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Provisional Peer-Reviewed Toxicity Values for

2-Naphthylamine
(CASRN 91-59-8)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
LOAEL	lowest-observed-adverse-effect level
$LOAEL_{ADJ}$	LOAEL adjusted to continuous exposure duration
$LOAEL_{HEC}$	LOAEL adjusted for dosimetric differences across species to a human
NOAEL	no-observed-adverse-effect level
$NOAEL_{ADJ}$	NOAEL adjusted to continuous exposure duration
$NOAEL_{HEC}$	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

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Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1) U.S. EPA's Integrated Risk Information System (IRIS).
2) Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. EPA's Superfund Program.
3) Other (peer-reviewed) toxicity values, including
   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in U.S. EPA's IRIS. PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and Resource Conservation and Recovery Act (RCRA) program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV document and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

There is no assessment of 2-naphthylamine (also known as β-naphthylamine and 2-aminonaphthalene) on IRIS (U.S. EPA, 2008). No reference toxicity values, standards, or criteria are listed for 2-naphthylamine on the HEAST (U.S. EPA, 1997), by the U.S. EPA (2006) Office of Drinking Water, or by the CalEPA (2002, 2005a,b). The Chemical Assessments and Related Activities (CARA) status reports (U.S. EPA, 1991, 1994) list a Health and Environmental Effects Profile (HEEP; the SRC [1986] draft was never finalized) and a cancer assessment (conducted on 9/05/1989; no specific details provided) for 2-naphthylamine. Neither the ATSDR (2008) nor the World Health Organization (WHO, 2008) have produced profiles for 2-naphthylamine.

The International Agency for Research on Cancer (IARC, 2008, 1974, 1987a,b) classifies 2-naphthylamine as a Group 1 carcinogen, with sufficient evidence of carcinogenicity in humans and animals. This classification is based on the observation of bladder cancer in humans exposed occupationally to 2-naphthylamine; bladder cancer in dogs, hamsters, monkeys, and rats; liver tumors in mice; and positive results in a lung adenoma bioassay in mice.

None of the agencies that regulate occupational exposure to hazardous chemicals list numerical standards for 2-naphthylamine because they all recognize it as a human carcinogen based on the observation of bladder cancer in exposed workers and follow-up studies with animals. The Occupational Safety and Health Administration (OSHA, 2008) has a standard for 2-naphthylamine and 12 other carcinogens (29 CFR 1910.1009; 29 CFR 1910.1003) that requires the use of engineering controls, work practices, and personal protective equipment, including the use of respirators, to eliminate contact with 2-naphthylamine. The National Institute for Occupational Safety and Health (NIOSH, 2005) lists 2-naphthylamine as a Potential Occupational Carcinogen (Appendix A) and cites OSHA's requirements for engineering controls, work practices, and personal protective equipment. The American Conference of Governmental Industrial Hygienists (ACGIH, 2001, 2007) lists 2-naphthylamine as an A1 (confirmed) human carcinogen and recommends avoiding exposure.

To identify toxicological information pertinent to the derivation of provisional toxicity values for 2-naphthylamine, literature searches were conducted in June 2007 using the following databases: MEDLINE (updated to June, 2008), TOXLINE (updated to June 2008), BIOSIS, TSCATS, CCRIS, DART/ETIC, GENETOX, HSDB, and Current Contents. A final search of the toxicological literature was conducted for the period from June 2008 through September 2009.

REVIEW OF PERTINENT DATA

Human Studies

There is an extensive database regarding human exposure to 2-naphthylamine. An excess of urinary bladder cancers among workers who used aromatic amines in the production of synthetic dyes was first recognized in the late 1800s by a German physician named Rehn (see Stern et al., 1985 for review). With the introduction of synthetic dye technology to other countries, increased numbers of cases of bladder cancer were reported, and by the 1930s, bladder cancer was widely recognized as an occupational hazard associated with this industry. In 1934, three cases of bladder cancer were reported to have occurred in workers exposed to 2-naphthylamine and/or benzidine at E.I. duPont de Nemours and Company's dye manufacturing facilities in the U.S.; by 1948, 139 workers at the duPont facility developed bladder cancer (Stern et al., 1985). The duPont de Nemours and Company ceased production and use of 2-naphthylamine in 1955 (Kaufmann, 1979; Castleman, 1979). Numerous other case reports of bladder cancer in workers exposed to 2-naphthylamine and other aromatic amines have been published and are reviewed elsewhere (Hueper, 1942; IARC, 1974, 1987a). Attempts to reproduce bladder cancer in laboratory animals were unsuccessful until Hueper et al. (1938) reported that exposure of dogs to commercial 2-naphthylamine by subcutaneous injection and dietary administration (later in the study) for approximately 2 years produced urinary bladder cancer that was similar to that seen in dye workers.

Based on English and Welsh death certificates obtained between 1921 and 1949 that mention bladder tumors, the occurrence of bladder tumors in the general population was more prevalent in men than in women (2.5 to 1), with mortality attributed to malignant tumors in 88% of the cases, and to benign tumors or papillomas[1] in 12% of the cases (Case et al., 1954). A similar trend was observed in dyestuff workers (reported below), with 95% of the case mortalities associated with cancerous tumors (predominantly transitional cell carcinomas) and the remaining cases associated with papillomas or benign tumors. Among the general population, most cases of bladder cancer occurred in older men, with only 14% of the adult male cases occurring before the age of 55 years.

Case et al. (1954) conducted the preeminent retrospective occupational cohort study of bladder cancer among workers exposed to dyestuff intermediates in the British chemical industry. The study was based on cases reported by firms in the British Chemical Manufacturing Association (21 firms participated), hospital records, and death records. The population at risk was considered to be all workers who were known to have any contact with aniline, benzidine,

[1]The classification of bladder tumors is complex and confusing. Papillomas can be classified as either malignant or benign, but in humans, truly benign papilloma is rare, accounting for less than 1% of papillary tumors of the bladder in humans. (Robbins et al., 1984).

1-naphthylamine, or 2-naphthylamine from 1920 onward (4622 men). All death certificates that mentioned bladder tumors for men in England or Wales between the years 1921 and 1949 were obtained and examined by the study investigators. Case et al. (1954) found that among 209 men employed only in the manufacture of 2-naphthylamine for >6 months between 1920 and 1950 in England and Wales, 55 (26%) developed bladder cancer and 27 (13%) died from bladder cancer by the time the study was conducted. Only 0.3 deaths from bladder cancer were expected for this cohort, based on the incidence of deaths from bladder cancer in the general male population of England and Wales between 1921 and 1949. Only 20% of the cases identified survived beyond 10 years following diagnosis. The average tumor induction time for 2-naphthylamine was estimated to be 16 years (range: less than 2 years to more than 45 years). The study authors concluded that the average induction time was not appreciably influenced by the severity or duration of exposure, but the percentage of men exposed to 2-naphthylamine who developed bladder tumors was correlated with the date of entry into the industry. Although this study did not estimate exposure levels or adjust for possible confounding factors such as age or smoking history, Boyko et al. (1985) reported that its impact was sufficient to lead to legislation banning 2-naphthylamine in the United Kingdom.

Several other retrospective cohort studies found evidence for elevated risks of bladder cancer in workers exposed to 2-naphthylamine and other aromatic amines, but none obtained adequate information on individual exposure levels. Brief reviews of some of these studies follow.

Goldwater et al. (1965) examined medical and employment records for men employed in a coal-tar dye factory between 1912 and 1962. Among 48 men who were exposed only to 2-naphthylamine, 12 (25%) had bladder cancer. A control or reference group was not included in this study.

Mancuso and El-Attar (1967) established a cohort of workers employed in 1938−1939 by a company manufacturing 2-naphthylamine and benzidine. By 1965, 79 deaths (37%) had occurred among 216 workers exposed to 2-naphthylamine and/or benzidine compared with 36 deaths (27%) among 134 nonexposed workers. Fourteen of the deaths (17%) in the exposed group were associated with bladder or urinary tract cancer, while no bladder or urinary tract cancer cases were reported for the deaths in the nonexposed group.

Within another cohort of 1385 workers employed between 1940 and 1972 in a U.S. dye plant that manufactured and used 2-naphthylamine, benzidine, and other aromatic amines (Stern et al., 1985; Schulte et al., 1985, 1986), five cases (4%) of bladder cancer were found by 1983 among 118 exposed workers. Exposed workers were defined as those with greater than "1 year of employment or any employment in two high-exposure departments in the plant." In contrast, eight cases (1%) of bladder cancer occurred among 1267 nonexposed workers (Schulte et al., 1986). An odds ratio of 6.96 (with 95% confidence interval limits of 3.9 and 12.4) was calculated, indicating an approximate 7-fold increased risk of bladder cancer in the exposed group.

Bladder tumors were identified in workers employed in the UK rubber industry who were inadvertently exposed to 2-naphthylamine (0.25%) that was a contaminant in the antioxidants used in manufacturing (Veys, 2004). Bladder tumors were found in 58 (2.8%) of 2090 men employed continuously for at least 1 year between 1946 and 1949 when the contaminant was

present, compared with 33.9 tumors, which would be expected based on national standardized registration rates (SRR = 171; CI = 130−221). Bladder tumors were identified in 39 (1.3%) of 3038 men employed continuously for at least 1 year after 2-naphthylamine had been removed from production (January, 1950 forward) in comparison with 38.3 that were expected on the basis of national standardized registration rates, suggesting that removal of the 2-naphthylamine contaminant resulted in a drop in cancer rates to the national level. There was no significant (95% confidence intervals [CI] were reported) mortality from bladder cancer among men at risk (i.e., 16 deaths among the 2090 men exposed to 2-naphthylamine between 1946 and 1949, compared with 16.5 expected), nor among any other groupings considered by the study authors. The lack of significant (95% CI were reported) mortality in the at-risk population was attributed to the fact that 12/58 (21%) of the cases of bladder cancer relevant to the study were still alive at study termination (December 1995). This observation is consistent with the conclusion by Case et al. (1954) that mortality from bladder cancer is not a good indicator of cancer risk following exposure to 2-naphthylamine. No measures of exposure were possible in this study, and smoking was not taken into account.

Bladder cancer accounted for 49/271 (18%) deaths that occurred by 1989 among a group of 664 workers employed for at least 1 year between 1922 and 1970 in an Italian dye manufacturing plant that used aromatic amines, including 2-naphthylamine (DeCarli et al., 1985; Piolatto et al., 1991). Based on national mortality rates, only 1.6 deaths from bladder cancer were expected. Using a statistical analysis of the data described by Brown and Chu (1983), DeCarli et al. (1985) noted no marked effect of age at first exposure on absolute excess risk of bladder cancer and a marked negative effect of age at first exposure on relative risk. Absolute excess risk was found to increase sharply during exposure and to continue to rise, although less sharply, after exposure had ceased. Relative risk decreased after cessation of exposure. These findings were interpreted by the authors, in the context of the multistage theory of carcinogenesis, to be consistent with 2-naphthylamine having both early stage (i.e., tumor-initiating) and late stage (i.e., tumor-promoting) effects. However, as noted by Case et al. (1954) and more recently by Veys (2004), mortality is not the best indicator of bladder cancer risk following exposure to 2-naphthylamine.

The incidences of malignant cancer and mortality were evaluated among 4581 workers employed at an aniline dye facility in Moscow from January 1975 and followed through December 31, 1989 (Bulbulyan et al., 1995). This study did not obtain useful estimates of exposure and did not control for smoking but is the only study that evaluates a sizable female population. The facility produced 2-naphthylamine from 1930 to 1951, with a 5-year gap in production between 1941 and 1945 due to World War II. Benzidine was produced between 1930 and 1988, with a 6-year gap from 1941−1947 due to the war. 2-Naphthylamine concentrations in air and on worker skin were roughly estimated from industrial hygiene samples but are not sufficient to draw meaningful conclusions about individual exposure. For example, in 1939−1940, of the 26 air samples that were collected, 12 (46%) had 2-naphthylamine concentrations greater than 0.003 mg/L; 5 (19%) were between 0.001 and 0.003; and 9 (35%) had less than 0.001 mg/L. In 1940, the weight of 2-naphthylamine recovered on a skin wipe taken after a shower was 6−37.5 mg. Factory wall wipes taken in 1948 indicated the presence of 2-naphthylamine at a concentration of 60.0−115 mg/m^3 on wall surfaces. Benzidine concentrations were not reported.

Cohort eligibility in this study (Bulbulyan et al., 1995) was based on job description and tenure. Workers with jobs that entailed exposure to 2-naphthylamine or benzidine for at least 1 month or who were employed in any capacity at the facility for at least 2 years were enrolled in the study. The cohort was divided by job description into five mutually exclusive categories based on employee records: (1) 2-naphthylamine production; (2) benzidine production; (3) exposure to other chemicals only; (4) maintenance jobs involving exposure to other chemicals; and (5) administrative/clerical jobs. Cohort statistics were as follows: 53% men; 47% women; 514 (21%) men and 287 (13%) women were exposed to 2-naphthylamine or benzidine; 170 (7%) men and 119 (5%) women were exposed to 2-naphthylamine or benzidine for at least 20 years; mean age of entry into the cohort was 49.3 years; and the mean age of cancer diagnosis was 66.4 years. Data on malignant cancer and mortality were obtained from cancer registries. The expected disease and mortality rates were calculated separately for men and women and were based on age, gender, and time-specific incidence and mortality rates for the general population of Moscow. Standardized mortality and incidence ratios (SMR and SIR, respectively) and 95% confidence intervals (CI) for each cancer were calculated based on the incidence of observed versus expected values.

Compared to the expected cancer mortality, male cohorts had greater mortality from all cancers (SMR = 125; CI = 110−142), greater mortality from bladder cancer (SMR = 279; CI = 192−391), and greater incidence of all cancers combined (SIR = 142; CI = 125−160). Also, the male cohorts had greater incidences of cancers of the esophagus (SIR = 203; CI = 108−347), respiratory tract (SIR = 154; CI = 120−194), and bladder (SIR = 394; CI = 268−559) than was expected on the basis of the general population of Moscow (Bulbulyan et al., 1995). Female cohorts had increased mortality from esophageal cancer (SMR = 313; CI = 124−664) and bladder cancer (SMR = 311; CI = 149−571), and increased incidences of total malignant cancers (SIR = 124; CI = 106−144), esophageal cancer (SIR = 348; CI = 140−719), and bladder cancer (SIR = 861; CI = 458−8002).

When job classification was taken into account, the relative risk for combined cancer was greatest for workers exposed to benzidine or 2-naphthylamine but was also significantly (95% CI were reported) elevated among workers exposed only to chemicals other than benzidine or 2-naphthylamine and maintenance workers. Clerical/administrative workers had the expected numbers and types of cancers. The observed incidences of cancer increased with decreasing age at diagnosis and decreasing age hired. The incidence of bladder cancer increased with duration of employment and age at first hire and was lower, though still elevated, in workers hired after 1951, when production of 2-naphthylamine had ceased. The incidence of bladder cancer was highest among workers exposed to either 2-naphylamine or benzidine (men: 19 observed, 1.76 expected, SIR = 1082; women: 5 observed, 0.24 expected, SIR = 2097) but was also significantly (95% CI were reported) increased among workers exposed to chemicals other than benzidine or 2-naphthylamine (11 observed, 3.54 expected, SIR = 311; women: 7 observed, 0.79 expected, SIR = 886). The study authors hypothesized that the increased incidences of stomach, esophageal, and lung cancers observed in their study did not increase with total years worked, age first hired, or year first hired and, as such, were likely associated with causal factors outside of the workplace (e.g., smoking, diet, etc.).

A cohort of 442 dyestuff workers (437 men, 5 women) employed from 1935 to 1988 at a single factory in Japan was studied through December of 1992 for early detection and treatment of urothelial cancer (Naito et al., 1995). Only results for males were discussed in the study. No industrial hygiene data were available to evaluate exposure. Workers in the cohort had been exposed to one or more aromatic amines, including benzidine, 2-naphthylamine, 1-naphthylamine, and dianisidine for an average time of 39.4 years since first exposure. Among these workers, 95 (21%) were exposed to 2-naphthylamine alone (median age at hire = 25 [17−48] years, median calendar year at hire = 1949 [1935−1958], median duration of exposure = 48 months [3−166]). Urinary examinations were conducted on workers every 3 months. Abnormal screening results were followed with subsequent tests. Only cases with histologically confirmed carcinomas were evaluated in this study. Mortality and incidence data were compared against statistics for the general population of Japan. The results were then segregated into groups that were directly involved in the manufacture of benzidine and 2-naphthylamine versus workers who used the chemicals as ingredients in the manufacture of industrial dyes. The results show that there was significantly (95% CI were reported) increased mortality from bladder carcinoma among male workers engaged in benzidine manufacture (SMR = 63.6), benzidine use (SMR = 27), and 2-naphthylamine manufacture (SMR = 48.4), but not among male workers who used 2-naphthylamine (SMR = 1.0) or 1-naphthylamine. The study authors estimated the crude incidence rate per 1000 person-years of bladder carcinoma in male workers at 8.7 for benzidine manufacture, 2.9 for benzidine use, 7.7 for 2-naphthylamine manufacture, and 1.0 for 2-naphthylamine use. The adjusted rate of bladder carcinoma increased with duration of exposure regardless of the class or type of exposure. No discussion about controlling for smoking or other confounding factors was presented in the study narrative.

The Drake Health Registry Study (DHRS) is an ongoing bladder cancer screening program that exists to assist employees who were exposed to 2-naphthylamine while employed at the Drake Chemical company from 1962 to 1981 (Marsh and Cassidy, 2003). A total of 407 employees worked at the facility. As of June 30, 2002, 277 had participated in at least one screening. Six cases of malignant cancer were detected prior to implementation of the screening program (three from death certificates and three through diagnoses by personal physicians), and an additional three were identified through a screening program, along with other bladder conditions, as follows. Of the 51 people eligible for diagnostic evaluation due to positive screening criteria (determined from urinalysis, papanicolaou (PAP) smears, and quantitative fluorescence image analysis), 40 completed subsequent evaluations, and the following cases were observed: one carcinoma in situ; two transitional cell papillomas; two transitional cell carcinomas developed from 14 cases of dysplasia; and 26 cases of bladder abnormalities, including chronic inflammation, chronic cystitis, atypical changes, atypia, hyperplasia, or papillary clusters. Of the six cases identified prior to implementation of the screening program, there was no consistency with regard to age, year of death (two were still alive at the time of study publication), time of hire, or duration of employment.

Clinical experiences with a cytostatic drug, chlornaphazine [*N*,*N*-bis(2-chloroethyl)-2-naphthylamine], provide some indirect support for the suggestion that exposure to fairly low doses of 2-naphthylamine can cause bladder tumors in humans. Chlornaphazine was used in the 1950s in Denmark and Italy for the treatment of *polycythemia vera* and Hodgkin's disease (Thiede et al., 1964; Thiede and Christensen, 1969; Schmähl et al., 1977). Prescribed daily dosages ranged from approximately 100−400 mg (1.4−5.7 mg/kg-day) (Thiede et al., 1964; Thiede and Christensen, 1969; Schmähl et al., 1977). Use of the drug was discontinued by 1963

in Denmark after cases of bladder cancer were reported among treated patients. Hydrolysis of the two chloroethyl groups from chlornaphazine is expected to occur in vivo, leading to the formation of 2-naphthylamine (Schmähl et al., 1977). Under the assumption of 100% hydrolysis of chlornaphazine, daily doses of 1.4−5.7 mg chlornaphazine/kg-day would correspond to 0.7−3.0 mg 2-naphthylamine/kg-day.

Schmähl et al. (1977) compiled 15 examples of bladder cancer in patients treated with chlornaphazine. The cases included seven men and eight women (with an average age of 57 years) who received daily doses of chlornaphazine ranging from 100−400 mg/day for periods ranging from 9 months to 10 years (average duration of treatment was 6 years). Estimated latency periods for bladder tumor development ranged from 2.5 to 10 years (with an average age of 6 years). Thiede and Christensen (1969) reported that among 61 polycythemic patients treated with chlornaphazine for various periods of time between 1951 and 1962, 10 (16%) developed bladder cancer and another 5 (8%) displayed atypical cells in their urine. It is possible that confounding factors may have contributed to the observed carcinogenic effects in these patients (e.g., smoking habits, disease predisposition, other treatments administered to the patients, and differential pharmacokinetic behavior between chlornaphazine and 2-naphthylamine). However, the relatively short exposure duration (an average of 6 years) and latency period (also an average of 6 years) for development of cancer suggest that chlornaphazine may be a potent carcinogenic agent.

A meaningful interpretation of the relationship between chlornaphazine administration and 2-naphthylamine-induced bladder cancer is complicated by the fact that chlornaphazine itself is one of a class of compounds known as nitrogen mustards. These chemicals, which contain the *N*,*N*-bis(2-chloroethyl)-moiety, can alkylate DNA and produce DNA cross-links. Bladder cancer has been observed in patients treated with at least one other nitrogen mustard (cyclophosphamide), which does not contain the 2-naphthylamine substituent (Schmähl et al., 1977). This suggests that, for cyclophosphamide, a sufficient alkylating agent reaches the bladder to induce cancer. No data are available from humans to estimate the extent to which chlornaphazine is excreted unchanged in the urine (i.e., reaches the bladder tissue), or conversely, is dealkylated to yield 2-naphthylamine. Dealkylated metabolites have been identified as excretion products in rats injected with chlornaphazine (Boyland and Manson, 1963a) and would be predicted to occur after oral administration in humans. However, lacking more specific data, the relative contributions to the induction of human bladder cancer by chlornaphazine itself, or its putative metabolite 2-naphthylamine, cannot be determined. Therefore, the human data for chlornaphazine cannot be used to estimate risk from exposure to 2-naphthylamine.

Human study data, as demonstrated in case reports and retrospective cohort studies, suggest a link between exposure to 2-naphthylamine and the occurrence of bladder cancer in workers exposed while manufacturing or using the compound. The available studies of occupational exposure, however, do not provide sufficient information concerning levels of exposure to 2-naphthylamine that can be used to estimate cancer risk as a function of exposure level. Clinical experiences with chlornaphazine, a cytostatic drug expected to be biotransformed to 2-naphthylamine, likewise, do not provide sufficient data to support a quantitative estimate of risk.

Animal Studies

Animal studies also suggest a link between exposure to 2-naphthylamine and a carcinogenic response. The existing animal studies for 2-naphthylamine are focused on this carcinogenic response and do not provide the full suite of toxicological endpoints normally evaluated in general toxicity studies. Observed carcinogenic responses to orally administered 2-naphthylamine in animals include bladder tumors in dogs (Hueper et al., 1938 [combined subcutaneous and oral exposure]; Bonser et al., 1956; Deichmann et al., 1965; Conzelman and Moulton, 1972; Radomski et al., 1978; Purchase et al., 1981), bladder tumors in rhesus monkeys (Conzelman et al., 1969), liver tumors in mice (Bonser et al., 1952; Yoshida et al., 1979; Osanai, 1976), bladder tumors in rats (Hicks and Chowaniec, 1977; Hicks et al., 1982), and bladder tumors in hamsters (Saffiotti et al., 1967). Parenteral administration of 2-naphthylamine produced pulmonary adenomas (Theiss et al., 1981; Walters et al., 1967) and liver tumors (Bonser et al., 1956) in mice. Studies examining carcinogenic responses in animals following inhalation or dermal exposure to 2-naphthylamine were not identified.

Only animal studies that provided sufficient and appropriate dose-response information for the estimation of lifetime oral cancer risk from 2-naphthylamine in humans are considered here. Studies meeting these criteria are restricted to a dog study by Conzelman and Moulton (1972), a monkey study by Conzelman et al. (1969), and a hamster study by Saffiotti et al. (1967). These studies, described in further detail below, were judged to be appropriate because they included control groups and groups treated with multiple oral doses. In addition, the carcinogenic response in dogs, monkeys, and hamsters is similar to the response in humans exposed to 2-naphthylamine (i.e., bladder cancer). Although details in the Saffiotti et al. (1967) study were limited, the study is considered here because the animals were exposed for their lifespan. The dog and monkey studies did not provide lifetime exposure (or observation) but were otherwise adequately designed, conducted, and reported. Mice appear to develop liver tumors, not bladder tumors, in response to oral 2-naphthylamine. Due to the absence of liver cancer in association with 2-naphthylamine exposure in human cohort studies, mouse studies are not included in this evaluation. Rat studies are not considered because rats appear to be less sensitive than dogs and monkeys to the carcinogenicity of 2-naphthylamine, apparently due to differences in urine pH, frequency of micturition, and resorption (Young and Kadlubar, 1982).

Conzelman et al. (1969) gave gelatin capsules containing 2-naphthylamine at various doses ranging from 6.25−400 mg/kg, 6 days/week, for up to 60 months, to 16 female and 8 male rhesus monkeys. The test material (Aldrich Chemical Co.) was purified by gradient sublimation before incorporation into gelatin capsules, but percentage purity was not reported. A group of three female monkeys served as controls. Complete necropsy was performed after 60 months or when the monkeys appeared moribund. The urogenital tracts were examined histologically. Table 1 describes the dosing schedule and findings concerning bladder tumors for the individual animals in this study. A total of seven treated monkeys appeared moribund before the end of the 60-month dosing period; 6/7 (86%) of these monkeys were found to have bladder tumors. Moribundity associated with the occurrence of bladder cancer was observed as early as 33 months after commencement of treatment. Overall, bladder carcinomas (described as either transitional cell carcinomas, carcinoma in situ, or papillary carcinomas) were identified in 9/24 (38%) treated monkeys. Additionally, two treated monkeys had bladder adenomas, and one treated monkey had a benign bladder papilloma (see Table 1). No bladder tumors were found in the three controls.

Table 1. Dosing Schedule and Bladder Tumor Occurrence in Rhesus Monkeys Orally Exposed to 2-Naphthylamine in Gelatin Capsules[a]

Animal Number	Sex	Dose and Duration (mg/kg, 6 days/week)	Microscopic Findings in Bladder
1129[b], 1422[c], 1683[b]	F	0 mg/kg for 60 months	no tumors
1425[c]	F	6.25 mg/kg for 6 months, 12.5 mg/kg for 54 months	papillary carcinoma
1426[c]	F	12.5 mg/kg for 60 months	no tumors
620[b]	M	12.5 mg/kg for 6 months, 25.0 mg/kg for 54 months	no tumors
1136[b]	F	12.5 mg/kg for 6 months, 25.0 mg/kg for 54 months	no tumors
1418, 1289[b]	F	25.0 mg/kg for 60 months	no tumors
671[b], 1421	F	25.0 mg/kg for 6 months, 50.0 mg/kg for 54 months	no tumors
1183[b], 1279[d]	F	50.0 mg/kg for 60 months	benign papilloma (1183); papillary carcinoma (1279)
1264[b,d]	F	100 mg/kg for 55 months	no tumors
2345	M	200 mg/kg for 33 months	transitional cell carcinoma
1772[b]	M	200 mg/kg for 18 months, 100 mg/kg for 42 months	no tumors
2338	F	200 mg/kg for 42 months, 100 mg/kg for 18 months	papillary adenoma
2333	M	200 mg/kg for 42 months, 100 mg/kg for 4 months	transitional cell carcinoma, invasive
1798[b], 1803[b]	M	200 mg/kg for 40 months, 100 mg/kg for 20 months	no tumors (1798); carcinoma in situ (1803)
1770[b]	F	400 mg/kg for 4 months, 200 mg/kg for 32 months, 100 mg/kg for 24 months	no tumors
1792[b]	F	200 mg/kg for 34 months, 100 mg/kg for 12 months	papillary adenoma
2377[b]	F	200 mg/kg for 33 months	carcinoma in situ
2616[b]	F	200 mg/kg for 32 months, 100 mg/kg for 10 months	transitional cell carcinoma, invasive
1877[b]	M	200 mg/kg for 24 months, 100 mg/kg for 12 months	carcinoma in situ
1894[b,d]	M	400 mg/kg for 12 months, 200 mg/kg for 24 months, 100 mg/kg for 24 months	no tumors

Table 1. Dosing Schedule and Bladder Tumor Occurrence in Rhesus Monkeys Orally Exposed to 2-Naphthylamine in Gelatin Capsules[a]

Animal Number	Sex	Dose and Duration (mg/kg, 6 days/week)	Microscopic Findings in Bladder
2321[b]	F	200 mg/kg for 33 months, 100 mg/kg for 27 months	transitional cell carcinoma, invasive

[a]Conzelman et al. (1969).
[b]These monkeys were infected with *Plasmodium cynomolgi* and treated with chloroquine at least 12 weeks before exposure to 2-naphthylamine.
[c]These monkeys were given single doses of *N*-(3-bromopropionamidomethyl)-acrylamide before assignment to this study.
[d]These monkeys were splenectomized during the 12-week period before 2-naphthylamine exposure.

Conzelman and Moulton (1972) administered 2-naphthylamine in gelatin capsules at doses of 0, 6.25, 12.5, 25.0, or 50 mg/kg, 6 days/week for 2−26 months, to groups of 4−10 dogs (both male and female). The test material (Aldrich Chemical Co.) was purified by gradient sublimation before incorporation into gelatin capsules, but the purity was not reported. Necropsies were performed immediately after treatment or at various periods (1−5 months) after treatment for a number of dogs (see Table 2). Urinary tracts were grossly and histologically examined for tumors. Early mortalities did not occur in control or treated dogs. Table 2 describes the dosing schedules and the histological findings for the individual dogs. Bladder tumors described as late squamous metaplasia with invasion into the mucosa or submucosa, invasive transitional carcinoma, invasive squamous carcinoma, or papillary carcinoma were found at incidences of 0/4, 4/9, 4/10, 8/10, and 4/5 for the 0, 6.25, 12.5, 25.0, and 50 mg/kg groups, respectively (see Table 2). Benign bladder papillomas without invasive metaplasia or carcinomas were observed in an additional three dogs in the 12.5-mg/kg group and one dog in the 50-mg/kg group (see Table 2).

Saffiotti et al. (1967) provided groups of 30 male and 30 female Syrian golden hamsters with diets containing 0, 0.1, or 1.0% by weight (w/w%) 2-naphthylamine (purity not specified) starting at 8 weeks of age and continuing until spontaneous death occurred. The authors estimated that animals received doses of 0, 60, or 600 mg 2-naphthylamine per week, based on average historical food consumption data for their hamster colony. Body weight and survival data were recorded but were not given in the only available report of this study. The authors stated that all animals were autopsied except for a few that were lost due to postmortem decomposition or cannibalism but did not provide any further details. The authors reported that all tumors and bladders and most livers, kidneys, and adrenals were histologically examined postmortem, but it is unclear whether this included the decomposed or cannibalized cases. No bladder tumors were found in the control group or in several hundred historical control hamsters from the authors' laboratory. No toxicologically significant changes were observed in the group fed the 0.1% diet, with the exception of the finding of one female at 97 weeks with papillomatous hyperplasia of the bladder. Bladder tumors were observed in the 1.0% group. Study authors reported that "Ten out of 23 (43%) effective males and 8 out of 16 (50%) effective females had bladder tumors, almost all typical transitional cell carcinomas." The meaning of "effective" animals is unknown but is assumed to be the number of animals examined. The first tumors were found in a male that died at 45 weeks and in a female that died at 49 weeks. Further details concerning the findings of this study were not provided. The authors stated that "more detailed description of the experimental details and detailed pathological findings" were to be reported elsewhere, but a more detailed account was not located in the databases or literature examined for this report.

Table 2. Dosing Schedule and Bladder Tumor Occurrence in Beagle Dogs Orally Treated with 2-Naphthylamine in Gelatin Capsules[a]

Animal Number and Sex	Dose and Duration (mg/kg, 6 days/week)[b]	Microscopic Findings in Bladder
1362 (M), 1501 (F), 1335 (M), 1594 (F)	0 mg/kg for 6 (1362), 9 (1501), 12 (1335) or 24 (1594) months	No preneoplastic lesions or tumors found in controls.
1306 (F), 1547 (M), 1162 (F), 1577 (F), 1565 (M), 1573 (M), 1566 (M), 1635 (M), 1623 (M)	6.25 mg/kg for 6 (1306), 9 (1547), 12 (1162), 15 (1577), 18 (1565), 21 (1573), 24 (1566, 1635[c]) or 25 (1623[c]) months	No lesions: 1573. Preneoplastic lesions but no tumors: 1306, 1547, 1162, 1577. Late squamous metaplasia with invasion into mucosa and submucosa: 1565, 1635. Invasive transitional carcinoma: 1566, 1623.
1550 (M), 1519 (F), 1381 (M), 1567 (M), 1574 (M), 1563 (F), 1655 (F), 1658 (M), 1608 (F), 1621 (F)	12.5 mg/kg for 6 (1550), 9 (1519), 12 (1381), 15 (1567), 18 (1574), 21 (1563), 22 (1655), 24 (1658, 1608[d]) or 26 (1621[c]) months.	Preneoplastic lesions but no tumors: 1550, 1519, 1381. Early papilloma, benign: 1574, 1563, 1655. Late squamous metaplasia with invasion into mucosa and submucosa: 1567, 1658. Invasive transitional carcinoma:1608, 1622.
1502 (F), 1548 (M), 1417 (F), 1569 (M), 1578 (F), 1571 (M), 1671 (M), 1575 (M), 1636 (M), 1624 (M)	25 mg/kg for 2 (1502), 9 (1548), 12 (1417), 15 (1569), 18 (1578), 21 (1571), 22 (1671c), 24 (1575, 1636[c]) or 25 (1624[d]) months.	No lesions: 1502. Preneoplastic lesions: 1548. Late squamous metaplasia with invasion into mucosa and submucosa: 1578. Papillary carcinoma with invasion into mucosa or submucosa: 1575, 1624. Invasive transitional carcinoma: 1636, 1571, 1671, 1569, 1417.
1677 (M), 1698 (F), 1697 (F), 1689 (M), 1609 (F)	50 mg/kg for 9 (1677), 18 (1698[d], 1697[d], 1689 [c]) or 21 (1609[d]) months.	Early papilloma, benign: 1677. Invasive transitional carcinoma: 1698, 1697, 1689, 1609.

[a]Conzelman and Moulton (1972).
[b]All dogs were necropsied immediately following the dosing period with the following exceptions:
[c]These dogs were necropsied 1−2 months after termination of the dosing period.
[d]These dogs were necropsied 3−5 months after termination of the dosing period.

Other Studies

2-Naphthylamine has a wide range of genotoxic activities. 2-Naphthylamine-induced reverse mutations in *Salmonella typhimurium* in the presence of mammalian metabolic systems (Mayer, 1982; Connor et al., 1983; Langenbach et al., 1983), mutations in growing, but not resting, cells of *Saccharomyces cerevisiae* and *Neurospora crassa* (Ong and deSerres, 1972; Callen and Philpot, 1977; Mayer, 1971, 1973), and unscheduled DNA synthesis in rat and hamster hepatocytes (Althaus et al., 1982; Kornbrust and Barfknecht, 1984). 2-Naphthylamine induced sister chromatid exchanges, chromosomal aberrations, and morphological transformations in mammalian cell cultures; it caused mutations in a mouse lymphoma cell assay but not in a Chinese hamster cell assay (deSerres and Ashby, 1981). Intraperitoneal administration of 2-naphthylamine to pregnant mice produced coat-color mutations in their offspring (Chauhan et al., 1983).

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 2-NAPHTHYLAMINE

No data on the noncarcinogenic effects of 2-naphthylamine by oral exposure that could be used to derive a subchronic or chronic RfD were located. In general, the animal studies on 2-naphthylamine are focused on a carcinogenic response and do not provide the full suite of toxicological endpoints normally evaluated in general toxicity studies.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 2-NAPHTHYLAMINE

No data on the noncarcinogenic effects of 2-naphthylamine by inhalation exposure that could be used to derive a subchronic or chronic RfC were located. In general, the animal studies on 2-naphthylamine are focused on a carcinogenic response and do not provide the full suite of toxicological endpoints normally evaluated in general toxicity studies.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 2-NAPHTHYLAMINE

Weight-of-Evidence Descriptor

According to criteria set forth by the U.S. EPA (2005) *Guidelines for Carcinogen Risk Assessment*, the weight-of-evidence indicates that 2-naphthylamine is "*carcinogenic to humans*." This classification is based on

- strong evidence of an association between bladder cancer in humans and occupational exposure to 2-naphthylamine (e.g., Case et al., 1954; Naito et al., 1995; Veys, 2004; Marsh and Cassidy, 2003; Bulbulyan et al., 1995; IARC, 1974, 1987a,b);
- quantitative and qualitative evidence of 2-naphthyamine-induced bladder cancer (i.e. transitional cell carcinoma) has been demonstrated in dogs (Hueper et al., 1938; Conzelman and Moulton, 1972), hamsters (Saffiotti et al., 1967), and monkeys (Conzelman et al., 1969) that is consistent with observations in humans (Marsh and Cassidy; 2003);
- strong evidence of a mutagenic mode of action (discussed in detail in the next section) that is supported by positive genotoxicity assays in multiple species (Mayer, 1982; Connor et al., 1983; Langenbach et al., 1983; Althaus et al., 1982; Kornbrust and Barfknecht, 1984; deSerres and Ashby, 1981; Chauhan et al., 1983), identification of reactive metabolites that covalently bind DNA and are present in the bladder following 2-naphthylamine exposure (Boyland and Manson, 1963b; Kadlubar et al., 1981a,b,c; Beland and Kadlubar, 1985, 1986; Radomski, 1979; Miller and Miller, 1981; Kadlubar et al., 1977; Yamazoe et al., 1985; Boyd and Eling, 1987; Flammang et al., 1989), demonstration that DNA arylamine adducts formed from reactive metabolites can cause mutation (Beland et al., 1983);
- strong evidence of DNA and tumor biomarkers in humans preceding and accompanying positive diagnosis of bladder cancer (Marsh and Cassidy, 2003); and a

pattern of early tumor development following short-term exposure (less than 1 year), with a proliferative sequence of hyperplasia, dysplasia, carcinoma in situ, and more invasive malignancies (e.g., transitional cell carcinoma, papillary carcinoma) that has been identified in both humans and animals (Robbins et al., 1984).

Mode-of-Action Discussion

A discussion of the carcinogenic mode of action (MOA) is not conducted when no cancer potency values are derived because of insufficient data.

Quantitative Estimates of Carcinogenic Risk

The available human studies regarding cancer in workers exposed occupationally to 2-naphthylamine demonstrate a strong association between exposure and the development of bladder cancer but lack quantitative estimate of exposure that can be used in dose-response modeling.

Oral Exposure

The animal studies conducted by Conzelman and Moulton (1972) with dogs, Conzelman et al. (1969) with monkeys, and Saffiotti et al. (1967) with hamsters can be used to derive quantitative oral risks for the development of bladder tumors. None of the studies is ideal in terms of design and duration of exposure.

Strengths of the monkey study (Conzelman et al., 1969) include the use of several doses and consideration that primates may reflect human toxicity better than other test animals. Weaknesses of the study include the small number of animals and the short duration of the study (i.e., 60 months, which is approximately 1/7 of the lifespan of the rhesus monkey). The dog study (Conzelman and Moulton, 1972), likewise, used several doses and an appropriate animal species but had small numbers of animals and was designed to study the sequential development of bladder tumors after less-than-lifetime exposures. Within each dose group, 1−2 dogs were scheduled for sacrifice at 2−4 month intervals up to a total of 26 months (see Table 2). Use of the dog and monkey data creates uncertainty due to termination of the studies well in advance of the natural lifespan of the test animals. As a consequence of the early termination of the Conzelman and Moulton (1972) and the Conzelman et al. (1969) studies, their use in oral cancer potency derivation would likely underestimate the potency. The hamster study (Saffiotti et al., 1967) used a larger number of animals per dose (60) and was designed as a lifetime study. However, details of the study, including the precise number of animals actually examined in each dose group, and the specific types of tumors identified are inadequately reported. For the reasons noted, it is inappropriate to derive provisional toxicity values for a 2-napthylamine OSF.

Inhalation Exposure

Derivation of an inhalation unit risk for 2-naphthylamine is not recommended. Although occupationally exposed workers who developed bladder cancer are expected to have been exposed by both the dermal and inhalation routes, no quantitative information regarding exposure levels was located in the available studies. No studies were located that looked for the occurrence of cancer in animals following inhalation exposure to 2-naphthylamine. An extrapolation from oral data to the inhalation exposure scenario is not recommended, because no

pharmacokinetic data were located that would support an estimation of air concentrations that would deliver doses (to the whole body or to the target organ) similar to those from oral exposure.

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