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Provisional Peer Reviewed Toxicity Values for

Adiponitrile
(CASRN 111-69-3)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
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

10-27-2005

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR ADIPONITRILE (CASRN 111-69-3)

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 Headquarters 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

Adiponitrile (CASRN 111-69-3) is an aliphatic dinitrile with the empirical formula of $CN-(CH_2)_4-CN$. It is a colorless liquid at room temperature with no distinctive odor; and is used in the manufacture of hexamethylenediamine, a precursor of Nylon 66 (U.S. EPA, 1987).

No RfD, RfC, or cancer assessment for adiponitrile is available in the HEAST (U.S. EPA, 1997). The source document for the HEAST, the Health and Environmental Effects Document (HEED) for Adiponitrile (U.S. EPA, 1987), concluded that the data were inadequate for a quantitative risk assessment and assigned adiponitrile to cancer weight-of evidence classification D based on lack of human and animal data. The group D assessment for carcinogenicity of adiponitrile is available on IRIS (U.S. EPA, 2005a). No RfD or RfC for adiponitrile is included on IRIS (U.S. EPA, 2005a) or the Drinking Water Standards and Health Advisories list (U.S.

EPA, 2002). The HEED is the only relevant document included in the Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994a). ATSDR (2003) has not produced a toxicological profile for adiponitrile and no Environmental Health Criteria Document is available (WHO, 2003). Neither NTP (2003) or IARC (2003) has assessed the carcinogenicity of adiponitrile. ACGIH (2003) recommended a threshold limit value - time weighted average (TLV-TWA) of 2 ppm (8 mg/m^3) for adiponitrile based on irregular respiration reported in rats exposed to vaporized adiponitrile for 2 weeks at concentrations ranging from 7 to 68 ppm (Smith and Kennedy, 1982). NIOSH (2003) recommended a relative exposure level - time weighted average (REL-TWA) of 4 ppm (18 mg/m^3) based on the comparative toxicity of isobutyronitrile and adiponitrile in animals in order to minimize the potential risk for respiratory and circulatory disturbances in exposed workers caused by hydrocyanic reactions of the nitrile group in adiponitrile upon absorption into the mammalian system (Lewis, 1999). OSHA (2003) has not established an occupational exposure limit for adiponitrile. Literature searches were conducted for the period from 1986 through 2003 for studies relevant to the derivation of provisional toxicity values for adiponitrile. Databases searched included: TOXLINE (supplemented with BIOSIS and NTIS updates), MEDLINE, CANCERLIT, TSCATS, RTECS, CCRIS, DART, EMIC/ EMICBACK, HSDB, and GENETOX. Additional literature searches were conducted by NCEA-Cincinnati from 2003 through December 2004 by using MEDLINE, TOXLINE, Chemical and Biological Abstracts databases.

REVIEW OF PERTINENT DATA

Human Studies

Accidental poisoning of an 18 year old worker occurred after he drank a few milliliters of adiponitrile. About 20 minutes after ingestion, his symptoms included vomiting, tightness in the chest, headache, profound weakness with difficulty standing, and vertigo. Upon medical examination at the company infirmary, he was observed to be cyanotic and exhibited respiratory difficulties, tachycardia, and low blood pressure. His pupils were dilated and barely responsive to light. Tonic-clonic contraction of the limbs and facial muscles and mental confusion were reported. The patient was hospitalized and recovered completely after medical treatments with sodium thiosulfate, a cyanide antagonist (Ghiringhelli, 1955).

Zeller et al. (1969) reported seven cases of skin irritation in workers dermally exposed to adiponitrile. Mild skin irritation and inflammation developed in six of the seven exposed workers within 15 minutes of exposure. The seventh worker experienced extensive damage to the skin of his foot after an adiponitrile spill drenched his shoe. His injury required surgical treatment and he was incapacitated for 117 days.

Nylon workers exposed to adiponitrile and hexamethylenediamine for 2-3 years showed a tendency for hyperchromic anemia of the hemolytic type and slight leukopenia (Ceresa, 1948a). Ceresa (1948b) and Ceresa and DeBlasis (1950) attributed these effects to exposure to both adiponitrile and hexamethylenediamine. These studies are not useful for hazard identification or dose-response analysis for adiponitrile, because exposure was to a mixture of chemicals, and no quantitative exposure data were available.

Animal Studies

Smith and Kennedy (1982) exposed groups of 10 young adult male Charles River CD rats for 4 hours to one of 10 concentrations of mixtures of adiponitrile vapors and aerosols ranging from 0.25 to 3.03 mg/L (250 to 3030 mg/m^3) . Rats were observed for up to 14 days following exposure. During exposure, rats displayed labored breathing, and at concentrations $\geq$710 mg/m^3, some rats experienced lethargy, salivation, and convulsions. Deaths occurred within 4 days of cessation of exposure at concentrations $\geq$710 mg/m^3. The actual range of exposures was highly variable and yielded a nonlinear dose response which the authors attributed to the difficulty experienced in generating and maintaining an atmosphere of adiponitrile with a constant vapor/aerosol ratio. An LC_{50} of 1710 mg/m^3 was estimated from these experiments with a 95% confidence interval of 870-2660 mg/m^3.

Smith and Kennedy (1982) then exposed groups of 10 male Charles River CD rats by inhalation in whole-body exposure chambers to adiponitrile at average concentrations of 0, 0.031, 0.095 or 0.268 mg/L (0, 31, 95 or 268 mg/m^3) (6 hours/day, 5 days/week) for 2 weeks. These exposure levels were selected based on the results of the acute inhalation study discussed above. Test atmospheres were designed to be generated as vapors, but the authors reported that aerosols also "may have been present in the exposure chambers." After the ninth exposure, blood and urine were collected for analyses. Following the tenth exposure, 5 rats per exposure group were sacrificed, and comprehensive histological examinations were conducted. Tissues examined histologically included the heart, kidneys, liver, lungs, spleen, testis, thymus, adrenal glands, sternal bone marrow, brain, cecum, colon, duodenum, ear, epididymides, eyes, mediastinal tissues, pancreas, skin, stomach, thyroids and trachea. The remaining rats were allowed to recover for 14 days prior to sacrifice for histologic examinations.

In the 2-week exposure study, rats exposed to adiponitrile exhibited slight to mild irregular breathing and mild salivation during exposure, but no incidence data on these effects were provided in the published report. All rats survived the exposure period (Smith and Kennedy, 1982). Mean body weights in the low- (31 mg/m^3) and mid-exposure (95 mg/m^3) groups after 1 and 2 weeks of exposure were within 95% of the control mean. In the high-exposure group (268 mg/m^3), mean body weights were decreased, compared with control values, by 10% and 6% after 1 and 2 weeks of exposure, respectively, though these decreases were not statistically significant. After 2 weeks of exposure, small, but statistically significant, decreases

in mean red blood cell count and hemoglobin concentration were measured, compared with control values, for the groups exposed to 31 mg/m^3 (4% and 3% decreases) or 268 mg/m^3 (6% and 5% decreases), but not in the 95 mg/m^3 group. Although the red blood cell counts and hemoglobin concentrations of the rats exposed to 31 mg/m^3 were statistically significantly lower than those of the controls, the measurements on the individual rats were within the normal range established for this rat strain (Smith and Kennedy, 1982). The highest exposure group also showed, relative to control values, increased plasma glucose (236%) and blood urea nitrogen (20%) concentrations, and increased urine osmolality (44%). Histological examination of tissues from animals sacrificed at the end of the 2-week exposure period revealed no differences in frequency or severity of lesions in exposed rats compared with control rats. Fourteen days post exposure, no statistically significant differences in clinical pathology determinations were found between exposed and control rats. Due to the questionable adversity of the effects on respiration and salivation qualitatively reported in the study, the results presented by Smith and Kennedy (1982) are consistent with the designation of 268 mg/m^3, as a minimal LOAEL and 95 mg/m^3 as a NOAEL for small decreases in body weight (6-10% decrease compared with control) and small decreases in red blood cell count (6% decrease) and hemoglobin concentration (5% decrease) in Charles River CD rats exposed for 2 weeks.

Short et al. (1990) conducted studies of the short term (4-week) toxicity, subchronic (13-week) toxicity, and reproductive toxicity of adiponitrile in rats following inhalation exposure in whole-body chambers to aerosol/vapor mixtures. In the short term phase of the experiment, groups of 18 male and 18 female Charles River CD rats were exposed to adiponitrile (purity $\geq$99%) at mean analytical concentrations of 0, 64, 114 or 493 mg/m^3 for 4 weeks (6 hours/day, 5 days/week). The test atmosphere was generated as an aerosol, with a mass medium aerodynamic diometer (MMAD) of 3-4 µm. However, based on comparison of analytical and gravimetric concentrations, the researchers suggested that the low- and mid-exposures (64 and 114 mg/m^3) were mostly vapors. In the subchronic phase, groups of 15 male and 15 female CD rats were exposed to mean analytical concentrations of 0, 13, 31 or 99 mg/m^3 for 6 hours/day, 5 days/week for 13 weeks. For this experiment, the researchers reported an MMAD of 3.5-4.2 µm, again with the caveat that a significant fraction of the material was present as vapor in the low- and mid-exposure (13 and 31 mg/m^3) groups.

In both the 4- and 13-week studies, animals were observed twice daily and weighed weekly (Short et al., 1990). Blood samples were collected from the periorbital sinus of the eye from the rats exposed for 4 weeks or the posterior vena cava from the rats exposed for13 weeks prior to sacrifice for hematological and blood chemistry determinations. At necropsy, the following organs weights were recorded: adrenals, testes with epididymis, heart, kidneys, liver, pituitary and spleen. A histopathological examination was conducted on a comprehensive set of tissues (abdominal aorta, adrenals, bone and bone marrow, brain, esophagus, eyes with optic nerve, ovaries, testes with epididymides, heart, intestine, kidneys, liver, lung, lymph node, mammary gland, nasal turbinates, pancreas, pituitary, prostate, salivary gland, sciatic nerve,

skeletal muscle, skin, spinal cord, spleen, stomach, thymus, trachea, thyroid/parathyroid, urinary bladder, uterus) and gross lesions.

In the short term study, 100% of males and 50% of females in the high exposure group (493 mg/m^3) died during the first week (Short et al., 1990). Mortality did not occur at lower exposure levels. The study authors did not attribute the deaths to any specific cause. Body weights in surviving high-exposure females were reduced by about 10% compared with controls. Surviving high-exposure females showed small, but statistically significant ($p<0.05$), differences from control in mean values for several red blood cell parameters, which were not apparent at the lower exposure levels: reduced red cell count (9% decrease), hematocrit (2% decrease), hemoglobin concentration (9% decrease) and mean corpuscular hemoglobin concentration (4% decrease), and increased mean corpuscular volume (11% increase). Males in the mid-exposure group (114 mg/m^3) had a statistically significant ($p<0.05$) reduction in hemoglobin concentration (7% decrease) and mean corpuscular hemoglobin (3% decrease); no hematological data were available for males in the high-exposure group, as they all died. The only reported histopathological finding in mid- and surviving high-exposure rats was an excessive presence of hemosiderin-like pigment and hemopoiesis in splenic tissue, but incidences of rats with these changes were not reported. The severity of the splenic changes were reported as slight to moderate at the high concentration, and slight at the mid concentration. In summary, the short term study identified a FEL for early mortalities in male and females at 493 mg/m^3, a minimal LOAEL of 114 mg/m^3 for small, but statistically significant ($p<0.05$), changes in hematological parameters indicative of slight anemia and slight to moderate hemosiderin-like pigmentation and hemopoiesis in splenic tissues, and a NOAEL of 64 mg/m^3 in Charles River CD rats exposed by inhalation for up to 4 weeks (6 hours/day, 5 days/week).

In the subchronic-duration study, no mortality occurred in Charles River CD rats exposed to adiponitrile concentrations up to 99 mg/m^3 for 13 weeks (Short et al., 1990). Body weights and weight gains of treated animals were comparable to control values throughout exposure. Compared with control values, females of the high-exposure group (99 mg/m^3) had a statistically significant ($p<0.05$) reduced red cell count (7% decrease), hematocrit (6% decrease), and hemoglobin concentration (7% decrease) and males showed an increased (2%) mean corpuscular hemoglobin concentration. No statistically significant differences were found between the mean hematological values for the mid- (31 mg/m^3) and low- (13 mg/m^3) exposure groups and control values. No treatment-related histopathologic changes were reported to have been found in rats exposed to adiponitrile for 13 weeks. The changes observed in the spleens of animals in the short term experiment were not seen in the rats subchronically exposed to adiponitrile. In summary, the subchronic-duration study identified 99 mg/m^3 as a LOAEL and 31 mg/m^3 as a NOAEL for small, but statistically significant ($p<0.05$), changes in hematological parameters indicative of slight anemia in female Charles River CD rats exposed by inhalation (6 hours/day, 5 days/week) to adiponitrile for up to 13 weeks. Histopathological examinations of a

comprehensive set of tissues and measurement of hematologic and blood chemistry parameters revealed no other exposure-related effects.

In the fertility assessment study, Short et al. (1990) evaluated the outcome of pregnancies resulting from the mating of unexposed rats with rats exposed to adiponitrile. The study group consisted of 12 males and 24 females per group. Prior to mating, the males were exposed for at least 10 weeks, 6 hours/day, 5 days/week to mean analytical concentrations of 0, 13, 31 or 99 mg/m^3, whereas the females were exposed for 3 weeks, 6 hours/day, 7 days/week to mean analytical concentrations of 0, 13, 32 or 104 mg/m^3. Treated males were mated with 3 untreated females over the course of 5 days or until evidence of mating was observed. Untreated females were sacrificed at mid- gestation and examined for number of implantation sites, resorptions, live implantations, and corpora lutea. Treatments for males were discontinued the day before sacrifice. Gross necropsy was performed on all treated males. Treated females were mated with untreated males over a 7 day period or until evidence of mating was observed. All exposure sessions ended after mating. Treated females were sacrificed at mid-gestation and examined for number of implantation sites, resorptions, live implantations, and corpora lutea.

Exposure to adiponitrile did not affect fertility in males exposed to up to 99 mg/m^3 and mated with untreated females, or in females exposed up to 104 mg/m^3 and mated with untreated males (Short et al., 1990). In the low-dose group (13 mg/m^3), 2 of the 12 males were judged nonfertile, and there was an increased preimplantation loss. The authors concluded these findings were not treatment related because all males exposed to higher concentrations of adiponitrile were fertile, no increase in preimplantation loss was seen at higher exposure levels, no dose-related responses were observed, and there was no histopathological evidence of adverse effects to male reproductive organs. In summary, no significant effects on fertility were found in male Charles River CD rats exposed to up to 99 mg/m^3 adiponitrile for 10 weeks (6 hours/day, 5 days/week) prior to mating, or in female Charles River CD rats exposed to up to 104 mg/m^3 for 3 weeks (6 hours/day, 7 days/week) prior to mating.

In an unpublished 4-week inhalation toxicity study, 4 groups of 18 male and 18 female Charles River CD rats [Crl:COBS®(CD)(SD)®BR] were exposed in whole-body chambers to atmospheres containing both aerosol and vapor of adiponitrile for 6 hours/day, 5 days/week for 4 weeks (Monsanto, 1984). This study appears to be a precursor study to the studies reported by Short et al. (1990), although the results were not mentioned in the published report. Average chamber concentrations were 0, 0.10, 0.26, or 0.95 mg adiponitrile/L air (0, 100, 260 or 950 mg/m^3). Although some fraction of the exposure atmosphere was present as vapor, the atmosphere was generated as an aerosol with an MMAD of 2-3 μm. All male and female rats exposed to the middle and high concentrations either died or were sacrificed *in extremis* within the first 8 days of the study; 14/18 males from the low-exposure (100 mg/m^3) group died before the end of the study. All female rats survived at the low concentration. The rats in all treated groups showed blood encrustation about the nares, rapid breathing and generalized paralysis.

Rats from the mid- and high-exposure groups also experienced convulsions. Body weight data were only available for the control and low-concentration groups. Statistically significant decreases in mean body weight were measured in the 100 mg/m^3 males at several intervals throughout exposure (ranging from 10% to 16% decreased compared with controls). In 100-mg/m^3 females, body weight was significantly ($p<0.05$) lower than control values (4% decreased) only at the end of the last week of exposure.

Many rats died in the inhalation chambers (Monsanto, 1984). When they were removed at the end of the 6-hour exposure period, many tissues were too autolyzed for meaningful autopsy/necropsy. At necropsy, a comprehensive set of tissues (see Short et al., 1990) were collected (when available) from up to 10 rats with non-autolyzed tissues per sex per group and processed for histologic examination. The number of rats available for autopsy were 18, 5, 7 and 16 for males in the control through high-concentration groups, respectively, and 18, 18, 5 and 3 for the female groups. The only autopsy observations that appeared to be related to exposure were hemorrhagic brains (respective incidences for control through high-concentration groups were 1/18, 0/18, 0/5, and 2/3 for females and 0/18, 1/5, 4/7, and 4/16 for males). Hemorrhagic spinal cords were also seen in 2/16 males in the highest exposure group, but not in any other group of control or exposed rats. Only the male and female control groups and the low-concentration (100 mg/m^3) female group contained sufficient numbers of rats with tissues suitable for histologic examination (i.e., 10 rats per group). The other groups had no suitable sample or only a few suitable samples of each tissue for histologic examination due to autolysis. The only apparent exposure-related lesions in the 100 mg/m^3 females were splenic hematopoiesis (3/10 versus 0/10 in controls) and hemosiderosis (4/10 versus 0/10 in controls). Blood and urine samples were collected after 4 weeks from up to 10 surviving rats of each sex in only the control (10 males and 10 females) and 100 mg/m^3 (4 males and 10 females) groups. Statistically significant ($p<0.05$) findings, compared with controls, were restricted to increased levels of thiocyanate in blood (2- to 3-fold increase) and urine samples (about 200-fold increase) in 100 mg/m^3 male and female rats and 12% decreased hemoglobin concentration and 10% decreased hematocrit in 100 mg/m^3 males.

Results from this study (Monsanto, 1984) clearly identify the lowest concentration, 100 mg/m^3, as a FEL for increased mortality in male, but not female, Charles River CD rats exposed for up to 4 weeks. Females died at the next level of exposure, 260 mg/m^3, in the study. However, the limited examinations of histologic, hematologic, and serum and urine chemistry parameters provide little additional information, other than to indicate that cyanide was metabolically released from adiponitrile (i.e., thiocyanate was detected in serum and urine samples) and that female rats which survived the lowest concentration showed no exposure-related tissue lesions, other than hemosiderin-like pigmentation in some spleens.

Chronic oral studies of adiponitrile in dogs and rats conducted by Svirbely and Floyd (1964) were reported by NIOSH (1978). The original study report was not available for review.

It appears that segments of the original study series were reported in abstract form, but only the fourth segment was located (Svirbely, n.d.). In the dog study, an unspecified number of female mongrel dogs were fed adiponitrile in the diet at equivalent concentrations of 10, 100, 500 or 1000 ppm for an unspecified period of time. Blood and urine values and tests for liver and kidney function were normal in dogs fed adiponitrile at ≤500 ppm. During the first week, dogs fed 1000 ppm were not able to consume the entire dose; the dogs vomited or consumed only a portion of the food.

In the rat study, an unspecified number of male and female Wistar rats were provided drinking water containing 0.5, 5 or 50 ppm of adiponitrile over a 2 year period (Svirbely and Floyd, 1964). Body weights remained normal and no hematological abnormalities were observed in animals over the course of the study. At study termination, advanced adrenal degeneration was found in male rats exposed to 50 ppm and in female rats receiving all three concentrations of adiponitrile in their drinking water. Degeneration of other organs was noted, but not considered to be compound related. Determination of organ (spleen, liver, and kidney) to body weight ratios revealed no significant differences. No effect on survival was reported.

In an unpublished abstract, Svirbely (n.d.) reported that Holtzman rats (number unspecified) exposed to 10, 100 or 500 ppm of adiponitrile in drinking water over 3 generations did not develop any adverse effects. Endpoints monitored included fertility, gestation, and viability, but additional details of this experiment are not available.

In a preliminary study, Johannsen et al. (1986) administered adiponitrile to groups of 5 pregnant Charles River, COBD CD rat dams via gavage at doses of 0, 10, 25, 50, 100 or 200 mg/kg-day on gestation days 6-19. “Moderate to severe” (not otherwise specified) reductions in mean maternal body weight and increased mean postimplantation loss were reported for dams at doses ≥100 mg/kg-day. Mortalities occurred in 1/5 and 5/5 dams in the 100- and 200-mg/kg-day groups, respectively. In the final study, adiponitrile was administered to 25 pregnant rat dams via gavage doses of 0, 30, 50 or 80 mg/kg-day by the same protocol. The dams in the final study were sacrificed on gestation day 20, and the number and location of viable and nonviable fetuses, early and late resorptions, and the total number of implants and corporea lutea were determined. Fetuses were examined for gross malformations. Half of the fetuses were examined for visceral malformations, and the remaining were evaluated for skeletal anomalies.

The only evidence of maternal toxicity in the final study was deaths, which occurred in 1/25 and 2/25 dams in the 50- and 80-mg/kg-day groups, respectively (Johannsen et al., 1986). No significant differences in mean maternal body weights at termination or maternal body weight gains were observed between exposed groups and the control group. No differences were found in uterine and fetal parameters measured at sacrifice. Mean fetal body weights in the 30-, 50- and 80- mg/kg-day groups (3.4±0.4, 3.7±1.0, and 3.4±0.3 g, respectively) were within 95% of the mean control value (3.6±0.2 g). There was a statistically significant ($p<0.05$) decrease in mean

fetal body weight reported at 80 mg/kg-day but not at 30 mg/kg-day, even though the mean fetal weights were essentially the same (3.4±0.3 and 3.4±0.4, respectively). Additionally, the mean fetal body weight in the 50 mg/kg-day group was actually higher than the mean control value. Therefore, no significant dose-response effect for decreased fetal weight was evident in this study. As all mean fetal body weights in the exposed groups were within 95% of the mean control value and due to the lack of an apparent dose-response relationship for the statistically significant decrease in fetal body weight at the highest dose, this effect is not judged to be biologically significant. No statistically significant increases in incidences of fetuses or litters with malformations or variations (e.g., extra ribs, unossified sternebrae) were found in any of the exposed groups compared with controls. The results are consistent with the designation of 50 mg/kg-day as a LOAEL and 30 mg/kg-day as a NOAEL for maternal toxicity (deaths in some dams without evidence of effects on maternal body weight) and 80 mg/kg-day as a free-standing NOAEL due to the absence of adverse developmental effects (fetotoxicity, fetal body weights, or increased incidence of fetuses or litters with malformations or variations).

Ceresa (1948b) and Ceresa and De Blasis (1950) applied an unspecified dose of adiponitrile onto the backs of guinea pigs daily for one month. Effects of treatment included: weight loss, decreased blood calcium levels, marked hyperchromic hemolytic anemia with leukopenia and lymphomonocytosis. Histological examination revealed swelling and congestion of nearly all internal organs. In a previous experiment, guinea pigs treated with hexamethylenediamine via subcutaneous injection showed similar effects, such as hemolytic anemia with leukopenia and degenerative changes in the liver and kidney. Based on similarity of effects, Ceresa and De Blasis (1950) concluded that both adiponitrile and hexamethylenediamine may contribute to the effects of the chemical exposure observed in humans.

Lethality data for adiponitrile in rats include oral LD_{50} values of 960 mg/kg (Plokhova and Rubakina, 1965) and 300 mg/kg (Hann and Jensen, 1974; NIOSH, 1978). An oral LD_{50} of 172 mg/kg in mice was reported by Tanii and Hashimoto (1985). A 4-hour LC_{50} of 1.71 mg/L (1710 mg/m^3) was reported in rats (Smith and Kennedy, 1982). LD_{50} values of 50 mg/kg (Ghiringhelli, 1955) and 200 mg/kg (NIOSH, 1978) were reported in guinea pigs and rats, respectively, via subcutaneous administration.

Other Studies

At dietary concentrations of adiponitrile ranging from 10-1000 ppm, approximately 50% of the adiponitrile consumed in the diet by female mongrel dogs was recovered in the urine as thiocyanate (Svirbely and Floyd, 1964). Blood thiocyanate levels in guinea pigs injected subcutaneously with adiponitrile at 3-30 mg/kg was proportional to the administered dose (Ghiringhelli, 1955). These observations are consistent with metabolic release of cyanide from adiponitrile, followed by conversion to thiocyanate catalyzed by the enzyme, rhodanese (U.S. EPA, 1999). As discussed in the following paragraph, there is evidence to suggest that the

release of cyanide is catalyzed by cytochrome P450 isozymes that can be inactivated by carbon tetrachloride (Tanii and Hashimoto, 1985). Other lines of evidence supporting this metabolic reaction (i.e., cyanide release is oxygen- and NADPH-dependent) are available for other aliphatic nitriles, such as acetonitrile (U.S. EPA, 2005a).

Cyanide, a major metabolite of adiponitrile and other aliphatic dinitriles, has been shown to cross the blood-brain barrier into the brain, and may be responsible for at least a portion of the acute lethality of adiponitrile. Tanii and Hashimoto (1985) reported cyanide levels of approximately 0.71 μg/g of wet tissue in the brains of male ddy mice administered a lethal oral dose of 4.8 mmol/kg (519 mg/kg) of adiponitrile. The brains were harvested from the animals at the time of death, approximately 83 minutes after adiponitrile treatment. In mice pretreated by I.P. injection with CCl_4 (to inhibit the hepatic mixed function oxidase system and therefore inhibit release of cyanide from adiponitrile), a 519 mg/kg dose of adiponitrile did not cause death within 83 minutes and cyanide was not detected in the brain of mice sacrificed at this time. Similarly, the adiponitrile oral LD50 value was 1.6 mmol/kg (95% CI=1.3-2.0) in male ddy mice injected with olive oil 24 hours before adiponitrile administration, whereas a value of 2.7 mmol/kg (95% CI= 1.9-3.6) was determined in mice pretreated with CCl_4. In an *in vitro* study using liver microsomes, the investigators also reported that 6.23 ng cyanide/mg protein/minute was formed from an adiponitrile concentration of 3.1 mM. When mice were pretreated with CCl_4 injections prior to microsome harvest, cyanide was not detected after adiponitrile was added to the isolated microsomes. In CCl_4-pretreated mice given oral doses of 8 mmol/kg adiponitrile, 6/8 mice, who died after a mean of 390 minutes (±SD=168 minutes), showed mean brain levels of cyanide that were essentially the same as levels in the two mice who survived to 720 minutes (0.09±0.03 μg/g tissue versus 0.08± 0.05 μg/g tissue, respectively). In contrast, mean brain levels of cyanide were almost 10-fold greater (0.83± 0.18 μg/g tissue) in 8/8 mice who died at a mean of 14±9 minutes after administration of 0.21 mmol/kg potassium cyanide. The results of this study are consistent with the hypothesis that the mode of action for the acute lethality of adiponitrile does not only involve cyanide release, but may also involve the parent compound and other metabolites of the parent compound.

Only the summary of a report was available for review of a metabolism study conducted in 3 male and 3 female Sprague-Dawley rats administered an average dose of 5.75 mg/kg of radiolabeled adiponitrile (1.38 mg adiponitrile and 8.9 μCi of ^{14}C-adiponitrile) (Monsanto, 1987). Radioactivity was determined post treatment in urine, feces, and expired air in 8 hour increments over 72 hours. Average levels of radioactivity in the urine, feces, and expired air were 82.86%, 5.83%, and 9.05 % in males and 81.64%, 6.66%, and 8.55% in females, respectively, of the administered dose.

Adiponitrile was not mutagenic to *Salmonella typhimurium* strains TA1535, TA1537, TA1538 and TA98, with or without metabolic activation (Dupont, 1976; NIOSH, 1978; Zeiger et al., 1988). *In vitro* studies for genotoxic activity of adiponitrile were negative in the mouse

lymphoma assay at concentrations up to 5 µl/ml, with or without metabolic activation (SRI, 1982), and negative in unscheduled DNA synthesis (UDS) tests with primary cultures of rat hepatocytes (SRI, 1985). Sprague-Dawley male and female rats administered a single dose of 300 mg/kg adiponitrile via gavage did not show a significant increase in frequency of chromosomal aberrations (Hazelton Corp., 1985).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR ADIPONITRILE

Human data of oral exposure to adiponitrile were limited to a single case report of a man who manifested symptoms of acute cyanide poisoning following ingestion of a few milliliters of adiponitrile (Ghiringhelli, 1955). The patient recovered following medical intervention and treatment with the cyanide antagonist, sodium thiosulfate.

Chronic oral toxicity data for adiponitrile in animals are limited to two studies for which details of experimental protocol and results are very limited: a feeding study with dogs and a 2-year drinking water study with rats (Svirbely and Floyd, 1964). Female dogs that consumed 500 ppm of adiponitrile in their food over an unspecified length of time showed normal liver and kidney function based on blood and urine test results. In the rat study, which provided drinking water containing 0.5, 5 or 50 ppm of adiponitrile, advanced adrenal degeneration was reported to occur in all exposed female groups and in males at the highest concentration. No changes in body weight, organ weights, or hematological values were noted, and no increase in mortality was reported. Adequate primary reports of these studies were not available for independent evaluation and review. This precludes use of these data for derivation of a p-RfD.

Other toxicity studies involving oral exposure of animals to adiponitrile are restricted to a developmental toxicity study and a 3-generation reproductive toxicity study. The developmental toxicity study found no developmentally toxic effects following exposure of rat dams during gestation to oral doses as high as 80 mg/kg-day, a dose that caused deaths in 2/25 dams (Johannsen et al., 1986). These data are precluded from consideration for p-RfD derivation due to maternal toxicity. In the 3-generation reproductive toxicity study, rats exposed to up to 500 ppm adiponitrile in drinking water did not develop any adverse effects on fertility, gestation or viability (Svirbely, n.d.). However, no details of the reproductive toxicity study are available to allow an independent evaluation of the report which precludes the use of these data for p-RfD derivation.

No oral p-RfD values for adiponitrile were derived due to the lack of adequate data.

Derivation of a p-RfD by analogy to cyanide was considered because adiponitrile is metabolized to cyanide *in vivo* (Ahmed and Hussein, 1990). However, the reported effects of

chronic oral exposure to adiponitrile on the adrenal gland of rats are inconsistent with the effects which are the basis of the current chronic RfD for free cyanide (U.S. EPA, 1987, 2003a). The RfD for cyanide is based on a NOAEL of 10.8 mg/kg-day and a LOAEL of 30 mg/kg-day cyanide for weight loss, decreased thyroxin levels, and myelin degeneration in rats (U.S. EPA, 2003a). In addition, results from studies on the acute lethal toxicity of orally administered adiponitrile and other aliphatic dinitriles suggest that this toxic action of adiponitrile does not only involve cyanide and may also involve the parent compound or other metabolic derivatives of the parent compounds (Tanii and Hashimoto, 1985). The uncertainty of using cyanide dose-response data to derive a p-RfD for adiponitrile appears too great to warrant such an approach.

Rats and mice show responses to repeated inhalation exposure to acetonitrile, an aliphatic mononitrile with empirical formula of CH_3CN, that are similar to responses of rats to subchronic inhalation exposure to adiponitrile (early mortality in some rats without a clear identification of a toxicity target). The RfC for acetonitrile is based on a chronic NOAEL of 200 ppm and a subchronic FEL of 400 ppm for early mortality in mice, but the available information on the oral toxicity of acetonitrile was judged to be inadequate for deriving an oral RfD (U.S. EPA, 2005a). Thus, deriving an oral p-RfD for adiponitrile based on analogy to acetonitrile is not supported by an adequate database for either chemical.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR ADIPONITRILE

Nylon workers exposed to adiponitrile and hexamethylenediamine for 2-3 years showed a tendency for hyperchromic, hemolytic anemia and slight leukopenia (Ceresa, 1948a). However, exposure was to a mixture of chemicals and no quantitative exposure data were available.

Although there are no adequate toxicity studies of animals exposed by inhalation to adiponitrile for chronic durations, there are several acute and repeated-exposure inhalation toxicity studies in Charles River CD rats (Monsanto, 1984; Short et al., 1990; Smith and Kennedy, 1982).

Deaths associated with lethargy, salivation, and convulsions have been shown to display a steep dose-response curve in several inhalation studies with adiponitrile. Additionally, the available mortality data are highly inconsistent. Acute 4-hour exposure of males by inhalation to mixtures of adiponitrile vapor and aerosol was associated with deaths at concentrations $\geq$ 710 mg/m^3 (Smith and Kennedy, 1982). No deaths occurred in groups of 10 rats within 2 weeks following a single 4-hour exposure to 250,360 or 830 mg/m^3, but 5/10 rats died following exposure to 710 mg/m^3 (Smith and Kennedy, 1982). A 4-hour LC_{50} of 1710 mg/m^3 (95% CI= 870-2660 mg/m^3) was estimated from these lethality data. With repeated exposure scenarios (all involving 6 hours/day, 5 days/week protocols), deaths were also observed: in 18/18 male and 9/18 female rats during the first week of exposure to 493 mg/m^3 in a 4-week study (Short et al.,

1990); in 18/18 males and 18/18 females during the first 8 days of exposure to 260 or 950 mg/m^3 in another 4-week study (Monsanto, 1984); and in 14/18 males during exposure to 100 mg/m^3 for up to 4 weeks (Monsanto, 1984). In contrast, no deaths occurred in groups of: 10 males exposed to 31, 95, or 268 mg/m^3 for up to 2 weeks (Smith and Kennedy, 1982); 18 females exposed to 100 mg/m^3 for 4 weeks (Monsanto et al., 1984); 18 males and 18 females exposed to 64 or 114 mg/m^3 for 4 weeks (Short et al., 1990); and 15 males and 15 females exposed to 13, 31 or 99 mg/m^3 for 13 weeks (Short et al., 1990). Additionally, no deaths occurred in females exposed to 12, 32 or 104 mg/m^3 (6 hours/day, 7 days/week) for 3 weeks (Short et al., 1990).

The results indicate that the threshold concentration for lethality in Charles River CD rats exposed for short term and subchronic durations may be in the vicinity of 100 mg/m^3 and that males may be more sensitive than females. No deaths occurred in males and females with 13 weeks of exposure to 99 mg/m^3 or with 4 weeks of exposure to 114 mg/m^3 (Short et al., 1990), or in females with 4 weeks of exposure to 100 mg/m^3 (Monsanto et al., 1984), but many males died with 4 weeks of exposure to 100 mg/m^3 (Monsanto et al., 1984) and twice as many males as females died with 4 weeks exposure to 493 mg/m^3. The test atmospheres were aerosol/vapor mixtures and differences in the amounts of aerosol vs. vapor, and in the particle size distribution of the aerosols, may explain the higher lethality in the Monsanto (1984) study. The highest concentration with the longest duration of exposure that produced no mortalities in any of these studies was the average concentration of 31 mg/m^3 in the 13-week study (Short et al., 1990).

Two fairly consistent findings from the inhalation toxicity studies are the absence of histologic tissue lesions in surviving rats exposed to adiponitrile and the small, but statistically significant ($p<0.05$), decreases in red blood cell counts and hemoglobin concentrations found in several studies. Histologic examination of comprehensive sets of tissues and organs revealed no exposure-related lesions in: surviving male and female rats exposed to 64, 114 or 493 mg/m^3 for 4 weeks, with the exception of slight to moderate hemosiderin-like pigmentation in spleens of surviving rats exposed to 114 or 493 mg/m^3 (Short et al., 1990); male and female rats exposed to 13, 31, or 99 mg/m^3 for 13 weeks (Short et al., 1990); and male rats exposed to 31, 95, or 268 mg/m^3 for 2 weeks (Smith and Kennedy, 1982). The histologic examination in the 4-week study reported by Monsanto (1984) was too limited to draw conclusions (due to tissue autolysis), other than concluding that female rats, which survived 4 weeks of exposure to the lowest exposure concentration, 100 mg/m^3, showed no exposure-related lesions besides increased incidence of spleens with hemosiderin-like pigmentation. Small, but statistically significant ($p<0.05$), decreases (3-9% compared with controls) in red blood cell count, hemoglobin concentration, or hematocrit have been observed in female rats exposed to 493 mg/m^3 for 4 weeks (Short et al., 1990); male rats, but not females, exposed to 114 mg/m^3 for 4 weeks (Short et al., 1990); females, but not males, exposed to 99 mg/m^3 for 13 weeks (Short et al., 1990); males, but not females, exposed to 100 mg/m^3 for 4 weeks (Monsanto et al., 1984); and male rats exposed to 268 mg/m^3, but not 95 mg/m^3, for 2 weeks (Smith and Kennedy, 1982).

Although the hematologic changes are of suspect biological significance, they have been observed with some consistency across studies. These results, along with the findings of splenic hemosiderosis in some rats exposed for 4 weeks to concentrations ≥100 mg/m^3 (Monsanto, 1984; Short et al., 1990), provide evidence that the red blood cell is a toxicity target of adiponitrile. Effects on hematologic parameters of a similar magnitude have been observed in F344 rats exposed for 13 weeks or 15 months by inhalation to another aliphatic nitrile, acetonitrile (U.S. EPA, 2005a), suggesting that small molecular weight aliphatic nitriles in general may be mildly cytotoxic to red blood cells.

Subchronic and chronic inhalation exposure of mice or rats to acetonitrile induced other effects that are similar to those induced in the short term and subchronic inhalation studies with rats exposed to adiponitrile. For example, in NTP-sponsored chronic bioassays with F344 rats and B6C3F1 mice, no clear evidence for exposure-related nonneoplastic lesions was found in any tissue or organs at three exposure levels below the lowest subchronic exposure level that induced mortality (U.S. EPA, 2005a). A chronic NOAEL of 200 ppm and a subchronic FEL of 400 ppm provided the basis of the chronic RfC for acetonitrile. The acetonitrile findings show a pattern similar to the findings of the short term and subchronic adiponitrile inhalation studies (Short et al., 1990) identifying 493 mg/m^3 as a short term FEL, 99 mg/m^3 as a minimal subchronic LOAEL for slight anemia without the occurrence of any nonneoplastic lesions, and 31 mg/m^3 as a subchronic NOAEL in rats. It is important to note, however, that Monsanto (1984) clearly identified a short term FEL (100 mg/m^3) for adiponitrile at a concentration nearly identical to the minimal subchronic LOAEL (99 mg/m^3) identified by Short et al. (1990). This, in essence, results in an adiponitrile NOAEL that is approximately 3 fold lower than the FEL. This is comparable to and just slightly higher than the 2 fold difference between the acetonitrile NOAEL (200 ppm) and FEL (400 ppm) and highlights the steep dose-response for mortality associated with these compounds.

Results from the available short term and subchronic studies on adiponitrile inhalation toxicity, coupled with similar supporting results from studies on acetonitrile inhalation toxicity (U.S. EPA, 2005a) and the report that no effects on male or female fertility occurred in rats exposed to adiponitrile concentrations as high as 99 mg/m^3 for 10 or 3 weeks, respectively (Short et al., 1990), are adequate for deriving a subchronic RfC for adiponitrile. The subchronic NOAEL of 31 mg/m^3 for slight anemia without any nonneoplastic lesions in rats (Short et al., 1990) is selected as the point of departure (POD) for the subchronic RfC. Following U.S. EPA (1994b) guidelines for an extrarespiratory effect from a category 3 gas (exposure was reported to be largely to vapor at this concentration), the POD is converted to a human equivalent concentration (HEC) by adjusting to a continuous exposure basis and multiplying by a ratio of blood:gas partition coefficients for rats and humans. In the absence of data for rat or human blood:gas partition coefficients for adiponitrile, the default value of the ratio is taken to be 1.

$$NOAEL_{HEC} = (31\ mg/m^3) \times (6\ hour/\ 24\ hour) \times (5\ day/\ 7\ day) \times 1 = 6\ mg/m^3$$

A provisional **subchronic RfC of 0.06 mg/m^3** is derived by dividing the $NOAEL_{HEC}$ by a composite uncertainty factor of 100 (3 for interspecies extrapolation, 10 for human variability, and 3 for database deficiencies). A partial uncertainty factor of 3 was used for interspecies extrapolation using the inhalation dosimetric equations (U.S. EPA, 1994b). A default uncertainty factor of 10 for intraspecies variability was used in the absence of information on pharmacokinetic and pharmacodynamic variability for adiponitrile in humans. A database deficiency uncertainty factor of 3 was used. An adequate 1-generation reproductive toxicity assessment of rats exposed by inhalation and an adequate developmental toxicity assessment of rats exposed orally are available. These studies (and the negative results which were obtained) preclude the use of a default uncertainty factor of 10 for the absence of reproductive and developmental toxicity data. Toxicity data for another animals species would decrease uncertainty in the database.

subchronic p-RfC = 6 mg/m^3 ÷ 100
= 0.06 or 6E-2 mg/m^3

A provisional **chronic RfC of 0.006 mg/m^3** is similarly derived by incorporating an additional uncertainty factor of 10 to extrapolate from subchronic to chronic durations (total UF = 1000):

p-RfC = 6 mg/m^3 ÷ 1000
= 0.006 or 6E-3 mg/m^3

Confidence in the principal short term and subchronic studies is medium to high. The subchronic study included 3 exposure levels (selected based on the results of the short term study), comprehensive histologic, hematologic, and clinical chemistry evaluations, and adequate numbers of animals of each sex for statistical analyses. Although a distinct toxicity target was not identified (the minimal hematologic effects observed were of questionable biological significance), the subchronic study included 3 exposure levels below the exposure level causing mortalities in the short term study. Confidence in the data base is medium to low. Available toxicity information comes from several short term and subchronic studies with only one strain of rats. Inconsistencies in lethality results among studies (Monsanto, 1984; Short et al., 1990) may have been related to differences in test atmospheres, and in particular the amount and particle size distribution of aerosol. It is not clear how other toxicity endpoints might have also been affected by these differences in test atmosphere. There is an adequate 1-generation inhalation reproductive toxicity study in rats and an adequate oral developmental toxicity study in rats, but no 2-generation reproductive toxicity study in any species exposed by any route is available. Resulting confidence in the subchronic and chronic p-RfC is medium to low.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR ADIPONITRILE

No data in humans or animals are available to assess the carcinogenic potential of adiponitrile. Limited data indicate that this chemical is not genotoxic in bacterial mutagenicity assays (Dupont, 1976; NIOSH, 1978; Zeiger et al., 1988). Adiponitrile was not active in assays for mutation in mouse lymphoma cells *in vitro* (SRI, 1982), induction of UDS in primary rat hepatocytes (SRI, 1985), nor *in vivo* bone marrow chromosome studies in rats (Hazelton Corp., 1985). As the available data are insufficient to assess carcinogenic potential in animals or humans, they are consistent with the hazard descriptor, "*inadequate information to assess carcinogenic potential*," as specified by the U.S. EPA (2005b) Guidelines for Carcinogen Risk Assessment.

Derivation of quantitative estimates of cancer risk for adiponitrile is precluded by the absence of carcinogenicity data for adiponitrile.

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