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Provisional Peer Reviewed Toxicity Values for

2,6-Toluenediamine
(CASRN 823-40-5)

Superfund Health Risk Technical Support Center
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U.S. Environmental Protection Agency
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Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
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
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level

MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
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**
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	**Provisional Peer Reviewed Toxicity Value**
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
μg	microgram
μmol	micromoles
VOC	volatile organic compound

**PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR
2,6-TOLUENEDIAMINE (CASRN 823-40-5)**

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) 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. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in 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 EPA's Integrated Risk Information System (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 EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions (or the EPA HQ Superfund Program) sometimes request that a frequently used PPRTV be reassessed. 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 manuscripts 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 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 manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other 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 EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

The HEAST (U.S. EPA, 1997) lists subchronic and chronic RfD values of 2E-1 mg/kg-day for 2,6-toluenediamine, based on a NOAEL of 16 mg/kg-day in a chronic feeding study in rats (NCI, 1980). The source document for this assessment was a Health and Environmental Effects Profile (HEEP) for Selected Toluenediamine (U.S. EPA, 1984). No RfC or cancer assessment for 2,6-toluenediamine is available in the HEAST (U.S. EPA, 1997) or HEEP (U.S. EPA, 1984). 2,6-Toluenediamine is not listed on IRIS (U.S. EPA, 2005a) or the Drinking Water Standards and Health Advisories list (U.S. EPA, 2002). The HEEP is the only relevant document included in the CARA list (U.S. EPA, 1991, 1994). ATSDR (2003) has not published a Toxicological Profile that includes 2,6-toluenediamine. An Environmental Health Criteria Document for Diaminotoluenes (WHO, 1987) is available, but does not include derivation of quantitative risk values. ACGIH (2003), NIOSH (2003), and OSHA (2003) have not developed

occupational exposure limits for 2,6-toluenediamine. IARC (2003) has not classified 2,6-toluenediamine as to possible human carcinogenicity. NCI (1980) conducted a chronic carcinogenicity bioassay of 2,6-toluenediamine in rats and mice, which served as the basis for the RfD values in the HEEP (U.S. EPA, 1984) and HEAST (U.S. EPA, 1997). Literature searches were conducted from 1983 through December, 2004 for studies relevant to the derivation of provisional toxicity values for 2,6-toluenediamine. Databases searched included: TOXLINE (supplemented with BIOSIS and NTIS updates), MEDLINE, CANCERLIT, TSCATS, RTECS, CCRIS, DART, EMIC/EMICBACK, HSDB, and GENETOX.

2,6-Toluenediamine is one of six diaminotoluene isomers that are components of crude or commercial grade mixtures used as intermediates in the production of dyes and pigments for commercial products (WHO, 1987). The crude mixture contains all six isomeric forms, while the two commercial mixtures are composed primarily of two isomers each. One commercial mixture, meta-diaminotoluene, contains the 2,4- and 2,6- isomers (80:20 or 65:35), and the other, ortho-diaminotoluene, contains the 2,3- and 3,4- isomers (40:60).

REVIEW OF PERTINENT DATA

Human Studies

No studies of the subchronic or chronic toxicity of 2,6-toluenediamine in humans were located in the available literature. Epidemiological studies of male workers exposed to diaminotoluene and dinitrotoluene mixtures were inconclusive as to whether there was an increased risk of reproductive effects (sperm production and viability of wife's pregnancies were evaluated) in the exposed workers (WHO, 1987).

Animal Studies

NCI (1980) exposed groups of 10 male and 10 female F344 rats to 0, 100, 300, 1000, 3000 or 10,000 ppm of 2,6-toluenediamine dihydrochloride in the diet for 91 days. Using body weight data supplied in the study report, U.S. EPA (1988) allometric equations for food consumption, and adjusting for molecular weight of the dihydrochloride salt, doses of 2,6-toluenediamine are estimated as 0, 6, 18, 62, 192 or 692 mg/kg-day in male rats, and 0, 7, 20, 70, 221 or 767 mg/kg-day in female rats. Clinical observations were made twice daily and animals were weighed weekly. At sacrifice, necropsies were performed on all animals and tissues were taken for histopathologic analysis. This study was conducted as a range-finding study for the cancer bioassay and a limited number of endpoints were evaluated.

Two out of 10 male rats and 7/10 female rats in the 10,000 ppm group died before the end of the study; no deaths occurred at any of the other dose levels (NCI, 1980). Body weight gains

and terminal body weights were depressed in a dose-related fashion in male and female rats (see Table 1). The reductions in the 3000 and 10,000 ppm groups were markedly larger than in the lower dose groups. The body weight data were not analyzed statistically by the researchers. Gross pathological changes, observed in surviving rats in the 10,000 ppm group, were slight to moderate thyroid enlargement and darkening of the spleen, lymph nodes, liver, kidney, adrenals, and nasal turbinates. Histological changes were nephrosis in 10,000 ppm males (5/8) and females (1/7), bone marrow hyperplasia in 10,000 ppm males (8/8) and females (7/7), and thyroid hyperplasia in 3000 and 10,000 ppm males (7/10 and 8/8, respectively) and 10,000 ppm females (3/7). No treatment-related lesions were seen in the 1000 ppm or lower dose groups. Based on large decreases in body weight in males and females and thyroid hyperplasia in males, the 3000 ppm level (192 mg/kg-day in males and 221 mg/kg-day in females) is a LOAEL and the 1000 ppm level (62 mg/kg-day in males and 70 mg/kg-day in females) a NOAEL in this study.

Table 1. Body Weight in Rats Fed 2,6-Toluenediamine Dihydrochloride in the Diet for 13 Weeks (NCI, 1980)

Dietary Level (ppm)	Mean Body Weights (g)			Change Relative to Controls (%)	
	Initial	Final	Gain	Final Body Weight	Body Weight Gain
Male					
0	110	298	188	----	----
100	110	271	161	-9	-14
300	110	269	159	-10	-15
1000	110	258	148	-13	-19
3000	110	229	119	-23	-36
10,000	110	158	48	-47	-74
Female					
0	98	180	82	----	----
100	98	177	79	-2	-3
300	98	176	78	-2	-5
1000	98	156	58	-13	-29
3000	98	123	25	-32	-70
10,000	98	103	5	-43	-91

A similar study was performed using B6C3F1 mice (NCI, 1980). However, it is unclear what dose levels were used. The text reports feeding levels of 0, 10, 30, 100, 300, or 1000 ppm. This would be consistent with the findings of a 14-day study by the same researchers, which found a high incidence of death associated with digestive tract hemorrhage in mice fed 3000 ppm. Table 4 of the NCI report, however, lists the dietary concentrations in mice as 0, 100, 300, 1000, 3000, and 10,000 ppm, and the discussion of results seems to correspond to these levels. No deaths or pathological changes were seen in the mouse study, but body weight gains were reduced 25-42% and terminal body weights 10-14% versus controls in males of the two high-dose groups and high-dose females.

NCI (1980) conducted 2-year carcinogenicity bioassays of 2,6-toluenediamine in F344 rats and B6C3F1 mice. Rats (n=50/sex) were exposed to 0, 250 or 500 ppm of 2,6-toluenediamine dihydrochloride in the diet for 103 weeks, while mice (n=50/sex) were exposed to 0, 50 or 100 ppm in the diet for 103 weeks. Animals were inspected twice daily, and body weights were recorded every 4 weeks. At sacrifice or upon death of the animal (provided it was not precluded by autolysis or cannibalization), gross examination was performed on all major tissues, and 26 organs and tissues were collected for histologic examination. Using body weight data graphically supplied in the study report, U.S. EPA (1988) allometric equations for food consumption, and adjusting for molecular weight of the dihydrochloride salt, doses of 2,6-toluenediamine are estimated as 0, 12 or 25 mg/kg-day in male rats; 0, 15 or 30 mg/kg-day in female rats; and 0, 5 or 10 mg/kg-day in male and female mice.

Treatment with 2,6-toluenediamine did not affect survival of rats, which was adequate for assessment of late-developing tumors (NCI, 1980). Body weight was reduced through much of the study in high-dose males, and low and high-dose females, in comparison to controls. Time-weighted average body weights (estimated from graphs in the study report) were approximately 387 g for control and low-dose males and 358 g for high-dose males, indicating a 7% decrease in the latter. The researchers reported that body weight gains in both treated male groups were within 10% of controls. For females, estimated time-weighted average body weights were 248 g in controls, 225 g in the low-dose group (9% decrease), and 221 g in the high-dose group (11% decrease). The researchers reported that mean body weight gains in females were reduced 17% in the low-dose group and 27% in the high-dose group, compared with controls. No treatment-related clinical signs were reported at any dose level in male or female rats. The incidence of nonneoplastic lesions in treated rats did not differ significantly from controls. The small decreases in body weight in treated rats are not considered an adverse effect, making the high dose of 500 ppm (25 mg/kg-day in males and 30 mg/kg-day in females) a NOAEL in this study.

There was a marginally significant dose-related trend for increased incidence of hepatic neoplastic nodules or hepatocellular carcinomas in males (0/50, 2/50, 4/50 in the control, low- and high-dose groups, respectively); however, the researchers did not consider this to be a treatment-related effect, as none of the treatment groups were significantly different from

controls in pairwise comparisons (NCI, 1980). Similarly, a dose-related trend was observed for the incidence of animals with islet-cell adenomas of the pancreas in male rats (0/45, 1/46, 4/45 in the control, low- and high-dose groups, respectively), but was not considered treatment-related by the researchers because pairwise comparisons did not attain statistical significance. Other neoplasms occurred with similar incidence in treated and control rats. The researchers concluded that 2,6-toluenediamine was not carcinogenic to rats in this bioassay, although it is not clear that the maximum tolerated dose (MTD) was achieved.

In mice, treatment with 2,6-toluenediamine did not result in any effects on survival (which was adequate for assessment of late developing tumors in all groups), clinical signs of toxicity, or body weight or body weight gain (NCI, 1980). No nonneoplastic changes, either at the gross or microscopic level, could be attributed to treatment with 2,6-toluenediamine. The high dose of 100 ppm (10 mg/kg-day in both males and females) is a NOAEL in this study.

A slight increase in the incidence of vascular neoplasms (hemangioma/ hemangiosarcoma) of the spleen and liver was seen in male mice (1/50, 5/50, 3/50 in the control, low- and high-dose groups, respectively), but no dose-related trend was seen, and the differences were not statistically significant (NCI, 1980). Also in male mice, there was a significant trend for increased lymphomas relative to controls (2/50, 8/50, 2/50 in the control, low- and high-dose groups, respectively). However, the only apparent change was in the low-dose group, and the increase in this group was not statistically significant after adjustment for multiple comparisons. Female mice showed a significant trend for hepatocellular carcinoma (0/50, 0/49, 3/49 in the control, low- and high-dose groups, respectively), but the researchers did not consider this change to be treatment related because pairwise comparisons were not statistically significant. The researchers concluded that 2,6-toluenediamine was not carcinogenic to mice in this bioassay, but acknowledged that the MTD was not achieved.

Other Studies

2,6-Toluenediamine is a potent mutagen in *Salmonella typhimurium* when tested with metabolic activation (Ashby and Tennant, 1988; Cheung et al., 1996; Cunningham et al., 1989; Dybing and Thorgeirsson, 1977; Florin et al., 1980; George and Westmoreland, 1991; Sayama et al., 1989). It is inactive in the absence of activation. In mammalian cells *in vitro*, 2,6-toluenediamine was negative in assays for unscheduled DNA synthesis (UDS) in primary cultured rat hepatocytes (Allavena et al., 1992; Butterworth et al., 1989; Selden et al., 1994), but was positive for UDS in primary cultured human hepatocytes (Butterworth et al., 1989). Assays for induction of micronuclei in Chinese hamster ovary (CHO) cells with or without S9 (Miller et al., 1995) and cell transformation in primary hamster embryo cells (Greene and Friedman, 1980) were also positive. An assay for DNA fragmentation in cultured rat hepatocytes was negative (Allavena et al., 1992), but low levels of covalent binding to DNA were reported in another study in cultured rat hepatocytes (Furlong et al., 1987).

In vivo, 2,6-toluenediamine did not induce mutations in *lac*I transgenic male mice (Hayward et al., 1995). Assays for UDS in hepatocytes isolated from male rats treated with 150 mg/kg of 2,6-toluenediamine by gavage in corn oil (Mirsalis et al., 1982) or 300 mg/kg by gavage in water (George and Westmoreland, 1991) were negative, but positive results were obtained in hepatocytes from males rats treated with 2000 mg/kg by gavage in aqueous carboxymethylcellulose suspension (Allavena et al., 1992). A bone marrow micronucleus assay in rats was negative at oral doses of 1000-2000 mg/kg in aqueous carboxymethylcellulose suspension (Allavena et al., 1992), but weak positive results were found in rats treated with 300-600 mg/kg by gavage in water in another study (George and Westmoreland, 1991), and intraperitoneal (*i.p.*) doses as low as 31 mg/kg produced significant increases in bone marrow micronuclei in mice (Shelby et al., 1993). Assays for detection of DNA fragmentation (alkaline elution/ electrophoresis) showed no evidence of DNA damage in the liver, kidney, bladder, colon, stomach, lung, brain or bone marrow of mice treated by oral gavage with 60 mg/kg (Sasaki et al., 1999) or in the liver of rats treated with 1000 mg/kg orally (Allavena et al., 1992), but did find significant increases in DNA fragments in rat liver after oral dosing with 2000 mg/kg (Allavena et al., 1992). Assays for formation of DNA adducts in liver were negative in rats treated with up to 500 mg/kg *i.p.* (La and Froines, 1993; Taningher et al., 1995). 2,6-Toluenediamine (50 mg/kg *i.p.* 5 days/week for 6 weeks) did not promote preneoplastic liver foci in partially hepatectomized male rats initiated with diethylnitrosamine (Taningher et al., 1995).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 2,6-TOLUENEDIAMINE

No studies examining the effects of 2,6-toluenediamine in orally exposed humans were located. NCI (1980) conducted subchronic and chronic feeding studies in rats and mice. The subchronic study identified a LOAEL of 3000 ppm (192 mg/kg-day in males and 221 mg/kg-day in females) in rats based on thyroid hyperplasia in males and large decreases in body weight in both sexes. Additional effects at the next higher dose of 10,000 ppm (692 mg/kg-day in males and 767 mg/kg-day in females) were grossly observed thyroid enlargement and darkening of the spleen, lymph nodes, liver, kidney, adrenals and nasal turbinates; microscopically observed nephrosis and bone marrow hyperplasia; and death. The NOAEL was 1000 ppm (62 mg/kg-day in males and 70 mg/kg-day in females). The only changes at this or lower doses were small decreases in body weight. The results of the chronic rat study are consistent with the subchronic study. In the chronic study, the high dose of 500 ppm (25 mg/kg-day in males and 30 mg/kg-day in females) was a NOAEL, with small decreases in body weight being the only effect observed. Due to poor reporting, the subchronic mouse study cannot be used quantitatively. However, it is noteworthy that the only effects in this study were small decreases in body weight. The chronic mouse study found no effects at all at the high dose of 100 ppm (10 mg/kg-day in both males and females).

A provisional **subchronic RfD of 0.06 mg/kg-day** for 2,6-toluenediamine is derived by applying to the rat oral subchronic NOAEL of 62 mg/kg-day from the NCI (1980) study an uncertainty factor of 1000 (10 for extrapolation from rats to humans, 10 for protection of sensitive individuals, and 10 for deficiencies in the database, including lack of reproductive and developmental toxicity studies), and the quality of the critical study especially the inability to address all possible adverse outcomes in humans. The subchronic p-RfD follows:

$$
\begin{aligned}
\text{subchronic p-RfD} \quad &= \quad \text{NOAEL / UF} \\
&= \quad 62 \text{ mg/kg-day} / 1000 \\
&= \quad 0.06 \text{ or } 6\text{E-2 mg/kg-day}
\end{aligned}
$$

Confidence in the principal study is low. The study included an adequate number of dose groups for male and female rats and mice, but group sizes were only minimally adequate. The study was conducted as a range-finding study for a cancer bioassay, and only a limited array of endpoints was evaluated, although histopathology was included. No statistical analyses were conducted. Reporting of study methods and results was adequate for rats, but poor for the mouse study. Both a NOAEL and LOAEL were identified for the rat study, but the results of the mouse study could not be interpreted quantitatively due to the poor reporting. Confidence in the database is low, as the only supporting study is the chronic cancer bioassay described in the same report. Overall confidence in the provisional subchronic RfD is low.

A provisional **chronic RfD of 0.03 mg/kg-day** for 2,6-toluenediamine is derived by applying to the rat oral chronic NOAEL of 25 mg/kg-day from the NCI (1980) study an uncertainty factor of 1000 (10 for extrapolation from rats to humans, 10 for protection of sensitive individuals, and 10 for deficiencies in the database, including lack of reproductive and developmental toxicity studies), and the quality of the critical study especially the inability to address all possible adverse outcomes in humans. The chronic p-RfD follows:

$$
\begin{aligned}
\text{p-RfD} \quad &= \quad \text{NOAEL / UF} \\
&= \quad 25 \text{ mg/kg-day} / 1000 \\
&= \quad 0.03 \text{ or } 3\text{E-2 mg/kg-day}
\end{aligned}
$$

Confidence in the principal study is low. The study included exposure throughout the two-year study period and adequate numbers of male and female rats and mice in each dose group, but only two treated groups. The study was performed as a cancer bioassay, and included only limited evaluation of noncancer endpoints. Statistical analysis of findings was performed only for cancer-related endpoints. The study did not identify a target organ effect or LOAEL in either species, indicating that doses tested were too low. Confidence in the database is low, as the only supporting study is the subchronic range-finding study described in the same report. Overall confidence in the provisional chronic RfD is low.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 2,6-TOLUENEDIAMINE

No chronic or subchronic inhalation studies examining the effects of 2,6-toluenediamine in humans or animals were located, precluding derivation of p-RfC values for this chemical.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 2,6-TOLUENEDIAMINE

No data in humans are available to assess the carcinogenic potential of 2,6-toluenediamine. NCI (1980) evaluated the carcinogenic effects of 2,6-toluenediamine in rats and mice in two-year feeding studies. No treatment-related neoplasms were seen in males or females of either species. However, it is not clear that doses used in these studies were appropriate. In rats, the only effects were small changes in body weight in both dose groups that were not clearly adverse or related to treatment. In mice, no effects of any type were noted in the treated mice. It, therefore, appears that doses were too low, such that the MTD was not achieved, in the mouse study and possibly also the rat study. Consequently, these studies do not rule out the possibility of a tumorigenic effect of 2,6-toluenediamine at doses higher than those tested. Genotoxicity studies indicate a strong potential for 2,6-toluenediamine to produce mutations in bacteria with metabolic activation, and some potential to produce DNA and chromosomal effects in mammalian cells as well, particularly at high doses. Taking into account the too-low doses in the negative cancer bioassays in rodents, and the demonstrated genotoxic potential of the chemical, the available data are considered insufficient to assess the carcinogenic potential of 2,6-toluenediamine in animals or humans. Under the U.S. EPA (2005b) Guidelines for Carcinogen Risk Assessment, there is inadequate information to assess the carcinogenic potential of 2,6-toluenediamine.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2003. TLVs® and BEIs®: Threshold Limit Values for Chemical Substances and Physical Agents, Biological Exposure Indices. Cincinnati, OH.

Allavena, A., A. Martelli, L. Robbiano and G. Brambilla. 1992. Evaluation in a battery of *in vivo* assays of four *in vitro* genotoxins proved to be noncarcinogens in rodents. Teratog. Carcinog. Mutagen. 12(1): 31-41.

Ashby, J. and R.W. Tennant. 1988. Chemical structure, *Salmonella* mutagenicity and extent of carcinogenicity as indicators of genotoxic carcinogenesis among 222 chemicals tested in rodents by the U.S. NCI/NTP. Mutat. Res. 204: 17-115.

ATSDR (Agency for Toxic Substances and Disease Registry). 2003. Toxicological Profile Information Sheet. U.S. Department of Health and Human Services, Public Health Service. Online. http://www.atsdr.cdc.gov/toxpro2.html

Butterworth, B.E., T. Smith-Oliver, L. Earle et al. 1989. Use of primary cultures of human hepatocytes in toxicology studies. Cancer Res. 49: 1075-1084.

Cheung Y.L., J. Snelling, N.N. Mohammed et al. 1996. Interaction with the aromatic hydrocarbon receptor, CYP1A induction, and mutagenicity of a series of diaminotoluenes: implications for their carcinogenicity. Toxicol. Appl. Pharmacol. 139(1): 203-11.

Cunningham, M.L., L.T. Burka and H.B. Matthews. 1989. Metabolism, disposition, and mutagenicity of 2,6-diaminotoluene, a mutagenic noncarcinogen. Drug. Metab. Disp. 17: 612-617.

Dybing, E. and S.S. Thorgeirsson. 1977. Metabolic activation of 2,4-diaminoanisole, a hair-dye component. Biochem. Pharmacol. 26: 729-734.

Florin, I., L. Rutberg, M. Curvall and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology. 18: 219-232.

Furlong, B.B., R.P. Weaver and J.A. Goldstein. 1987. Covalent binding to DNA and mutagenicity of 2,4-diaminotoluene metabolites produced by isolated hepatocytes and 9000 g supernatant from Fischer 344 rats. Carcinogenesis. 8: 247-251.

George, E. and C. Westmoreland. 1991. Evaluation of the *in vivo* genotoxicity of the structural analogues 2,6-diaminotoluene and 2,4-diaminotoluene using the rat micronucleus test and rat liver UDS assay. Carcinogenesis. 12: 2233-2237.

Greene, E.J. and M.A. Friedman. 1980. *In vitro* cell transformation screening of 4 toluene diamine isomers. Mutat. Res. 79: 363-375.

Hayward, J.J., B.S. Shane, K.R. Tindall and M.L. Cunningham. 1995. Differential *in vivo* mutagenicity of the carcinogen/non-carcinogen pair 2,4- and 2,6-diaminotoluene. Carcinogenesis. 16(10): 2429-2433.

IARC (International Agency for Research on Cancer). 2003. Search IARC Monographs. Online. http://193.51.164.11/cgi/iHound/Chem/iH_Chem_Frames.html

La, D.K. and J.R. Froines. 1993. Comparison of DNA binding between the carcinogen 2,6-dinitrotoluene and its noncarcinogenic analog 2,6-diaminotoluene. Mutat. Res. 301(2): 79-85.

Miller, B.M., E. Pujadas and E. Gocke. 1995. Evaluation of the micronucleus test *in vitro* using Chinese hamster cells: results of four chemicals weakly positive in the *in vivo* micronucleus test. Environ. Mol. Mutagen. 26: 240-247.

Mirsalis, J.C., C.K. Tyson and B. E. Butterworth. 1982. Detection of genotoxic carcinogens in the *in vivo-in vitro* hepatocyte DNA repair assay. Environ. Mutagen. 4: 553-562.

NCI (National Cancer Institute). 1980. Bioassay of 2,6-Toluenediamine Dihydrochloride for Possible Carcinogenicity. U.S. Dept. of Health and Human Services, Public Health Service, National Institutes of Health, Bethesda, MD. Technical Report Series No. 200. NTP No. 80-20.

NIOSH (National Institute for Occupational Safety and Health). 2003. Online NIOSH Pocket Guide to Chemical Hazards. Online. http://www.cdc.gov/niosh/npg/npgdcas.html

OSHA (Occupational Safety and Health Administration). 2003. OSHA Standard 1910.1000 Table Z-1. Part Z, Toxic and Hazardous Substances. Online. http://www.osha-slc.gov/OshStd_data/1910_1000_TABLE_Z-1.html

Sasaki, Y.F., K. Fujikawa, K. Ishida et al. 1999. The alkaline single cell gell electrophoresis assay with mouse multiple organs: results with 20 aromatic amines evaluated by the IARC and U.S. NTP. Mutat. Res. 440: 1-18.

Sayama, M., M. Mori, T. Shirokawa et al. 1989. Mutagenicity of 2,6-dinitrotoluene and its metabolites, and their related compounds in *Salmonella typhimurium*. Mutat. Res. 226: 181-184.

Selden, J.R., F. Dolbeare, J.H. Clair et al. 1994. Validation of a flow cytometric *in vitro* DNA repair (UDS) assay in rat hepatocytes. Mutat. Res. 315: 147-167.

Shelby, M.D., G.L. Erexson, G.J. Hook and R.R. Tice. 1993. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: results with 49 chemicals. Environ. Mol. Mutagen. 21(2): 160-179.

Taningher, M., M. Peluso, S. Parodi et al. 1995. Genotoxic and non-genotoxic activities of 2,4- and 2,6-diaminotoluene, as evaluated in Fischer-344 rat liver. Toxicology. 99: 1-10.

U.S. EPA. 1984. Health and Environmental Effects Profile for Selected Toluenediamine. Prepared by the Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EPA600/X-84/148. NTIS PB88-131073/AS.

U.S. EPA. 1988. Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Prepared by Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EPA 600/6-87/008. NTIS PB88-179874/AS.

U.S. EPA. 1991. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. April 1991.

U.S. EPA. 1994. Chemical Assessments and Related Activities (CARA). Office of Health and Environmental Assessment, Washington, DC. December 1994.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. FY-1997 Update. Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. July. EPA/540/R-97/036. NTIS PB97-921199.

U.S. EPA. 2002. 2002 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. Summer 2002. EPA 822-R-02-038. Online. http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf

U.S. EPA. 2005a. Integrated Risk Information System (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Online. http://www.epa.gov/iris/

U.S. EPA. 2005b. Guidelines for Carcinogen Risk Assessment. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. EPA/630/P-03/001F.

WHO (World Health Organization). 1987. Environmental Health Criteria 74. Diaminotoluenes. Online: http://www.inchem.org/documents/ehc/ehc/ehc74.htm#PartNumber:4