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Provisional Peer-Reviewed Toxicity Values for

3-(N,N-Dimethylamino)propionitrile
(CASRN 1738-25-6)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMD	benchmark dose
BMCL	benchmark concentration lower bound 95% confidence interval
BMDL	benchmark dose lower bound 95% confidence interval
HEC	human equivalent concentration
HED	human equivalent dose
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 reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
POD	point of departure
RfC	reference concentration (inhalation)
RfD	reference dose (oral)
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
WOE	weight of evidence

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 3-(N,N-DIMETHYLAMINO)PROPIONITRILE (CASRN 1738-25-6)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

QUESTIONS REGARDING PPRTVS

Questions regarding the contents and appropriate use of this PPRTV assessment should 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).

INTRODUCTION

3-(N,N-Dimethylamino)propionitrile (DMAPN) is used as a catalyst in the manufacture of polyurethane or as a polymerization stimulator in the production of polyacrylamide gels (HSDB, 2003). It belongs to a class of chemicals called propionitriles, which have the basic structure of ($X\text{-}CH_2\text{-}CH_2\text{-}CN$). These compounds have a wide variety of toxic effects that depend on the identity of the X moiety (Pestronk et al., 1980). DMAPN (see Figure 1) has been shown to have neurotoxic properties. The neurotoxic effects of DMAPN were first identified during an epidemic of urinary retention, sexual dysfunction, and peripheral neuropathy that occurred when workers in polyurethane foam manufacturing plants were exposed to this compound in 1976 and 1977 (Keogh, 1983; Keogh et al., 1980; Kreiss et al., 1980; Baker et al., 1981). Most affected workers recovered promptly, but some had persisting neuropathy, sexual and bladder dysfunction, and central nervous system (CNS) symptoms. The outbreak ceased abruptly when DMAPN use was stopped. The catalyst that caused the problem—NIAX catalyst ESN (a mixture of 95% DMAPN/dimethylaminopropionitrile and 5% bis-dimethylaminoethyl ether)—was withdrawn from the market in the United States after rapid governmental action (Keogh, 1983). Table 1 provides a list of the selected physicochemical properties for DMAPN.

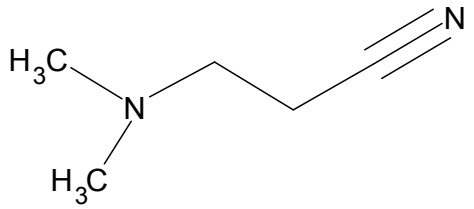

Figure 1. 3-(N,N-dimethylamino)propionitrile Structure

Table 1. Physicochemical Properties of 3-(N,N-dimethylamino)propionitrile (CASRN 1738-25-6)[a]

Property (unit)	Value
Boiling point (ºC)	171
Melting point (ºC)	−44.6
Density (g/cm^3)	0.8701 at 20ºC
Vapor pressure (hPa at 30ºC)	2.4
pH (unitless)	10.8 at 100g/L and 20ºC
Solubility in water (g/100 mL at 25ºC)	Miscible
Relative vapor density (air = 1)	ND
Molecular weight (g/mol)	98.2

[a]IUCLID (2000).
ND = no data

No Reference Dose (RfD), Reference Concentration (RfC), or cancer assessment for DMAPN is included in the United States Environmental Protection Agency (U.S. EPA) Integrated Risk Information System (IRIS) (U.S. EPA, 2010) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009). No RfD or RfC values are reported in the Health Effects Assessment Summary Tables (U.S. EPA, 2003). The Chemical Assessments and Related Activities (CARA) list does not include any EPA documents for DMAPN (U.S. EPA, 1994). The California Environmental Protection Agency (CalEPA, 2008, 2009) has not derived toxicity values for exposure to DMAPN.

The toxicity of DMAPN has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2010) or the World Health Organization (WHO, 2011). No occupational exposure limits for DMAPN have been derived or recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2010), the National Institute of Occupational Safety and Health (NIOSH, 2011), or the Occupational Safety and Health Administration (OSHA, 2006). However, in May 1978, OSHA and NIOSH jointly published the Current Intelligence Bulletin (CIB) 26: NIAX® Catalyst ESN (NIOSH, 2011). In this CIB, OSHA and NIOSH recommended that occupational exposure to NIAX® Catalyst ESN, its components, DMAPN and bis(2-(dimethylamino)ethyl)ether, as well as formulations containing either component, be minimized. They stated that exposures should be limited to as few workers as possible, while minimizing workplace exposure concentrations with effective work practices and engineering controls. In addition, exposed workers should be carefully monitored for potential disorders of the nervous and genitourinary system (NIOSH, 2011). The Registry of Toxic Effects of Chemical Substances (RTECS, 2007) reports a Russian short-term occupational exposure limit of 10 mg/m^3 for DMAPN.

The HEAST (U.S. EPA, 2011) does not report any cancer values for DMAPN. The International Agency for Research on Cancer (IARC, 2010) has not reviewed the carcinogenic

potential of DMAPN; the compound is not included in the *12th Report on Carcinogens* (NTP, 2011), and CalEPA (2008) has not prepared a quantitative estimate of carcinogenic potential for DMAPN.

Literature searches were conducted on sources published from 1900 through August 2011, for studies relevant to the derivation of provisional toxicity values for 3-(N,N-dimethylamino)propionitrile, CAS Number (1738-25-6). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: AGRICOLA; American Chemical Society; BioOne; Cochrane Library; DOE: Energy Information Administration, Information Bridge, and Energy Citations Database; EBSCO: Academic Search Complete; GeoRef Preview; GPO: Government Printing Office; Informaworld; IngentaConnect; J-STAGE: Japan Science & Technology; JSTOR: Mathematics & Statistics and Life Sciences; NSCEP/NEPIS (EPA publications available through the National Service Center for Environmental Publications (NSCEP) and National Environmental Publications Internet Site (NEPIS) database); PubMed: MEDLINE and CANCERLIT databases; SAGE; Science Direct; Scirus; Scitopia; SpringerLink; TOXNET (Toxicology Data Network): ANEUPL, CCRIS, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HEEP, HMTC, HSDB, IRIS, ITER, LactMed, Multi-Database Search, NIOSH, NTIS, PESTAB, PPBIB, RISKLINE, TRI, and TSCATS; Virtual Health Library; Web of Science (searches Current Content database among others); World Health Organization; and Worldwide Science. The following databases outside of HERO were searched for risk assessment values: ACGIH, ATSDR, CalEPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for DMAPN and includes all potentially relevant repeated short-term-, subchronic-, and chronic-duration studies. NOAELs, LOAELs, and BMDL/BMCL are provided in HED/HEC units for comparison except that oral noncancer values are not converted to HEDs and are identified in parentheses as (Adjusted) rather than HED/HECs. Principal studies are identified. Following the table, important aspects of all the studies in the table are provided in the same order as the table. Reference can be made to details provided in Table 2. The phrase, "statistical significance," used throughout the document, indicates a p-value of <0.05.

Table 2. Summary of Potentially Relevant Data for 3-(N,N-Dimethylamino)Propionitrile (CASRN 1738-25-6)

Notes[a]	Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)
Human								
1. Oral (mg/kg-d)[b]								
NA	Subchronic	ND						
NA	Chronic	ND						
NA	Developmental	ND						
NA	Reproductive	ND						
NA	Carcinogenicity	ND						
2. Inhalation (mg/m^3)[b]								
NA	Subchronic	ND						
PR	Long-term	139/2 workers at Facility A, 64/11 workers at Facility B, work exposure, ≈9 mo	NA	Symptoms of urinary retention among workers at both facilities were reported. These included straining, hesitancy, decreased flow, intermittent flow, bladder distension, and the need for manual pressure to empty the bladder. Increased incidence of sexual dysfunction also was found among workers working in the production line.	NA	DU	NA	Keogh et al. (1980)

Table 2. Summary of Potentially Relevant Data for 3-(N,N-Dimethylamino)Propionitrile (CASRN 1738-25-6)								
Notes[a]	**Category**	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry[b]**	**Critical Effects**	**NOAEL[b]**	**BMDL/ BMCL[b]**	**LOAEL[b]**	**Reference (Comments)**
PR		213 (no. sex not reported), work exposure, ≈9 mo	NA	Symptoms were identified among 104 workers, most of whom worked at the production line. These symptoms were -neurogenic bladder dysfunction, characterized by hesitancy, need to strain, decreased stream, and increased duration of urination. -sexual difficulties.	NA	DU	NA	Kreiss et al. (1980)
PR		11 (mostly male), ≈9 mo	NA	Decrease in the overall prevalence of urologic and neurological symptoms for the 11 persons interviewed 2 yr after the exposure; however, high rates of some persistent symptoms were observed (sexual dysfunction).	NA	DU	NA	Baker et al. (1981)
NA	Developmental	ND						
NA	Reproductive	ND						
NA	Carcinogenicity	ND						
Animal								
1. Oral (mg/kg-d)[b]								
NPR	Subchronic	6 (no. sex not reported), Sprague-Dawley, rat, diet, 7 d/wk, 56 d	0 or 175 mg/kg-d (Adjusted)	No deaths occurred, no skeletal changes of weanlings, no lathyrogenic (type of neurological) effects.	NDr	DU	NDr	Bachhuber et al. (1955)
NPR	Chronic	(no. animals, sex, species not reported), rat, drinking water, 2−9 mo	450 mg/kg-d (Adjusted)	Enlarged distal motor and spindle axons with disordered neurofilaments and enlarged motor nerve terminals were observed.	NDr	DU	NDr	Pestronk et al. (1979, as cited in Pestronk et al., 1980)

Table 2. Summary of Potentially Relevant Data for 3-(N,N-Dimethylamino)Propionitrile (CASRN 1738-25-6)

Notes[a]	Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	BMDL/ BMCL[b]	LOAEL[b]	Reference (Comments)
NA	Developmental	ND						
NPR	Reproductive	0/2, Sprague-Dawley, rat, diet, at 17th d of pregnancy	150 mg/kg-d (Adjusted)	No toxic effects were reported. Normal litters were born.	NDr	DU	NDr	Stamler (1955)
NA	Carcinogenicity	ND						
2. Inhalation (mg/m^3)[b]								
NA	Subchronic	ND						
NA	Chronic	ND						
NA	Developmental	ND						
NA	Reproductive	ND						
NA	Carcinogenicity	ND						

[a]Notes: IRIS = utilized by IRIS, date of last update; PS = principal study; PR = peer reviewed; NPR = not peer reviewed.
[b]Dosimetry: NOAEL, BMDL/BMCL, and LOAEL values are converted to human equivalent dose (HED in mg/kg-day) or human equivalent concentration (HEC in mg/m^3) units.
DU = data unsuitable; NA = not applicable; ND = No data; NDr = Not determined; NR = Not reported; NR/Dr = Not reported, but determined from data.

HUMAN STUDIES

Oral Exposures

No studies investigating the effects oral exposure to DMAPN in humans have been identified.

Inhalation Exposures

The effects of inhalation exposure of humans to DMAPN have been evaluated in two occupational studies (Keogh et al., 1980; Kreiss et al., 1980) and in one follow-up study (Baker et al., 1981).

Long-term Studies

Keogh et al., 1980

Keogh et al (1980) performed a clinical investigation on workers who had been occupationally exposed to a catalyst containing 95% DMAPN, 5% bis(2-(dimethylamino)ethyl)ether, and <1% acrylonitrile and dimethylamine at two polyurethane foam manufacturing plants in the United States (Maryland and Massachusetts plants). The investigation was conducted after complaints of dizziness, weakness, temporary clouding of vision, and paresthesias were reported in workers at these plants. The cause of these symptoms was thought to be due to a new catalyst NIAX-catalyst ESN, which had been introduced in large quantities into the production line of polyurethane in August 1977, some months before the epidemic began. Based on this, the use of the catalyst was stopped in the plant and the study authors carried out their clinical investigation on all workers at the affected plant (Plant A, Maryland) to explore the potential health effects of DMAPN exposure. They also examined workers at a nearby plant (Plant B, Massachusetts) owned by the same company, which made polyurethane but used little of the suspected catalyst in production.

Of 234 eligible employees (across the plant from production line, finishing, supply, storage, laboratory, and clerical areas), 216 agreed to participate in the study (141 employees from Plant A [139 men and 2 women] and 75 employees from Plant B [64 men and 11 women]). Workers were thought to have experienced dermal as well as inhalation exposures. The workers were tested between April 11 and May 2, 1978, almost 1 year after the introduction of the ESN catalyst (August 1977). Participants were asked to complete questionnaires focused mainly on symptoms observed on the skin, the lungs, the CNS, and the genitourinary system. They were asked specifically about straining, hesitancy, decreased flow, intermittent flow, distension, frequency of urination, the need for manual pressure to empty the bladder, and sexual function. Complete physical examination was conducted on all participants and the results were recorded on a standard form. Limited neurological assessments were carried out. These included testing for cranial nerves and examining motor strength, deep tendon reflexes, and vibratory sensation at the ankles, station, and gait. Pulmonary function was assessed by performing a spirometry test in all participants. An intravenous pyelography (IVP) with postvoid film was ordered for workers who had persisting symptoms of urinary retention. Laboratory analyses including routine blood and complete urine tests were also performed. The prevalence of specific symptoms was assessed individually. Statistical analyses included the χ^2 test to analyze symptoms and clinical signs.

The results of the clinical and physical examinations indicated that occupational exposure to unknown concentrations of the ESN catalyst for 8 months resulted in neurological and

urologic effects (e.g. urinary retention, paresthesias, weakness, impotence, irritability, and insomnia). The prevalence of a variety of symptoms reported by the exposed groups is shown in Table B.1. Among the reported symptoms, urinary retention and irritability were the most common symptoms. Also, the prevalence of these symptoms in Plant A workers was significantly higher ($p < 0.01$) than that found in Plant B workers (see Table B.1). After exposure was discontinued, these symptoms decreased or disappeared as reported by the exposed workers. Among all subjects, 65 workers were identified to undergo an IVP. Seventeen of these workers had abnormal postvoid retention of contrast material in the bladder (see Table B.2). However, the study authors stated that this finding was not conclusive evidence of bladder dysfunction. Therefore, the bladder dysfunction was further assessed by performing cystoscopy and cystometrograms (CMGs) in exposed workers whose symptoms, examination, and roentgenograms suggested intervention might be needed to prevent hydronephrosis. As a result, bladder dysfunction was diagnosed in only four workers as confirmed by CMG tests but none needed surgical intervention. Decreased sensation in lower sacral dermatomes and hands and feet was reported in three workers. The findings of other examinations (nerve conduction studies, urinalysis, and blood tests) were reported to be normal. A clear association between jobs having the highest exposure to warm foam containing ESN and the incidence of urinary retention was observed (see Table B.3). Production line employees were reported to have a high incidence of urinary retention as compared with those working in the supervisory and clerical areas.

In addition to the above, other symptoms such as visual disturbances, upper respiratory tract irritation, dermatitis, and pulmonary symptoms were also reported by workers in both plants. A significantly higher ($p < 0.01$) incidence of these symptoms was observed at Plant A (see Table B.4). Visual disturbances were the most common problem reported. The results of the spirometry assessment of pulmonary function were abnormal in many workers. This incidence of this abnormality showed no relation to the length of employment and was explained by the study authors to be due to the presence of other factors such as toluene diisocyanate (TDI, the monomer employed in polyurethane foam production) and cotton. A high incidence of upper respiratory tract irritation and dermatitis was also observed at both plants. This was considered by the study authors to be due to high exposure to irritant fumes and the lack of protective clothing or adequate respiratory protection worn at the plants. The severity and frequency of these symptoms were not decreased after the removal of the catalyst.

In summary, increased incidence of urinary retention, muscle weakness, paresthesia, insomnia, and sexual dysfunction were observed in employees working in the manufacture of polyurethane foam. The highest rates of illness occurred in production workers who were exposed to the greatest amounts of warm foam with ESN. The study authors concluded that the new catalyst ESN was the causative agent for these symptoms. The reasons for their conclusion were (1) there was a temporal relationship between the introduction of the catalyst and the onset of the epidemic, (2) the symptoms of retention, paresthesia, weakness, insomnia, and sexual dysfunction were largely confined to the plant where the catalyst was used most heavily (Plant A) and (3) no new cases occurred after the use of catalyst was stopped. The study authors also stated that DMAPN, the major component of the catalyst, was probably the neurotoxin responsible for these effects. Because the level of exposure to DMAPN was not measured in the study, no NOAEL or LOAEL could be identified.

Kreiss et al., 1980

Kreiss et al. (1980) investigated the extent of an epidemic discovered among workers employed in another polyurethane manufacture plant in Massachusetts. The outbreak occurred in a plant that manufactured automobile seat cushions from polyurethane foam. The study authors stated that a new catalyst, DMAPN, which was recently introduced into the manufacturing process, could be the cause of this epidemic. The investigation was conducted 8 to 13 days after the catalyst was withdrawn from the manufacturing process (March 29, 1978).

Of 230 eligible employees (across the plant), 213 agreed to precipitate in the study (number of men and women participants were not reported). The median age of the cases at entry into the cohort was 37.9 years for females and 31.3 years for males. Participants were administered a questionnaire that collected information on medical history and general symptoms. Information on job description, use of protective equipment, personal hygiene, and genitourinary and neurological symptoms were collected by personal interview. Blood sampling and urinalyses were performed. The blood was analyzed for complete blood cell count, differential white blood cell (WBC) count, and levels of electrolytes, glucose, blood urea nitrogen (BUN), creatinine, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), lactic dehydrogenase, alkaline phosphatase, bilirubin, calcium, and uric acid and for antinuclear antibody titer. Neurologic examinations were performed on eight symptomatic workers (five men and three women) 2½ weeks after cessation of DMAPN exposure. The neurological examinations included testing for cranial nerves, reflexes, coordination, sensory system and gait (e.g., skin temperature-nerve conduction studies), and mental status. The criteria for clinical neuropathy included upper and lower extremity distribution of one abnormality, or the occurrence of at least two of the following: numbness, paresthesia, decreased pinprick sensation, decreased vibratory sensation, decreased tendon reflexes, and muscle weakness. The urologic evaluation included cystometrography. Bladder dysfunction was characterized by hesitancy, need to strain, decreased stream, and increased duration of urination. The study authors defined a case of bladder dysfunction as any employee who experienced any two of these four symptoms. A late improver case was defined as a worker who had persistent urinary symptoms at the 3 month reinterview. The employees were grouped and analyzed according to the departments in which they worked. Workers from the production or finishing rooms were considered to be at higher risk of exposure to DMAPN than those working in the nonmanufacturing areas such as the warehouse.

Of 213 workers who participated in the study, the symptoms of 208 employees' were analyzed. Of these, 166 employees (36 women and 130 men) were identified to be at risk for developing bladder dysfunction while no risk was associated with the remaining 42. The prevalence of a variety of urinary tract symptoms reported by the exposed groups is shown in Table B.5. There were 104 employees who met the case definition of bladder dysfunction.[1] The case rates for women and men were 55.6% and 64.5%, respectively. No increase in this case rate with age was observed. Also, there were no sex-specific differences in the proportion of cases experiencing specific urinary tract symptoms. A high rate of bladder dysfunction was mainly observed among the production line workers (the specific rate could not be determined as the data were represented in the original study as a graph without individual data points). Most of the affected employees were second- and third-shift workers where the workers were exposed to

[1] Case defined by the study authors is an employee who experienced any two of the four symptoms of bladder dysfunction (hesitancy, need to strain, decreased stream, and increased duration of urination).

more scrap and waste foam than on the first shift. Bladder symptoms were observed in subjects with and without significant skin contact with the catalyst or foam product. Based on this, the study authors suggested that inhalation could be the possible route of exposure. There was also a clear association between the amount of catalyst used (from June 1977−April 1978) and the number of cases of bladder dysfunction reported in plant workers (data were represented in the original study as a graph). Most patients (85%) experienced no improvements in their symptoms as long as DMAPN was still in use. However, 8−13 days after exposure to the catalyst had been discontinued, 51% of the patients showed improvement, and an additional 21% were back to normal. Three months later, 86% of the cases were asymptomatic and the remainder reported improvement. Only 14 cases were identified as late improvers (4 women and 10 men). Neurologic testing of eight cases of bladder dysfunction revealed that seven lacked either detrusor reflex or normal sensation of bladder filling; seven had a subclinical sensory abnormality; three had prolonged sacral-evoked responses; and two of these three had limb motor neuropathies (see Tables B.6, B.7, and B.8). Results of urinalysis and blood tests did not reveal any abnormalities. Other symptoms reported included pain and burning on urination, as well as impotence. Sexual difficulties were noted in 23 cases and in 6 noncases (employees who had no bladder dysfunction symptoms) while dysuria was noted in all 14 late improver cases. These 14 patients were older, on average, than the other patients, with a mean age of 36.4 years (ages ranged from 21 to 54 years).

The above results suggested that there was an association between occupational exposure to the DMAPN catalyst and signs and symptoms of bladder neuropathy. The investigators stated that the results of this study were in line with the occurrence of similar epidemics in at least five other polyurethane foam plants that had introduced the catalyst. Accordingly, DMAPN was identified as the cause of this outbreak. Employees exposed to the catalyst experienced symptoms of bladder dysfunction, sexual dysfunction, and CNS symptoms. The urinary symptoms, however, occurred with greater frequency than somatic nerve symptoms and sexual dysfunction. Follow-up evaluations performed 3 months after the substance was removed from the workplace revealed that approximately 85% of the workers who were initially symptomatic had recovered. In conclusion, DMAPN was identified by the study authors as a unique industrial neurotoxin because of its effect in producing bladder dysfunction without producing frequent complaints of other organ or nerve dysfunction. Because no environmental measurements were obtained while DMAPN was used in production, the quantitative exposures associated with this epidemic were unknown. Therefore, no NOAEL or LOAEL can be identified from this study.

Baker et al., 1981

Baker et al. (1981) performed a follow-up investigation in 1980 at the Massachusetts polyurethane foam factory that had been examined in 1978 by Kreiss et al. (1980). The study focused on the evaluation of long-term morbidity among the 14 patients who were identified as late improvers in the Kreiss et al. (1980) 3-month follow-up interview (July 1978). The study design was similar to that of Kreiss et al. (1980). Briefly, clinical and laboratory examinations included personal interviews to obtain information on medical history (1978−1980), job history, urinary symptoms, alcohol consumption, medication, and sexual history. Physical, neurological, and urological examinations were performed in the same laboratory under similar conditions and, in most instances, by the same physician as in 1978. For nerve conduction testing, a group of 29 age- and sex-matched machinists, nonexposed to neurotoxins were used as a reference group. Also for the neurological testing, four out of eight subjects that previously were tested in 1978 were reexamined again (these eight subjects are the eight cases of bladder dysfunction that

were selected by Kreiss et al. [1980] for neurological examinations, see Tables B.7 and B.8). In total, 11 of the 14 late improver participants were interviewed and 10 of them underwent complete physical, neurological, and urological examinations.

Based on the clinical history, the 11 late improvers continued to report urologic and abnormal symptoms (see Table B.9). Of these, 9 were male, English speaking and relatively young (median age 36). The overall prevalence of these symptoms was less than in 1978 except for an increase in sexual difficulties and paresthesias (see Table B.9). No clear associations between job category, age, or demographic characteristics and disease persistence were seen. Neurological abnormalities (sensorimotor neuropathy and hyperreflexic knee jerks) were observed in three out of ten as confirmed by physical examination. Follow-up neurological examinations and testing for the four subjects that were tested in 1978 revealed that three of the four who had signs of sensory or sensorimotor neuropathy in 1978 were normal 2 years later (see Table B.10). However, signs of sensorimotor neuropathy persisted in one of the three individuals while all three workers still had abnormalities affecting the lower limbs (see Table B.10). These results correlated weakly with the urologic studies that showed clear improvement associated with a reduction in the intensity of urologic symptoms among the four individuals after 2 years (see Table B.11). Compared with the referent group, no significant differences in the nerve conduction tests were observed (see Table B.12).

In summary, persistent symptoms of urinary tract dysfunction, along with some neurological damage, were observed in a small group of workers exposed to the industrial catalyst DMAPN 2 years previously. Their symptoms improved considerably after removal from exposure to the substance but continued improvement ceased. The study authors were unable to identify any individual factor that would account for the persistence of symptoms in this group compared with the vast majority of workers at the plant who recovered without residual effects. No quantitative data with regard to the exposure level are reported in the study, and, therefore, no NOAEL or LOAEL can be identified.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure of animals to DMAPN have been evaluated in one subchronic-duration (i.e., Bachhuber et al., 1955), one chronic-duration (i.e., Pestronk et al., 1979, as cited in Pestronk et al., 1980), and one reproductive study (i.e., Stamler, 1955). These studies provide very limited information.

Subchronic Studies

Bachhuber et al., 1955

Bachhuber et al. (1955) evaluated the subchronic lathyrism toxicity of DMAPN administered to rats in the diet. (Lathyrism is a neurotoxic disease which results from excessive consumption of the pea, *Lathyrus sativus*, and certain related species). The assay was part of a study investigating the lathyrism effects of Beta-aminopropionitrile (BAPN) and related compounds since BAPN is known to be the causative agent in producing skeletal deformities in rats fed *Lathyrus odoratus*. The study authors performed a series of toxicity assays on substances chemically related to BAPN to investigate the relation between the structure and the biological activity. With regard to the DMPAN assay, a group of six Sprague-Dawley rats (sex and age were not provided) was given a synthetic diet (consisting of casein, dried brewer's yeast,

and cerelose) to which DMAPN was added at a concentration of 0.35% for 56 days, corresponding to an average dietary intake of 175 mg/kg-day (as reported in the secondary source IUCLID [2000]; the primary reference did not report the mg/kg-day equivalent). Control rats (five) were given the same synthetic diet for 55−64 days. The animals were observed daily for mortality and body weight was recorded weekly. In the control rats, weight gain was poor and skeletal abnormalities were not observed. Alteration in skeletal deformities, malformation of the femurs, hind limb paralysis, hernias and spontaneous aortic ruptures were assessed. No further information was provided by the study authors on data obtained on this assay. No mortality was seen in animals given DMAPN in the diet at 175 mg/kg-day for 56 days. In addition, no changes in body weight or skeletal alterations were observed. Only one rat showed a presence of bronchopneumonia, which was an unusual observation. Based on the results of the assays on the BAPN-related chemicals, including DMAPN, the study authors stated that if one or two methyl groups are incorporated on the amino group in BAPN, this results in a loss of biological activity. Thus, the lathyrism activity of BAPN is not due solely to the presence of a nitrile group and is greatly influenced by the presence of a reactive amino group. Based on the study design (only one dose was applied), no NOAEL/LOAEL can be determined.

Chronic Studies

Pestronk et al., 1979, as cited in Pestronk et al., 1980

Pestronk et al. (1979, as cited in Pestronk et al., 1980) investigated the long-term effects of DMAPN administered to rats in drinking water. Rats fed 0.5% DMAPN in drinking water (equivalent to 450 mg/kg-day, as reported in the secondary source IUCLID [2000] which cites Keogh, 1983 which cites Pestronk et al., 1980; neither of which report the mg/kg-day equivalents) for 2 to 9 months showed enlarged motor nerve terminals. Electron microscopy showed enlarged distal motor and spindle axons with disordered neurofilaments. No further information was provided in the secondary sources. Due to the lack of information on this study, no NOAEL/LOAEL can be determined.

Developmental Studies

No studies investigating the developmental effect of oral exposure to DMAPN in animals have been identified

Reproductive Studies

Stamler, 1955

In a study investigating the reproductive effects on rats fed *Lathyrus* peas or aminonitriles by Stamler (1955), normal litters (total of 9 litters) were born to female rats (two albino Sprague-Dawley rats) fed a diet containing 0.3% of DMAPN (equivalent to 150 mg/kg-day as reported in the secondary source IUCLID [2000)]; the primary reference did not report the mg/kg-day equivalent) when given beginning the 17th day of pregnancy. No further information was provided on this particular experiment. It was stated in IUCLID (2000) that only three maternal animals were used, and the study was inadequately reported and not carried out in accordance with current guidelines. No NOAEL or LOAEL could be determined.

Carcinogenicity Studies

No oral carcinogenic studies were identified for DMAPN.

Inhalation Exposures

Data on DMAPN-induced toxicity in animals following inhalation exposure are limited to one short-term study (i.e., BASF, 1989, as cited in IUCLID, 2000; see Other Data section below).

Subchronic Studies

No inhalation subchronic studies were identified for DMAPN.

Chronic Studies

No inhalation chronic studies were identified for DMAPN.

Developmental Studies

No inhalation developmental studies were identified for DMAPN.

Reproductive Studies

No inhalation reproductive studies were identified for DMAPN.

Carcinogenicity Studies

No inhalation carcinogenic studies were identified for DMAPN.

Other Studies

Mumtaz et al. (1991b) describe the in vitro and in vivo metabolism of DMAPN, but present no relevant information for the derivation of reference values. Llorens et al. (2011) pose a unifying hypothesis for the neurotoxic effects of nitriles but also do not present information useful for deriving reference values for DMAPN.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

A few studies on genotoxicity, exposures other than oral or inhalation, short-term toxicity and toxicokinetics of DMAPN are available. These are summarized in Tables 3A and 3B.

Table 3A. Summary of DMAPN Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	20−5000 µg/plate	−	−	None	BASF, 1989 (as cited in IUCLID, 2000)
SOS repair induction	ND					
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	ND					
Recombination induction	ND					
Chromosomal aberration	ND					
Chromosomal malsegregation	ND					
Mitotic arrest	ND					
Genotoxicity studies in mammalian cells—in vitro						
Mutation	ND					
Chromosomal aberrations	ND					

Table 3A. Summary of DMAPN Genotoxicity

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					
DNA adducts	ND					
Genotoxicity studies in mammals—in vivo						
Chromosomal aberrations	ND					
Sister chromatid exchange (SCE)	ND					
DNA damage	ND					
DNA adducts	ND					
Mouse biochemical or visible specific locus test	ND					
Dominant lethal	ND					
Genotoxicity studies in subcellular systems						
DNA binding	ND					

[a]Lowest effective dose for positive results, highest dose tested for negative results.
[b]+ = positive, ± = equivocal or weakly positive, − = negative, T = cytotoxicity, NA = not applicable, ND = no data, NDr = Not determined, NR = Not reported, NR/Dr = Not reported, but determined from data

Table 3B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Other toxicity studies (exposures other than oral or inhalation)	Five male rats were administered daily dosage level of 0.01, 0.1, 0.25, 0.5, or 1.0 mL/kg of DMAPN for 2 wk (i.p.). Five male mice were administered daily dosage level of 0.25, 0.5, or 1.0 mL/kg of DMAPN (i.p.) for 2 wk (i.p.).	Death occurred in both mice and rats at the two highest doses (1.0 and 0.5 mL/kg). At 0.01 mL/kg—loss of micturition reflex in rats; at 0.25 mL/kg—tremors, convulsions, and cardiovascular effects.		Gad et al. (1979)
	Rats were administered a mixture of ESN catalyst (95% DMAPN and 5% A-99/bis-dimethylaminoethyl ether) (i.p.) at 0.2 or 2.0 mL/kg. Rats were administered a mixture of ESN catalyst (95% DMAPN and 5% A-99/bis-dimethylaminoethyl ether) by gavage at 0.31 or 0.62 mL/kg for 3 d. In both experiments, the doses were given to the rats twice for one day. The animals were sacrificed on Day 3.	In the i.p. experiment; high dose (2.0 mL/kg) rapidly produced CNS excitation followed by depression and death. In the gavage study, urinary bladder lesions were observed at both doses tested (0.31 and 0.62 mL/kg).	ESN catalyst with DMAPN as the most prominent components is toxic to rats.	Jaeger et al. (1980)
Short-term studies	LD_{50} studies in rats, mice, and rabbits	1305−2600 mg/kg (oral) in rats and 1500 mg/kg (oral) in mice. 1227−1410 mg/kg (dermal) in rabbits, 435−1740 mg/kg (i.p. in rats), and 180 mg/kg (i.v.) in mice.		BASF, undated; Deckert et al., 1982; BASF, 1975; RTECS, undated, Patty, 1962; Smyth et al., 1962; all as cited in IUCLID, 2000 ; Pestronk et al., 1980
	12 rats were administered DMAPN by inhalation for 3−8 hr and 6 rats were administered DMAPN by inhalation for 8 hr	12 rats: No deaths at 3 hr and 1 death at 8 hr; 6 rats: No deaths at 8 hr.		BASF, 1975; Smyth et al., 1962; as cited in IUCLID, 2000

Table 3B. Other Studies

Test	Materials and Methods	Results	Conclusions	References
	5 male Sprague-Dawley rats were administered DMAPN orally at dose level of 350 mg/kg-d, 5 d/wk for 2 wk or 525 mg/kg-d once a day for 2 d.	Decrease in body weight, high water consumption during the first 7 d (2 wk study); kidney effects, increased urea nitrogen, creatinine in plasma, decreased urea nitrogen, creatinine in urine (2 d study).		Mumtaz et al., 1991a
Short-term studies	Rats were exposed to inhaled DMAPN at doses of 0, 0.01, 0.1, or 1 mg/L, 6 hr/d, 5 d/wk, for 2 wk.	No deaths occurred. Decrease in body weight gain and changes of behavior such as reduced fright reactions were observed at the highest dose.		BASF, 1989 as cited in IUCLID, 2000
Metabolism/ toxicokinetic	Male Sprague-Dawley rats were administered 0, 75, 350, or 525 mg/kg DMAPN by gavage and an in vitro study was also done.	Metabolites were identified as beta-aminopropionitrile, cyanide, formaldehyde, and cyanoacetic acid and metabolism occurred in the microsomal fraction of the liver, kidney, and bladder. About 44% of the dose was excreted unchanged in 5 d.	DMAPN is primarily metabolized via the cytochrome P450-dependent mixed function oxidase system.	Mumtaz et al., 1991b
	Rats were administered DMAPN (174 mg/kg) i.p. and an in vitro study was also done.	Thiocyanate was identified in the urine of rats. An in vitro study reported cyanide and formaldehyde as intermediates.		Froines et al., 1985
	Rats and mice were administered orally 0, 175, 350, or 700 mg/kg DMAPN twice on Day 1. Animals were killed at 36 hr posttreatment. In another study, rats were administered 525 mg/kg once daily for 2 d.	An increase in the bladder urine retention with an increase in the DMAPN dosage was observed. In mice, maximal urine retention was observed at 350 mg/kg; at 700 mg/kg urine retention was not observed. Rats excreted about 44% of the unchanged DMAPN and mice excreted about 6% of the unchanged DMAPN. Mice metabolized DMAPN to a higher extent to beta-aminopropionitrile and cyanoacetic acid.	DMAPN-induced urinary retention in rats and mice was time dependent. Mice metabolize DMAPN more than rats.	Mumtaz et al., 1991a

ND = No data

Tests Evaluating Carcinogenicity, Genotoxicity, and/or Mutagenicity

The genotoxic effects of DMAPN were assessed in vitro in *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA 1537—both with and without metabolic activation systems (BASF, 1989, as cited in IUCLID, 2000). Negative results were reported. No other genotoxicity data (either in vitro or in vivo) were identified for DMAPN.

Other Toxicity Studies (Exposures Other Than Oral and Inhalation)

Several studies have examined intraperitoneal (i.p.) exposure to DMAPN in rats and mice. Gad et al. (1979) administered DMAPN at 0.01−1.0 mL/kg, and reported a loss of micturition reflex in rats at 0.01 mL/kg and tremors, convulsions, and cardiovascular effects in rats and mice at 0.25 mL/kg. Jaeger et al. (1980) administered a mixture of 95% DMAPN and 5% A-99/bis dimethylaminoethyl ether to male Holtzman rats at doses of 0.2 or 2.0 mL/kg twice in 1 day. Doses of 2.0 mL/g produced central nervous system excitation, depression, and then death. At 0.2 mL/kg, reduction in motor activity, rapid breathing, and prostration were observed. These signs disappeared in survivors over a period of 10−15 minutes.

Short-term Studies

Several studies have evaluated the acute toxicity of DMAPN in animals following oral, inhalation, i.p., or dermal exposure (BASF, undated; Deckert et al., 1982; BASF, 1975; Patty, 1962; RTECS, undated; Smyth et al., 1962; all as cited in IUCLID, 2000; Pestronk et al., 1980). Two week oral and inhalation animal studies were also identified (Mumtaz et al., 1991a, as cited in IUCLID, 2000; BASF, 1989, as cited in IUCLID, 2000)

Oral LD_{50} values in rats ranged from 1305−2600 mg/kg (BASF, undated; Deckert et al., 1982; BASF, 1975, 1982; RTECS, undated; all as cited in IUCLID, 2000) and an LD_{50} value of 1500 mg/kg was reported in mice (Patty, 1962; RTECS, undated; all as cited in IUCLID, 2000). No mortality was observed when 12 rats were exposed for 3 hours by inhalation to DMAPN, while 1 rat died within 8 hours in this study (BASF, 1975, as cited in IUCLID, 2000). In an additional inhalation study, no mortality was observed when 6 rats were exposed for 8 hours to DMAPN (Smyth et al., 1962, as cited in IUCLID, 2000).

Dermal LD_{50} values in rabbits were reported at 1227 and 1410 mg/kg (Smyth et al., 1962; RTECS, undated; all as cited in IUCLID, 2000 and Pestronk et al., 1980). The i.p. LD_{50} values in rats ranged from 435−1740 mg/kg (BASF, undated; Deckert et al., 1982; BASF, 1975, 1982; all as cited in IUCLID, 2000) and an intravenous (i.v.) LD_{50} value in mice was reported at 180 mg/kg (RTECS, undated; as cited in IUCLID, 2000).

Mumtaz et al. (1991a) administered groups of five male Sprague-Dawley rats 0 or 350 mg/kg DMAPN orally, once a day, 5 days/week, for 2 weeks. Animal weight, water consumption, and urine volume were recorded every 24 hours and morphologic and histologic studies on the liver, bladder, and kidney were done at the end of the 2-week study. Rats who received 350 mg/kg showed a gradual decrease in body weight between Day 6 and 12 and a sharp decrease between Day 12 and 15. Water consumption of rats at 350 mg/kg was slightly—but significantly—higher than controls during the first 7 days and greatly decreased after that and urine volume followed the same pattern. Histological examination of the bladder showed submucosal and subserosal edema, severe congestion of submucosal capillaries, and petechial hemorrhages. No quantitative data were available in the 2-week study. In another study by

Mumtaz et al. (1991a), male Sprague-Dawley rats were administered 525 mg/kg DMAPN once a day for 2 days. Hydronephrosis in the kidney, characterized by marked dilation of the renal pelvis with blunting of the renal papilla, was observed. Plasma levels of urea nitrogen and creatinine were significantly increased above control values, and urinary levels of urea nitrogen and creatinine were decreased below control values.

BASF (1989), an unpublished study, as cited in IUCLID (2000), documented the effect of short-term inhalation of DMAPN to rats. The study authors exposed rats (number, sex and strain not provided) to 0, 0.01, 0.1, or 1 mg/L DMAPN for 6 hours per day, 5 days per week, for 2 weeks. No further information with regard to the data obtained was reported in the secondary source. IUCLID (2000) reported that no deaths were observed during the treatment and a decrease in body weight gain and changes of behavior such as reduced fright reactions were observed at the highest dose.

Toxicokinetics

Limited information is available on the toxicokinetics of DMAPN. Mumtaz et al. (1991b) administered 0, 75, 350, or 525 mg/kg DMAPN by gavage to male Sprague-Dawley rats and β-aminopropionitrile was identified as a metabolite. About 44% of the dose of DMAPN was excreted unchanged in rats after 5 days, and peak excretion occurred during the first 12 hours. The excretion of β-aminopropionitrile increased with time until 24 hours after dosing. In the in vitro part of this study, DMAPN was shown to be metabolized to cyanide, formaldehyde, and cyanoacetic acid. Metabolism took place in the microsomal fraction of the liver, kidney, and urinary bladder and was dependent on the cytochrome P450 mixed function oxidase system. Froines et al. (1985) reported an in vivo study in which rats were administered DMAPN by i.p. exposure and thiocyanate was found in the urine and an in vitro study on the metabolism of DMAPN which demonstrated the generation of cyanide and formaldehyde. In Mumtaz et al. (1991a), rats and mice were administered 0, 175, 350, or 700 mg/kg DMAPN and in a time-course study, male rats were administered 525 mg/kg. The time-course study showed that rats excreted about 44% of unchanged DMAPN and mice excreted only about 6% of the dose of DMAPN.

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 present a summary of noncancer and cancer reference values, respectively. IRIS data are indicated in the table, if available.

Table 4. Summary of Reference Values for 3-(N,N-dimethylamino)propionitrile (CASRN 1738-25-6)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
*S*ubchronic p-RfD (mg/kg-d)	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Chronic p-RfD (mg/kg-d)	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Subchronic p-RfC (mg/m^3)	NDr	NDr	NDr	NDr	NDr	NDr	NDr
Chronic p-RfC (mg/m^3)	NDr	NDr	NDr	NDr	NDr	NDr	NDr

NDr = Not determinable

Table 5. Summary of Cancer Values for 3-(N,N-dimethylamino)propionitrile (CASRN 1738-25-6)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	NDr	NDr	NDr	NDr
p-IUR	NDr	NDr	NDr	NDr

NDr = Not determinable

DERIVATION OF ORAL REFERENCE DOSES

No reports of human ingestion of DMAPN were identified. The available oral toxicity studies in laboratory animals are too limited in scope to be used to identify NOAEL or LOAEL values for DMAPN as only one dose level was employed in each study (Bachhuber et al., 1955; Pestronk et al., 1979, as cited in Pestronk et al., 1980; Stamler, 1955). Both Stamler (1955) and Bachhuber et al. (1955) studies were reported in very limited detail with respect to the experimental design (whether it was compliant with GLP), endpoints measured, and number of animals. Also no DMAPN treatment-related effects were observed in these studies. With regard to Pestronk et al. (1979, as cited in Pestronk et al., 1980), the study was unpublished and the results were briefly reported in the secondary sources (Pestronk et al., 1980; Keogh, 1983; IUCLID, 2000). Based on this, the available studies on the oral toxicity of DMAPN in animals are not sufficient for deriving RfD or screening RfD values for DMAPN.

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

A subchronic p-RfD was not derived for DMAPN due to inadequate data.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

A chronic p-RfD was not derived for DMAPN due to inadequate data.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

The available data concerning health effects in humans following inhalation exposure to DMAPN are derived from workers exposed occupationally to the catalyst ESN-NIAX, which consists approximately 95% dimethylaminopropionitrile in the period of 1977−1978 at two polyurethane foam-manufacturing plants in the United States (Keogh et al., 1980; Kreiss et al., 1980). Workers were thought to have experienced dermal (skin absorption) as well as inhalation exposure. Data taken from these studies showed that workers exposed for up to 6 months to unknown concentrations of this compound experienced urinary problems, impotence, and peripheral neuropathies. The urinary problems consisted of difficulty in initiating urination, decreased force of urine stream, urgency, and dysuria while peripheral neuropathies included paresthesia in feet and hands. Urinary retention was the predominant symptom in exposed workers. Impotence and decreased libido were the next most remarkable findings. These symptoms are largely reversible and disappeared once exposure was eliminated. Upon follow-up of the exposed workers 2 years after the end of the exposure, a majority of the symptomatic workers were normal and showed full recovery, although some individuals had persistent symptoms of difficulty in urinating and sexual dysfunction (Baker et al., 1981).

Because levels of exposure to DMAPN were not provided in these studies, NOAELs or LOAELs could not be established for the observed urological and neurological effects in the occupationally exposed workers. Accordingly, health effects data in these workers are unsuitable for derivation of an RfC.

Animal studies on the toxicity of DMAPN following inhalation exposure were limited to one short-term study (2 weeks). The study was unpublished and the results were briefly reported in the secondary source (IUCLID, 2000) with no adequate information on the experimental design, endpoints measured, number of animals and GLP status were provided. Thus, this study is considered inadequate for derivation of an RfC.

Derivation of Subchronic Provisional RfC (Subchronic p-RfC)

A subchronic p-RfC was not derived for DMAPN due to inadequate data.

Derivation of Chronic Provisional RfC (Chronic p-RfC)

A chronic p-RfC was not derived for DMAPN due to inadequate data.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTION

The U.S. EPA has not assigned a carcinogenicity classification for DMAPN under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005). In accordance with these guidelines, data are inadequate for an assessment of the human carcinogenic potential of DMAPN (see Table 6). This WOE determination is based on the fact that no adequate data, such as reliable human epidemiological studies or well-conducted, long-term animal studies are available to perform a carcinogenicity assessment for DMAPN.

Table 6 identifies the cancer WOE descriptor for DMAPN.

Table 6. Cancer WOE Descriptor for 3-(N,N-dimethylamino)propionitrile.

Possible WOE Descriptor	Designation	Route of Entry (Oral, Inhalation, or Both)	Comments
"Carcinogenic to Humans"	NA	NA	There are no human data available.
"Likely to Be Carcinogenic to Humans"	NA	NA	There is not enough evidence to support this statement.
"Suggestive Evidence of Carcinogenic Potential"	NA	NA	There is not enough evidence to support this statement.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**NA**	**No adequate information available to assess the carcinogenic potential by the inhalation or oral routes of exposure.**
"Not Likely to Be Carcinogenic to Humans"	NA	NA	There is not enough evidence to support this statement.

NA = not applicable

MODE-OF-ACTION (MOA) DISCUSSION

The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005) define MOA as "A sequence of key events and processes starting with the interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in cancer formation"

(p. 10). Examples of possible modes of carcinogenic action include mutagenic, mitogenic, antiapoptotic (inhibition of programmed cell death), cytotoxic with reparative cell proliferation, and immune suppression.

There are no studies available that examine the mode of carcinogenic activity of DMAPN.

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

No p-OSF can be derived due to a lack of carcinogenicity data.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

No p-IUR can be derived due to a lack of carcinogenicity data.

APPENDIX A. PROVISIONAL SCREENING VALUES

Appendix A is not applicable.

APPENDIX B. DATA TABLES

Table B.1. Prevalence of Neurologic and Urologic Symptoms Reported by Workers in Polyurethane Manufacturing Plants A and B[a]

Symptoms	Plant A (*n* = 141) Average Age, 31.6 yr		Plant B (*n* = 75) Average Age, 34.6 yr		*P**
	Number	Percent	Number	Percent	
Urinary retention	85	60	6	8	<0.01
Urinary frequency	2	1	1	1	NS
Impotence or decreased libido	49	35	6	8	<0.01
Constipation	13	9	3	4	NS
Insomnia	44	31	3	4	<0.01
Irritability	71	50	16	21	<0.01
Muscle weakness	32	22	4	5	<0.01
Paresthesias	37	26	1	1	<0.01
Headaches	40	28	14	19	NS

[a]Keogh et al. (1980).
*Determined by χ^2.
NS = not specified

Table B.2. Prevalence Of Postvoid Residual On Intravenous Pyelograms (IVPs) Among Workers Working in both Polyurethane Manufacturing Plants[a]

Description	Number
Workers with symptoms of urinary retention	91
Workers who had IVPs (*n* = 65)	
with Normal IVP	48
with IVP showing postvoid retention of contrast material	17
Workers with IVP showing postvoid retention of contrast material (*n* = 17)	
Large residual	3
Moderate residual	9
Minimal residual	5

[a]Keogh et al. (1980).

Table B.3. Number of Workers* Reporting Symptoms at Plant A with Regard to Their Working Area[a]

Work Area, No.	Average Age (yr)	No. (%) of Workers with Symptoms				
		Urinary Retention	Muscle Weakness	Paresthesias	Insomnia	Sexual Dysfunction
Bridge (*n* = 7)	31.3	5 (71)	1 (14)	2 (28)	2 (28)	5 (71)
Section cutting[b] (*n* = 7)	31.6	6 (85)	0 (0)	3 (42)	3 (42)	4 (57)
Hole-boring back room[b] (*n* = 13)	33.5	10 (76)	4 (31)	4 (31)	5 (38)	4 (31)
Material-handling back room[b] (*n* = 7)	24.5	3 (42)	1 (14)	0 (0)	1 (14)	0 (0)
Peeling[b] (*n* = 63)	30.5	39 (61)	15 (23)	18 (29)	17 (26)	21 (33)
Quality control peeling[b] (*n* = 5)	33.4	4 (80)	2 (40)	2 (40)	3 (60)	3 (60)
Compressing[b] (*n* = 5)	31.4	1 (20)	1 (20)	0 (0)	0 (0)	1 (20)
Shipping (*n* = 9)	26.4	5 (55)	1 (18)	1 (18)	3 (33)	3 (33)
Maintenance (*n* = 6)	37.6	3 (50)	3 (50)	2 (33)	3 (50)	0 (0)
Scrap baling (*n* = 3)	39.0	1 (33)	0 (0)	0 (0)	0 (0)	0 (0)
Supervisory and clerical (*n* = 16)	36.5	7 (43)	4 (25)	5 (31)	7 (43)	6 (37)

[a]Keogh et al. (1980).
*Total number of workers reported symptoms at Plant A is 141.
*Areas of highest exposure

Table B.4. Prevalence of Other Symptoms Reported by Workers in Polyurethane Manufacturing Plants A and B[a]

Symptoms	Plant A (*n* = 141) Average Age, 31.6 yr		Plant B (*n* = 75) Average Age, 34.6 yr		*P**
	Number	Percent	Number	Percent	
Visual disturbances	113	80	36	48	<0.01
Dermatitis	92	65	32	43	<0.01
Bad taste	58	41	17	23	<0.01
Sore throat	55	39	14	19	<0.01
Cough	42	30	21	28	NS
Wheezing	64	45	21	28	<0.02
Chest tightness	79	56	23	31	<0.01

[a]Keogh et al. (1980).
*Determined by χ^2.
NS = not specified

Table B.5. The Prevalence of Urinary Tract Symptoms Reported by Workers in Polyurethane Manufacturing Plant (Massachusetts, 1978)[a,b]

Symptoms	Number of Cases[c] (*n* = 104)	Number of Noncases[d] (*n* = 104)
Increased duration	102	1
Hesitance	98	0
Need to strain	98	0
Decreased stream	94	4
Subjective retention	70	4
Dysuria	70	13
Abdominal discomfort	61	6
Urgency	47	3
Decreased frequency	47	1
Increased frequency	44	23
Urethral discharge	19/84	2/80
Nocturia	15	10
Gross hematuria	12	4

[a]Kreiss et al. (1980).
[b]Total number of workers reported their symptoms was 208.
[c]Case as defined by the study authors is an employee who experienced any two of the four symptoms of bladder dysfunction (hesitancy, need to strain, decreased stream, and increased duration of urination). Of the 208, 104 employees met this case definition and are considered as cases.
[d]Noncase: an employee who did not experience any two of the four symptoms of bladder dysfunction. Of the 208, 104 employees were identified as noncases.

Table B.6. Results of the Neurological Examinations of Eight Cases of Bladder Dysfunction Identified in Polyurethane Foam Manufacturing Plant (Massachusetts, 1978)[a]

Age/Sex	Sensory Abnormalities	Motor Abnormalities	Clinical Impression
26/M	Numbness; decreased vibration, both lower extremities	Hyporeflexia; absent ankle jerks	Sensorimotor neuropathy
45/M	Decreased vibration; proprioception; light touch in toes	Decreased ankle jerks	Sensorimotor neuropathy
23/M	Decreased vibration, left lower extremity	None	Probably normal
30/M	Decreased proprioception, lower extremities	None	Sensory abnormality
42/M	Numbness; decreased light-touch, pinprick, both lower extremities	None	Sensory neuropathy
29/F	Minimal decreased vibration, all limbs distally	None	Sensory neuropathy
37/F	Mid hyperesthesia, feet	None	Sensory abnormality
24/F	Decreased light-touch, pinprick, both lower extremities distally	None	Sensory neuropathy

[a]Kreiss et al. (1980).

Table B.7. Results of the Neurological Testing of Eight Cases of Bladder Dysfunction Identified in Polyurethane Foam Manufacturing Plant (Massachusetts, 1978)[a]

Age/Sex	Electrodiagnostic Neurological Testing					
	Peroneal Motor Nerve				Sural Nerve	
	Motor Velocity (m/s)	Distal Latency (m/s)	Amplitude (mv)		Sensory Velocity (m/s)	Amplitude (mv)
			Ankle	Knee		
26/M	43.4	6.8*	0.65*	0.65*	32.5*	21.0
45/M	47.3	4.3	4.0	4.0	35.0*	3.5*
23/M	48.6	4.6	2.8	2.8	46.6	14.0
30/M	44.6, 46.0	5.5	5.6	5.0	38.8*	6.0
42/M	49.5	4.0	3.0	3.0	43.5	NR
29/F	63.0	5.0	3.5	3.5	48.8	NR
37/F	58.5	3.9	9.0	7.5	46.0	25
24/F	54.6	4.0	7.5	7.5	56.0	33
Normal range	38−59	3−6.5	2.2−14.8		40−54.7	6−42

[a]Kreiss et al. (1980).
*Outside the normal range.
NR = Not reported

Table B.8. Results of the Urological Testing of Eight Cases of Bladder Dysfunction Identified in Polyurethane Foam Manufacturing Plant (Massachusetts, 1978)[a]

Age/Sex	Electrodiagnostic Testing		Cystometrogram		Comments
	Sacral Latency (ms)	Sphincter Electromyogram	First Sensation of Filling (mL)	Detrusor Reflex (mL)	
26/M	43*	Increased polyphasia	100	Absent	Positive bethanecol test
45/M	120*	Increased polyphasia	175*	Absent	Negative bethanecol test; impotence; testicular discomfort, 800-mL urinary retention
23/M	38	Normal	50	Absent	NC
30/M	38	Normal	50	Absent	Negative bethanecol test
42/M	50*	Normal	80	Present at 275	Impotence; testicular discomfort
29/F	37	Normal	100	Absent	Negative bethanecol test
37/F	NR	Normal	150*	Present at 450	NC
24/F	35, high threshold	Normal	300*	Present at 425	NC
Normal range	<42		≤125		

[a]Kreiss et al. (1980).
*Outside the normal range.
NR = Not reported; NC = No comments provided

Table B.9. Prevalence of Symptoms Reported by Late Improvers in 2 Years Follow Up Study[a]

Symptoms	Number with Symptoms (*n* = 11)	
	1978	1980
Urinary hesitancy	11	7
Need to strain to urinate	11	5
Incomplete bladder emptying	9	6
Sexual difficulties	3	5
Paresthesias	3	6
Dry mouth	5	1
Weakness in arms/legs	5	5

[a]Baker et al. (1981).

Table B.10. Results of the Neurological Testing of Dimethylaminopropionitrile-Exposed Workers in 1978 and 1980[a]

Age/Sex	Electrodiagnostic Neurological Testing					
	Peroneal Motor Nerve				Sural nerve	
	Motor Velocity (m/s)	Distal Latency (m/s)	Amplitude (mv)		Sensory Velocity (m/s)	Amplitude (mv)
			Ankle	Knee		
47/M						
1978	47.3	4.3	4.0	4.0	35*	3.5*
1980	46.0	8.5*	4.0	3.0	Absent	Absent|*
29/M						
1978	43.4	6.8*	0.6*	0.6*	32.5*	21.0
1980	45.0	6.4	0.4*	0.4*	46.0	11.0
32/M						
1978	46.0	5.5	5.6	5.0	38.8*	6.0
1980	44.2	5.0	6.0	6.0	38.0*	12.0
44/M						
1978	49.5	4.0	3.0	3.0	43.5	--
1980	50.8	4.2	2.0*	2.0*	44.8	25.0
Normal range	38−59	3−6.5	2.2−14.8		40−54.7	6−42

[a]Baker et al. (1981).
*Outside the normal range.

Table B.11. Results of the Urological Testing of Dimethylaminopropionitrile-Exposed Workers in 1978 and 1980[a]

Age/Sex	Electrodiagnostic testing		Cystometrogram	
	Sacral Latency (ms)	**Sphincter Electromyogram**	**First Sensation of Filling (mL)**	**Detrusor Reflex (mL)**
47/M				
1978	120*	Increased polyphasia	175*	Absent
1980	38	Normal	Not done	Not done
29/M				
1978	43*	Increased polyphasia	100	Absent
1980	33	Normal	200*	700
32/M				
1978	38	Normal	50	Absent
1980	28	Normal	250*	450
44/M				
1978	50	Normal	80	275
1980	35.2	Normal	100	325
Normal range	<42		≤125	

[a]Baker et al. (1981).
*Outside the normal range.

Table B.12. Results of the Nerve Conducting Study on Workers Exposed to Dimethylaminopropionitrile and Referents[a]

Group	Nerve					
	Peroneal Motor Nerve				Sural Nerve	
	Motor Velocity (m/s)	Distal Latency (m/s)	Amplitude (mv)		Sensory Velocity (m/s)	Amplitude (mv)
			Ankle	Knee		
Exposed (*n* = 10)						
Mean	49.44	4.73	4.04	3.78	40.58	18.1
SD	4.60	1.60	2.03	2.15	14.57	12.25
Referents (*n* = 29)						
Mean	48.87	4.17	5.69	5.33	47.75	13.88
SD	4.34	0.86	2.39	2.33	5.12	6.58
***t*-Value**	0.033	1.06	1.81[b]	1.91[b]	1.22	1.09

[a]Baker et al. (1981).
[b]$p < 0.05$, one-tailed *t*-test.

APPENDIX C. BMD OUTPUTS

Appendix C is not applicable.

APPENDIX D. REFERENCES

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