above expected rates.

A recent study (Selden, 1997) on a Swedish cohort of workers (n = 6,454) from seven aluminum foundries and three secondary aluminum (scrap) smelters showed that there was a significantly elevated risk estimated for cancer of the lung (51 cases; SIR = 1.49, 95%CI = 1.11-1.96), anorectal cancer (33 cases; SIR 2.13, 95%CI = 1.47-2.99), and sinonasal cancer (4 cases; SLR = 4.70, 95%CI = 1.28-12.01). Some of these workers were exposed to a suite of chemicals that are present in coal tar pitch volatiles, including naphthalene, benzo(a)pyrene, and a host of other PAHs. However, workers in the secondary aluminum smelters would not be expected to have been significantly exposed to naphthalene. Thus, one cannot determine the causative agent of the four cases of sinonasal cancer. It is also not known if the four cases were in workers exposed to naphthalene. In summary, it is the *sole* study that AMEC identified that reported nasal tumors at rates that exceeded the expected rates for workers for any of the many industries that involve naphthalene exposures.

A second study (Dong *et al.*, 1995) followed 15,007 construction workers who died between 1975 – 1987 and were aged 20 - 64 years. Some of the workers were roofers who were exposed to coal tar fumes. Nine tumors were reported in nasal cavities (ICD 160), but the expected rate in this population was 10. Accordingly, there was no increased risk of nasal cancer due to naphthalene or any other cause. In addition, as in the above paper, only some of the construction workers studied would have been exposed to naphthalene, and it is not known if the nine workers with nasal cancers were ever exposed to naphthalene.

3. SUMMARY OF SELECTED EPIDEMIOLOGY STUDIES

In this section, AMEC presents information from epidemiology studies that involved sufficient numbers of workers that would likely have shown nasal tumors if the data from the NTP rat study were relevant to human health. No cases of nasal tumors were reported in these studies.

Karlehagen, S, Andersen, A. & Ohlson, C. G., 1992, Cancer Incidence Among Creosote-Exposed Workers. Scand J Work Environ Health, 18, 26-29.

These researchers studied the cancer incidence data on 922 timber creosote workers at 13 plants in Sweden and Norway. Most cancer rates were not elevated compared to national statistics. Specifically, there was no increase in lung cancer, bladder cancer, or other cancers. Nasal cancer was not specifically discussed, but if this rare tumor had been seen in any of the workers, it most likely would have been a topic of discussion. However, lip cancer and nonmelanoma skin cancer rates were elevated. Of these, the lip cancer rate was not statistically significantly elevated compared to national statistics and can be discounted. The non-melanoma skin cancer rates were statistically

significantly elevated, and the rate was 2.4 times higher than national rates. However, the study has several methodological flaws that should be considered when evaluating the significance of the skin cancer results.

The study did not control for exposure to sunlight. According to the authors, the excess skin cancers "could probably be attributed to the combination of exposure to creosote and sunlight." This is due partly because the exposed workers had greater contact to sunlight than did the control population (national cancer rates) to which worker cancer rates were compared. Specifically, the authors stated: "as to the difference in cancer rates between urban and rural areas, the use of national rates could well have introduced bias because most of the plants were located in rural areas."

In addition, the study did not control for smoking, and workers were exposed to other wood treating formulations in addition to creosote.

When discussing their results in 1991 before the paper was published, the authors stated: "This study does not confirm that exposure to creosote in the wood preserving industry has caused an excess of total cancer morbidity. The study indicates, however, that exposure to creosote might increase the incidence of skin cancer." Thus, the authors were quite tentative about the biological significance of their finding of an increased risk of non-melanoma skin cancer.

Nokso-Koivisto, P. and E. Pukkala. 1994. Past Exposure to Asbestos and Combustion Products and Incidence of Cancer Among Finnish Locomotive Drivers. Occupational and Environmental Medicine, 5, 1330-334.

These authors studied the incidence of cancer in a cohort of 8,693 Finnish locomotive drivers. The authors state in the paper that such workers were exposed to creosote, coal tar, lubricating oils, diesel fuel, coal and other substances. Naphthalene is present in creosote, coal tar, lubricating oils, and fuels. The only cancer that was statistically significantly elevated compared to Finnish national statistics was mesothelioma, which was attributed to asbestos exposure. Rates of cancer of the oral cavity/pharynx and non-melanoma skin cancer were increased, but not statistically significantly so. Other cancer rates were not elevated, including stomach, lung, trachea, prostate, kidney, bladder, ureter and urethra, skin melanoma, lymphatic tissue, Hodgkin's disease, and leukemia. No nasal tumors were reported.

Cote, R.W., Keller, M.D., Lanese, R.R. 1976. Epidemiological Evaluation of Koppers Company, Inc. Employee Deaths

In this statistical analysis of Koppers Company employee deaths, the period of analysis was 1962 to 1975. In the Forest Products group, there were no increases in lung cancer or bladder cancer deaths. There was no difference in mortality by any cause when comparing high and low creosote-exposed groups. No nasal tumors were reported.

Costantino, J.P., C.K. Redmond, and A. Bearden.1995.Occupationally Related Cancer Risk Among Coke Oven Workers: 30 Years Of Follow-Up. JOEM. 37:597-604

15,818 coke oven workers were followed over 30 years. No nasal cancers were reported. 12 bucchal/pharangeal cancers were reported, but they were not statistically elevated compared to the expected number. 9 respiratory cancers were reported that were not in the lungs, bronchus or trachea. Based on the reported information, it cannot be ruled out that some of these cancers could have been cancers of the nasal cavities (ICD 160), but these cancers were at a lower rate than expected in the general population. Because of their rarity, nasal tumors would likely have been reported if observed.

Swaen, G. M. H. and J. M. M. Slangen.1997.Mortality In A Group Of Tar Distillery Workers And Roofers. Int. Arch. Occupy. Environ. Health 70:133-137.

907 tar distillery workers were followed for an average period of follow up of 28 years. No nasal cancers were reported. No mouth/pharynx cancers or larynx cancers were reported. There were 48 trachea/lung cancers, but the rate was not elevated above the expected rate. Lastly, there were 4 nonspecified respiratory cancers, but the rate was not elevated above the expected rate. Again, some of the nonspecific respiratory cancers could have been nasal cancers, but it is more likely that nasal cancers would have been reported if observed.

866 roofer workers were followed for an average period of follow up of 28 years. No nasal cancers were reported. Two mouth/pharynx cancers were reported, but the rate was not elevated above the expected rate. There was one larynx cancer, but the rate was not above the expected rate. There were 39 trachea/lung cancers, but this rate was not elevated above the expected rate. Lastly, there was one nonspecified respiratory cancer that was not elevated above the expected rate.

Hurley, J.F., R. Mcl. Archibald, P.L. Collings, D.M. Fanning, M. Jacobsen and R.C. Steel. 1983. The Mortality of Coke Workers in Britain. American Journal of Industrial Medicine. 4: 691-704.

In this study, 6,767 coke over workers were followed for a period of 12 years. No nasal tumors were reported; 168 "other" tumors were classified as all ICD 140-209 (less 151-154 and 162). Thus cancers of the nasal cavity would be included in the other category. "Other tumors" were less than the expected rate. Because the "other" category is so broad, no conclusions can be made here about nasal tumors, but because of the rarity of this tumor type, it is clear that nasal tumors would have been reported if even one case had been seen.

Romundstad, P., Haldorsen, T., and Anderson, A.. 2000. Cancer Incidence and Cause Specific Mortality among Workers in Two Norwegian Aluminum Reduction Plants. Am. J. Ind. Med. 37(2): 175-183.

5,627 aluminum reduction workers were followed for an average of 25 years. There were no nasal cancers reported; 26 "other" tumors which were defined as all tumors in ICD categories 140-209 (less 140, 151-154, 157, 161-163, 177-178, 180-181, 190, 191, 193, 199, and 200-204) were reported. Thus cancers of the nasal cavity would be included in the "other category". "Other tumors" were less than the expected rate. Again, because the "other" category is so broad, no conclusions can be made here about nasal tumors, but because of the rarity of this tumor type, it is clear that nasal tumors would have been reported if even one case had been seen.

Redmond, C. K., B. R. Strobino, and R.H. Cypess. 1976. Cancer Experience Among Coke By-Product Workers. Ann. NY. Acad. Sci. 271:102-115.

1,316 coke oven workers were followed for six years. No nasal cancers were presented. There were 34 cancers of the respiratory system of which 33 were cancers of the lungs, bronchus, and trachea. Therefore it cannot be ruled out that one cancer may have been a nasal tumor.

Lloyd W.J., Ciocco A., 1971. Long Term Mortality Study of Steelworkers - V. Respiratory Cancer in Coke Plant Workers. Journal of Occupational Medicine. 13(2): 53-66.

1,327 coke oven workers were followed for six years. No nasal cancers were reported. There were 31 cancers of the respiratory system of which 29 were cancers of the lungs, bronchus, and trachea. Therefore the maximum number of cases that could have been nasal tumors was two.

Rockette, H.E., Arena, V.C. 1983. Mortality Studies of Aluminum Plant Workers: Potroom and Carbon Department. J. Occup. Med. 25(7): 549-557

Death certificates were evaluated for a cohort of 21,829 aluminum plant workers with 5 or more years of employment between 1946 and 1977 at 14 aluminum reduction plants using various processes (Soderberg, pre-bake, other). The study was negative for lung cancer. "Although the results of other studies relative to an excess of lung cancer in aluminum workers were not confirmed, there were indications of a higher than expected mortality in pancreatic cancer, lympho-hematopoetic cancers, genitourinary cancer, nonmalignant respiratory disease and benign and unspecified neoplasms." "The most consistent finding in this study was the excess of pancreatic cancer." "There is an increasing risk of pancreatic cancer with increasing length of employment in the potroom departments for workers in both the prebake and horizontal Soderberg potrooms." "Since the pancreatic cancers occur in the potrooms of both processes, it is unlikely that the cause for this excess is exposure to coal tar pitch volatiles."

No nasal cancers were reported. Out of 21,829 workers, there were 284 observed cases of respiratory cancer of which 272 were lung cancer and 12 were "other respiratory cancers." It cannot be ruled out that some of these "other" tumors may have been nasal cancers, but the expected number in this group was 19 based on general population statistics. "Other respiratory cancers" were not elevated in these workers.

Maizlish, N., Beaumont, J., Singleton, J. 1988. Mortality among California Highway Workers. Amer. J. Indust. Med. 3:363-379.

570 California DOT deceased workers were studied. 327 were involved in highway maintenance where they may have been exposed to asphalt fumes, coal tar, diesel exhaust, or fuels. Many other exposures were co-occurring. No statistically significant increase in cancer, including lung and skin, was seen in highway maintenance workers. No nasal cancers were reported.

Armstrong, B., Tremblay, C., Baris, D., Theriault, G. 1994. Lung Cancer Mortality and Polynuclear Aromatic Hydrocarbons: A Case-Cohort Study of Aluminum Production Workers in Arvida, Quebec, Canada. American Journal Of Epidemiology.139:250-262

In this case-control study of 338 lung cancer deaths and a random sample of 1138 workers from 16,297 men (who had worked at least 1 year between 1950 and 1979 in manual jobs at a large aluminum production plant) relative risk for lung cancer was significant for Soderberg pot workers with 20-41 years exposure. The paper has no discussion of nasal tumors.

Bender, A.P., Parker, D.L., Johnson, R.A., Scharber, W.K., Williams, A.N., Marbury, M.C. and Mandel, J.S., 1989. Minnesota Highway Maintenance Worker Study: Cancer Mortality. Amer. J. Indust. Med. 15:545-556

This study observed 4,849 workers with at least one year of exposure to diesel fuels, diesel exhaust, asphalts, coal tar, gasoline, and PAHs. The cohort was followed-up for 40 years. The average period of follow-up for a worker was 20 years. No increases in cancer mortality were seen in the entire study population. When older workers were compared, a statistically significant increase was observed for kidney and bladder cancer with five excess deaths and for leukemia with five excess deaths. No nasal tumors were reported. Out of 4,849 workers, there were 57 observed cases of respiratory cancer of which 54 were cancer of the trachea, bronchus or lung, and 3 were "other respiratory cancers." It cannot be ruled out that some of these "other" tumors may have been nasal cancers, but the expected number in this group was 5 based on general population statistics. Thus, "other respiratory cancers" were not elevated in this worker population.

Ronneberg, A. and Andersen, A., 1995. Mortality and Cancer Morbidity in Workers from an Aluminum Smelter with Prebaked Carbon Anodes- Part II: Cancer Morbidity. Occup. Environ. Med. 52:250-254.

This study investigates associations between cancer incidence and exposure to coal tar pitch volatiles, asbestos, pot emissions, heat stress and magnetic fields in 1137 workers from a Norwegian aluminum smelter (prebake) that operated from 1914- 1975. The average follow-up period was 29 years. The report found a significant excess of bladder and lung cancer cases in workers with <3 years exposure and no increase in workers

with >3 years exposure. No statistically significant increased risk was associated with exposure to coal tar pitch volatiles.

No nasal cancers were reported, but 6 cases of "upper respiratory tract" cancers [IDC codes 141,143-8, 160-1] were reported, although they were not significantly increased above the expected number..." It cannot be ruled out that some of these "other" tumors may have been nasal cancers, but the cancer types lumped into this broad category include 9 ICD codes. In addition, "other respiratory tract" cancers were not elevated in this worker population.

Spinelli, J. J., Band P. R., Svirchev L. M., Gallagher R. P., 1991. Mortality and Cancer Incidence in Aluminum Reduction Plant Workers. J. Occup. Med. 33(11): 1150-1155.

In this historical cohort study of 4,213 people who worked for 5 years or more at a Soderberg aluminum reduction plant, skin cancer rates were not elevated. Brain / CNS cancer mortality and bladder cancer incidence were statistically significantly elevated. Lung cancer incidence and mortality were not elevated. No nasal cancers were reported.

Phair, J.J., Sterling, T. (The Kettering Laboratory, University of Cincinnati, OH). 1961. Competing Causes of Death in Coal Tar Workers.

This report studied the cause of death in 780 people who died among 6,203 individuals involved in several aspects of the coal tar industry, who were alive in 1940 and had a history of at least 5 years of work before 1950. Most of the people studied were involved in either (1) coal handling, (2) coke production and handling, or (3) gas handling and lighting oil recovery. For white workers, categories that involved coal tar included (1) tar distillation (including pitch), (2) ammonia, tar bases and other chemicals and (3) "all other" which included tar recovery, tar distillation (naphthalene), phenols and other tar acids, impregnation (tar and asphalt), impregnation (creosote oil), and laboratory workers. For non-white workers, all of the coal tar, pitch and creosote workers were classified under "all other" because of small numbers in each category. The study showed no increases in death rates due to any causes for coal tar, pitch or creosote workers: "there is a striking agreement between the total observed and expected deaths for all ages for cancer and cardiovascular disease in the white workers, but the non-whites have fewer than the number predicted." "The only significant finding is the excess number of observed lung cancer deaths in the non-white workers in coke production and handling." No nasal tumors were reported.

CONCLUSION

If one evaluates any single study and asks whether nasal tumors would be expected in the workers exposed to naphthalene-containing mixtures if naphthalene were a risk factor for nasal tumors in humans, one might conclude that the study population was too small to see an effect. However, many thousands of naphthalene-exposed workers have been studied over the years when the many studies of creosote workers, coke oven workers, aluminum reduction workers, roofers, pavers, and others are viewed in

their entirety. AMEC concludes from evaluating the whole body of literature that there is no evidence that naphthalene exposure causes nasal tumors in humans, and the numbers of workers whose health status was evaluated is more than adequate to detect such an effect.

Many of the studies reported "all respiratory tumors" and "tumors of the trachea, bronchi, and lungs." When the former exceeded the latter in a study, the tumor type was not reported, but the number of categories that these "other" tumors could have fallen into was large. While some of these "other" respiratory tumors might have been nasal tumors, it is extremely unlikely that a rare malignancy such as nasal tumors would have gone undetected in all of these studies. If the workers had been diagnosed with nasal cancer, surely this fact would have been reported in the scientific studies.

Thus, there is no evidence in the literature that naphthalene exposure causes nasal tumors in humans despite the fact that there have been scores of health surveys and epidemiology studies of worker populations who are exposed to naphthalene as a component of complex mixture exposures. Given this information on humans, AMEC strongly recommends that NTP not list naphthalene as "reasonably anticipated to be a human carcinogen."

III. TYPICAL EXPOSURE LEVELS FOR NAPHTHALENE

Naphthalene is present in gasoline, diesel oil, fuel oil, lubricating oils, car, truck, and railroad exhaust, heating oil exhaust, wood smoke, smoke from trash burning, cigarette smoke, mothballs, toilet bowl disinfectants and many other sources. Accordingly, the general population is routinely exposed to naphthalene and has been throughout the twentieth century. In fact in the U.S., the presence of 2-naphthol in the urine of 75% of the tested population indicates that daily exposure to this compound is nearly ubiquitous (Needham *et al.*, 1995).

In this section, exposure concentrations are summarized from the literature to provide a basis for determining the risks posed to various groups of people who routinely come into contact with naphthalene vapors. These risks are estimated assuming that the nasal tumor response in rats were relevant to human health despite evidence to the contrary.

A. Background Exposures - Typical Levels of Naphthalene Encountered Indoors:

Because of cigarette smoke, fireplace smoke and other sources, naphthalene is routinely found when indoor residential air samples are analyzed. Levels associated with routine and normal activities in the home range from <1-70 ug/m^3 in reference documents in AMEC's files. These references are described below.

B. Naphthalene Levels in Homes Not Specified as to Presence of Smokers:

- Hawthorne et al. (1985): 9 ug/m^3

- EPA (1991): Mean concentration in German homes: 2.3 ug/m^3
- Gold and Naugle (1993): Indoor air concentrations in residences: 0.6 - 4 ug/m^3.
- Chan et al. 1990: Average concentration in 12 residences: 13.9 ug/m^3.
- Hung et al. (1992): Average concentration indoors: 32.2 ug/m^3.
- DeBortoli et al. (1984): Concentrations in 14 homes and 1 office building: <1-70 ug/m^3.

SUMMARY: <1-70 ug/m^3

C. Naphthalene in Homes without Smokers

- EPA (1991): Mean concentration in U.S. homes without smokers: 1.8 ug/m^3.
- Chuang et al. (1991): Mean inside homes, nonsmoking: 1.0 ug/m^3;
- Mumford et al. (1991): Concentration in one nonsmoking home: 2.3 ug/m^3.

SUMMARY: 1-2 ug/m^3.

D. Naphthalene in Homes with Smokers

- EPA (1991): Mean concentration in U.S. homes with smokers: 2.2 ug/m^3
- Chuang et al. (1991): Mean inside smoking homes: 1.6 ug/m^3.
- Singer et al. (2002): Mean concentration in laboratory settings simulating smoking homes: 0.1-1.2 ug/m^3.

SUMMARY: <1-2 ug/m^3.

E. Naphthalene in Homes with Combustion Sources

- Hawthorne et al. (1985): Mean concentration in homes with combustion sources such as fireplaces, wood stoves and kerosene heaters: 46 ug/m^3

SUMMARY: 46 ug/m^3

F. Naphthalene in Ambient Air:

Because of vehicle exhaust and other sources, naphthalene is routinely found when outdoor residential air samples are analyzed. Levels associated with routine and normal activities associated with urban and suburban living range from <1 to 22 ug/m^3 in reference documents found in AMEC's files.

- Chan et al. (1990): Average naphthalene: 2 ug/m^3.
- EPA (1988): Mean levels of naphthalene in EPA's Ambient VOC database (67 samples): ug/m^3
- Propper (1988): Mean ambient concentration in Torrance CA air: 3.3 ug/m^3.
- Hung et al. (1992) : Ambient concentration of 21.9 ug/m^3 outdoors
- DeBortoli et al. (1984): Ambient concentrations: <1-11 ug/m^3.
- Raymond and Guichon (1974): Ambient concentrations: 3.8-11.2 ug/m^3.
- Arey *et al.* (1987): Ambient concentrations: 2.8 ug/m^3 night and 3.3 ug/m^3 day.
- NTP (2002): 1 ug/m^3 average ambient concentration

SUMMARY: <1 – 22 ug/m^3.

G. Naphthalene in Special Background Environments:

- Lofgren et al. (1991): Cars in traffic: 4.5 ug/m^3.
- Hampton et al. (1983): Concentration in tunnels: 4-10 ug/m^3.
- Kim et al. (2001): Concentration in cars: 5 ug/m^3; trafficked roads: 12 ug/m^3.
- Recochem (1995) Data: In a controlled experiment on mothball use "typical household situations following the product label directions," Recochem found 1-12 ug/L = 1,000 to 12,000 ug/m^3 in closed areas. "A person moving within the treated room was exposed to levels of approximately 0.3-1.6 microg/L for all three trials." This equals 300 ug/m^3 to 1,600 ug/m^3.
- EU (2003) cites the Recochem (1995) mothball exposure data. They evaluate exposure by saying that someone could be exposed to 12,000 ug/m^3 for 1 hour a day (1 hour in closet) and 820 ug/m^3 for 23 hours (23 hours in bedroom). This yields 1,300 ug/m^3 on average over a day.
- Lau et al. (1995) : 350 ug/m^3 naphthalene in a cupboard containing mothballs

- Gammage and Matthews (1987) reported measurements from a photoionization meter in a home of a person who "had liberally scattered mothballs in her closets." Conservatively assuming that naphthalene is two times more responsive to the instrument than is benzene, which was used to calibrate the instrument, the levels in the closet were 6,000 – 9,000 ug/m^3. Levels in the bedroom were 1,000 – 1,400 ug/m^3. Levels in the living room were 800 – 1,000 ug/m^3. Levels in the attached garage were 300 – 400 ug/m^3 and levels outdoors were 200- 250 ug/m^3.

- One sample from the living room was collected and analyzed in the laboratory by gas chromatography with a flame ionization detector (Hawthorne et al., 1985). The level of naphthalene was confirmed to be 675 ug/m^3, which is consistent with the above measurements from the photoionization meter.

H. Conclusions

From the above data, AMEC has made the following assumptions concerning the average naphthalene concentrations in certain environments.

Indoor and Outdoor Air: 5 ug/m^3.
The unspecified building concentrations range from 1-70 ug/m^3. Buildings without smokers ranged from 1-2 ug/m^3 and buildings with smokers ranged from <1-2 ug/m^3. Ambient air ranged from <1-70 ug/m^3, and air in cars ranged from 5-12 ug/m^3. Air in tunnels ranged from 4-10 ug/m^3. It is reasonable to assume that the average naphthalene concentration to which Americans of all types has been exposed, including indoor and outdoor exposures is and has been historically in the twentieth century at least as high as 5 ug/m^3. As noted above this value is a conservative estimate, because many other measurements in the literature are considerably higher.

Indoor Air of Homes with Combustion Sources: 46 ug/m^3.
AMEC assumes that people who live in homes that have fireplaces, wood stoves, or kerosene heaters are exposed to an average concentration of 46 ug/m^3.

Indoor Air of Homes with Naphthalene Mothballs in Use: 300-12,000 ug/m^3
AMEC uses the estimate of average naphthalene concentrations in homes using naphthalene mothballs of 1,300 ug/m^3. This value takes into account higher levels in closets, drawers, and other enclosed spaces and lower levels in the bedrooms and living rooms of homes.

Summary:
AMEC is aware that naphthalene exposure concentrations will vary widely in homes and buildings, but the values presented here are reasonable average estimates that can be used to estimate the exposure doses experienced by large numbers of people.

IV. ESTIMATES OF POPULATIONS EXPOSED TO NAPHTHALENE

In this section, AMEC makes assumptions about the numbers of people exposed to naphthalene in various environments. In these comments, AMEC concludes that there have been enough people exposed to naphthalene at high enough levels for long enough time to have caused some nasal tumors in the exposed population if the nasal tumor endpoint observed in the NTP study were relevant to human health. Thus, the population estimates are screening level estimates, and they represent the exposed population currently and historically, because no tumors of any type would be expected to occur until many years of exposure have occurred.

General Population: The population of the United States is assumed to be 281,421,906 according to census statistics for 2000.

General Population with Combustion Sources: According to High and Skog (1989), the fraction of residential households having wood burning stoves or fireplaces is was 29% both in 1980 and in 2000. This amounts to 81,612,353 people per year.

Naphthalene Mothball Users: ATSDR's "Toxicological Profile for Naphthalene" (ATSDR, 1995) reports that the consumption of naphthalene for use as a moth repellant was ~15 million pounds in 1994. If one assumes (a) half of this amount (7.5 million pounds) was used as a pesticide in domestic homes, (b) a box of mothballs weighs one pound, (c) one box is used per year, and (d) the size of the "average family" is 2.5 persons per household, then one can estimate that approximately 7 percent of homes in the US use mothballs. AMEC makes a conservative estimate for current use and use in the past of 5% from these assumptions. This amounts to 14,071,095 people per year.

General Population without Combustion Sources or Mothball Usage: 66% of the population amounts to 185,738,458 people per year.

V. SCREENING LEVEL POPULATION RISK ASSESSMENT

Despite the fact that naphthalene has not be classified as a potential human carcinogen by NTP, EPA, IARC or any other scientific body, EPA Region VIII has calculated a unit risk level of 0.04 $(mg/m^3)^{-1}$ using the data from the NTP rat bioassay in male rats. EPA based the unit risk on total tumors (neuroblastoma of the olfactory epithelium + adenoma of the respiratory epithelium). This unit risk is equivalent to a Cancer Slope Factor of 0.14 $(mg/kg/day)^{-1}$. AMEC does not endorse the use of a Unit Risk or Cancer Slope Factor based on a combination of benign and malignant tumors. Additionally, as noted elsewhere in these comments, neuroblastoma of the olfactory epithelium is a rare tumor. Lastly, there are many reasons to conclude scientifically that the rat tumor endpoints in this study do not have relevance to human health. Thus, EPA should not have derived such a Cancer Slope Factor. However, for the sake of argument, it is assumed for this exercise that the Cancer Slope Factor is 0.14 $(mg/kg/day)^{-1}$ for nasal tumors. This section of the comments estimates the population burden of nasal tumors that would be expected in the population of the United States if naphthalene, indeed, poses a risk to humans for nasal cancer.

AMEC has summarized exposure information and population information for several categories of people. It should be noted that there are many other groups of people who are exposed to naphthalene. Thus, this exercise is a screening level exercise.

The results of this screening exercise are presented in the table below. If it is assumed that the Cancer Slope Factor is as noted above and that the general population is exposed every day for 350 days a year for 30 years to the average naphthalene concentrations presented in Section III (Conclusions), then the incremental excess lifetime cancer risk for nasal tumors would be predicted to range from $8x10^{-5}$ for the general population not exposed to wood smoke in the home to $2x10^{-2}$ for people who use naphthalene moth balls in their homes. The risks for one year of exposure would be predicted to range from $3x10^{-6}$ to $7x10^{-4}$ per year. Multiplying the risk estimates by the populations and summing, one obtains a tumor burden of 371,000 tumors expected after a 30-year exposure or 12,400 nasal tumors per year. Since these exposures to naphthalene are not a recent phenomenon and have occurred since the early part of the twentieth century, ample latency time has elapsed such that these tumors ought to have been seen every year for many years now. As noted above, however, the observed numbers of nasal tumors each year from all causes is approximately 2,000 per year, and this includes tumors of the nasal cavity, the middle ear, and accessory organs due to the disease classification codes used. The observed rate of nasal neuroblastomas is even less, at about 100 per year from all causes as discussed in Section I.

Table 6.

Estimation of the Incremental Risk of Naphthalene in the United States using a Tentative USEPA-Derived Screening Cancer Slope Factor[1]

Receptor[2]	Air Concentration (mg/m3)	Incremental Risk	Estimate of Exposed Population	Expected Incremental Cancers
Mothball Users	1.300	2.10E-02	14,071,095	295,008
Combustion Indoors	0.046	7.42E-04	81,612,353	60,545
General U.S. Population	0.005	8.06E-05	185,738,458	14,977
Total Number of Annual Cancers Expected in U.S. Population:				370,530

[1]Assumes a CSF of 0.14 $(mg/kg/day)^{-1}$, per USEPA memo of R. Benson, Ref. 8P-W-MS, 4/23/02.

[2]Assumes the standard inhalation exposure scenario for domestic residence or worker per USEPA Human Health Risk Assessment Guidance. (i.e., inhalation rate of 10-20 m3/day, 70 kg body weight, 250-350 day exposure, 30 year exposure duration, etc.)

AMEC offers this screening level analysis of the predicted annual general population burden of nasal tumors (based on U.S. EPA dose-response modeling of the recent NTP rat bioassay results) to demonstrate that it is more likely that the tumorigenic response to high dose naphthalene exposure is unique to the rat. A Mode of Action analysis in accordance with current governmental guidelines would conclude that the Mode of Action in the rat is not plausible in humans, and naphthalene would be shown not to

pose a hazard to humans for nasal tumors. AMEC recommends that NTP consider this screening level analysis in performing such a Mode of Action analysis and not list naphthalene as "reasonably anticipated to be a human carcinogen." AMEC notes that the NTP Executive Committee Working Group for the Report on Carcinogens – RG2 voted four-to-four on listing or not listing.

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