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Provisional Peer-Reviewed Toxicity Values for

3-Nitro-4-chlorobenzotrifluoride
(CASRN 121-17-5)

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Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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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	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-NITRO-4-CHLOROBENZOTRIFLUORIDE (CASRN 121-17-5)

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-Nitro-4-chlorobenzotrifluoride, CAS No. 121-17-5, is a substituted nitrobenzene with the chemical structure, $C_7H_3ClF_3NO_2$, shown in Figure 1, and Table 1 presents the physicochemical properties. 3-Nitro-4-chlorobenzotrifluoride is a chemical intermediate of the herbicide Fluorodifen (HSDB, 2003).

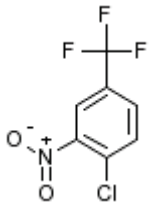

Figure 1. 3-Nitro-4-chlorobenzotrifluoride Structure

Table 1. Physicochemical Properties Table for 3-Nitro-4-chlorobenzotrifluoride (CASRN 121-17-5)[a]

Property (unit)	Value
Boiling point (ºC)	222
Melting point (ºC)	−2
Density (g/mL at 25°C)	1.511
Vapor pressure (Pa at 25ºC)	ND
pH (unitless)	ND
Solubility in water	Insoluble
Relative vapor density (air = 1)	ND
Molecular weight (g/mol)	225.55

[a]Source: Chemical Book (2010).

ND = No data.

No Reference Dose (RfD), Reference Concentration (RfC), or cancer assessment values for 3-nitro-4-chlorobenzotrifluoride are included in the IRIS database (U.S. EPA, 2011a) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2009). No RfD or RfC values are reported in the HEAST (U.S. EPA, 2011b). The Chemical Assessments and Related Activities (CARA) list does not include a Health and Environmental Effects Profile (HEEP) for 3-nitro-4-chlorobenzotrifluoride (U.S. EPA, 1994). The toxicity of 3-nitro-4-chlorobenzotrifluoride has not been reviewed by the ATSDR (2011) or the World Health Organization (WHO, 2011). CalEPA (2008, 2009) has not derived toxicity values for exposure to 3-nitro-4-chlorobenzotrifluoride. No occupational exposure limits for 3-nitro-4-chlorobenzotrifluoride have been derived by the American Conference of Governmental

Industrial Hygienists (ACGIH, 2011), recommended by the National Institute of Occupational Safety and Health (NIOSH, 2010), or adopted by the Occupational Safety and Health Administration (OSHA, 2006).

The HEAST (U.S. EPA, 2011) does not report a U.S. EPA (1986) cancer weight-of-evidence classification or an oral slope factor for 3-nitro-4-chlorobenzotrifluoride. The International Agency for Research on Cancer (IARC, 2011) has not reviewed the carcinogenic potential of 3-nitro-4-chlorobenzotrifluoride. 3-Nitro-4-chlorobenzotrifluoride is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2008) has not prepared a quantitative estimate of the carcinogenic potential of 3-nitro-4-chlorobenzotrifluoride.

Literature searches were conducted on sources published from 1900 through July 26, 2011 for studies relevant to the derivation of provisional toxicity values for 3-nitro-4-chlorobenzotrifluoride, CAS No. 121-17-5. Searches were conducted using the 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 toxicity values: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, ACToR, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

Table 2 provides an overview of the relevant database for 3-nitro-4-chlorobenzotrifluoride and includes all potentially relevant repeated short-term-, subchronic-, and chronic duration studies. The phrase, "statistical significance," used throughout the document, indicates a p-value of <0.05.

Table 2. Summary of Potentially Relevant Data for 3-Nitro-4-chlorobenzotrifluoride (CASRN 121-17-5)

Category	Number of Male/female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
Human								
1. Oral (mg/kg-day)[a]								
Subchronic	ND							
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							
2. Inhalation (mg/m^3)[a]								
Subchronic	ND							
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							
Animal								
1. Oral (mg/kg-day)[a]								
Subchronic	**10/0, Sprague-Dawley rat, gavage, 28 or 38 d**	**0, 1, 10, or 100 for 28 d; or 100 for 28 d + 300 for 10 d (Adjusted)**	**Decreased relative brain weight; increased triglycerides**	**ND**	**NDr**	**1**	**Bucchi et al. (1983)**	**PS, PR**
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							

Table 2. Summary of Potentially Relevant Data for 3-Nitro-4-chlorobenzotrifluoride (CASRN 121-17-5)

Category	Number of Male/female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (Comments)	Notes[b]
2. Inhalation (mg/m^3)[a]								
Subchronic	ND							
Chronic	ND							
Developmental	ND							
Reproductive	ND							
Carcinogenicity	ND							

[a]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. All long-term exposure values (4 weeks and longer) are converted from a discontinuous to a continuous (daily) exposure. Values for inhalation (cancer and noncancer) and oral (cancer only) exposure are further converted to an HEC/D. Values from animal developmental studies are not adjusted to continuous exposure.
[b]Notes: PS = Principal study, PR = Peer reviewed.

ND = No data, NDr = Not determinable.

HUMAN STUDIES

Oral Exposures

No studies were identified.

Inhalation Exposures

No studies were identified.

ANIMAL STUDIES

Oral Exposures

The effects of oral exposure to 3-nitro-4-chlorobenzotrifluoride have been evaluated in animals in one subchronic-duration study (Bucchi et al., 1983).

Subchronic-duration Studies

Bucchi et al. (1983)

The peer-reviewed study by Bucchi et al. (1983) is selected as the principal study for derivation of the screening subchronic p-RfD. Although the original source was written in Italian and published in a foreign journal, EPA had the article translated on February 1, 2011. Articles published in this foreign journal are peer reviewed, but there is no statement regarding GLP compliance. Male Sprague-Dawley rats (10/treatment group) were administered 0, 1, 10, or 100 mg/kg-day of 3-nitro-4-chlorobenzotrifluoride (purity not reported) daily in dietary milk via gavage for 28 days. A separate group of 10 rats were administered 100 mg/kg-day 3-nitro-4-chlorobenzotrifluoride for 28 days followed by 300 mg/kg-day for 10 days (average daily dose of 153 mg/kg-day). There is no indication that there was a control for this group—so results from this group are of limited use. The rats were weighed daily and food and water consumption were measured every 2 days. Urine was collected from two rats per group on Days 14, 21, and 28 and analyzed for sedimentation, albumin, glucose, and acetone levels. At study termination, blood was collected for hematology (specifics not provided) and clinical chemistry (proteinaceous nitrogen, glucose, cholesterol, triglycerides, aspartate aminotransferase [AST, referred to by study authors as SGOT], alanine aminotransferase [ALT, referred to by study authors as SGPT], gamma glutamyl transferase [γGT], and bilirubin). After necropsy, the brain, heart, lungs, thymus, liver, spleen, pancreas, kidneys, adrenal glands, testes, bladder, and seminal vesicles were weighed. Although it was stated that cytochrome P-450, analine hydroxylase, and *p*-nitroanisole-*O*-demethylase were measured in the microsomal fraction of the liver, no results were presented for these endpoints. Statistical methods used were not reported. The data are presented only visually without error bars and are reported in text as percent changes from control. The lack of standard deviations or individual data preclude verifying the statistical results.

All animals survived until the end of treatment. The study report only provides figures for endpoints that were considered significant. No treatment-related changes in body weight, food consumption, or urinalysis were observed, but these data were not provided in the study report. Animals treated with 100 mg/kg-day or 100 mg/kg-day followed by 300 mg/kg-day showed yellowing of their fur on the ventral zone. It was stated that all treated groups consumed 12−23% more water than the controls, but no specifics were provided for each dose nor was it indicated whether this increase was dose related. Changes in clinical chemistry, hematology, and organ weights are presented in Table B.1. There was a statistically significant increase in blood glucose levels in animals that received 100 mg/kg-day 3-nitro-4-chlorobenzotrifluoride (24.5% higher than control values) and in the 100 + 300 mg/kg-day group (41.1% increase

compared to controls). There was a statistically significant increase in triglyceride levels in animals that received 1, 10, or 100 mg/kg-day (27.8, 39.8, and 34.1% increases compared to controls, respectively). In the 100 + 300 mg/kg-day group there were also significant increases in cholesterol (22.9% increase compared to controls) and ALT and γGT (51.4% increase compared to controls). Changes in hematology were sporadic but included a statistically significant decrease in erythrocytes at 10 mg/kg-day (18.5% decrease), an increase in leukocytes at 100 mg/kg-day (80.6% increase compared to controls), and a increase in hemoglobin in the 100 + 300 mg/kg-day group (6.6% increase compared to controls).

At necropsy, there were overt signs of cardiac damage and marked yellow coloration of the adrenal glands in rats administered 100 mg/kg-day or 100 + 300 mg/kg-day. Although body weight was stated to have been unaffected (data not shown), several changes in the relative organ weights were reported. There was a statistically significant increase in relative liver weights at doses ≥10 mg/kg-day (an 11.6% increase in the 10-mg/kg-day group, 12.1% increase in the 100-mg/kg-day group, and a 22.4% increase in the 100 + 300 mg/kg-day group compared to controls). There was a statistically significant decrease in relative brain weights in the rats administered 1, 10, or 100 + 300 mg/kg-day (11.9%, 11.7%, and 24.7%, respectively compared to controls). The 100-mg/kg-day group also had a decrease in brain weight, but this change was not statistically significant and was not reported quantitatively. However, based on graphical representation of the data, the change was of a similar magnitude to that observed in the 1- and 10-mg/kg-day dose groups. Thymus weight was increased 33% in the 10 mg/kg-day group and decreased 26.6% in the 100 + 300 mg/kg-day group compared to controls. The weight of the testes decreased by 13.2% at 10 mg/kg-day and the weight of the spleen decreased by 15.1% at 100 + 300 mg/kg-day compared to controls. Although the study authors noted a tendency for increased relative pancreas weights proportional to dose, this change was not statistically significant at any dose. Histopathological results were only preliminary and were stated to show generalized vascular damage across all organs in all treatment groups, but the incidence data were not provided.

No NOAEL could be determined from the data. A LOAEL of 1 mg/kg-day is available from the data based on decreased brain weight and increased triglycerides.

Chronic-duration Studies
No studies were identified.

Developmental Studies
No studies were identified.

Reproductive Studies
No studies were identified.

Carcinogenicity Studies
No studies were identified.

Inhalation Exposures

There is no suitable information to provide in this regard.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Several in vitro studies were identified that examined 3-nitro-4-chlorobenzotrifluoride for its potential genotoxicity (Benigni et al., 1982; Haworth et al., 1983; Mazza et al., 1986). Table 3A summarizes these in vitro genotoxicity studies, and they are further discussed below. No studies were identified that investigated the genotoxic potential of 3-nitro-4-chlorobenzotrifluoride in vivo. Other studies that were identified were limited to acute toxicity tests. Table 3B summarizes these studies, and they are further discussed below.

Table 3A. Summary of 3-Nitro-4-chlorobenzotrifluoride Genotoxicity Studies

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	0.25 µL	−	−	The study authors stated that the cytotoxic effects of 3-nitro-4-chlorobenzotri-fluoride only permitted testing at low doses.	Benigni et al. (1982)
Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	NR	−	−	At least 5 dose concentrations were tested. A range-finding test was conducted in *S. typhimurium* TA100 at up to 10 mg/plate or to the limit of solubility; however, the specific dose concentrations tested were not reported.	Haworth et al. (1983)
Reverse mutation	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, TA1538	2500 µg/plate	−	−	In an accompanying test for antimicrobial activity in *S. typhimurium* TA100, 315 µg/mL was observed to be minimally inhibitory.	Mazza et al. (1986)
SOS repair induction	ND					
Genotoxicity studies in nonmammalian eukaryotic organisms						
Mutation	ND					
Recombination induction	*Aspergillus nidulans* strain P, heterozygous for *p*-fluoro-phenylalanine resistance	1.0 µL	−	−	Results were also reviewed in Crebelli (1987).	Benigni et al. (1982)
Chromosomal aberration	ND					

Table 3A. Summary of 3-Nitro-4-chlorobenzotrifluoride Genotoxicity Studies

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Chromosomal malsegregation	*Saccaromyces cerevisiae* strain 6117	2000 µg/mL	−	−	In an accompanying test for antimicrobial activity in *S. cerevisiae* strain 6117, 1250 µg/mL was observed to be minimally inhibitory.	Mazza et al. (1986)
Mitotic arrest	ND					
DNA Damage	Rec-assay in *Bacillus subtilis* strains PB 1652 (*trpC2 metB10 lys3*) and PB 1791 (*trpC2 metB10 recE4*)	1000 µg/disk	−	NDr	5000 and 10,000 µg/disk dose concentrations were also tested; however, complete inhibition of the growth of the tester strains was observed at these dose concentrations. In an accompanying test for antimicrobial activity in *B. subtilis* PB 1652, 315 µg/mL was observed to be minimally inhibitory.	Mazza et al. (1986)
Genotoxicity studies in mammalian cells—in vitro						
Mutation	ND					
Chromosomal aberrations	ND					
Sister chromatid exchange (SCE)	ND					

Table 3A. Summary of 3-Nitro-4-chlorobenzotrifluoride Genotoxicity Studies

Endpoint	Test System	Dose Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
DNA damage	Epithelial-like human cells collected from skin and muscle explants from human embryos	1.0 µL/mL	+	NDr	Unscheduled DNA synthesis was observed. The study authors state that the positive results did not fit a dose-response curve; 10 µL/mL was also tested but the results were negative.	Benigni et al. (1982)
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 by the study author but determined from data.

Table 3B. Other 3-Nitro-4-chlorobenzotrifluoride Studies

Test	Materials and Methods	Results	Conclusions	References
Carcinogenicity studies (exposures other than oral or inhalation)	ND			
Other toxicity studies (exposures other than oral or inhalation)	4 (sex not reported), New Zealand White rabbit, acute dermal toxicity (clipped/intact or abraded skin), 24-hr exposure; 316, 1000, 3160, or 10,000 mg/kg	Absence of feces followed by death observed in 1/4 animals on Day 8; body weight loss in 2/4 animals; depression, labored respiration in an unspecified number of animals Numerous cyst-like structures throughout the lobes of the liver observed in 1/4 animals administered either 3160 or 10,000 mg/kg	LD_{50} ≥≥ 10,000 mg/kg	Hazleton Labs (1992)
Short-term studies	5/5 (M/F), Sprague-Dawley rat, single gavage, observed for 14 d; 460, 613, 791, 1025, 1319, or 1706 mg/kg	Dark red lungs, mottled liver, pale spleen, dark zone between the cortex and medulla of the kidney, body weight loss and moderate to severe autolysis observed at death in animals administered ≥460 mg/kg Depression, labored respiration after 1 hr in males and females administered ≥613 mg/kg Convulsions in 1/5 males observed 4 hr after administration of 791 mg/kg Blanched stomach observed in animals administered 1025 mg/kg Distended stomach with thin walls observed in animals administered ≥1319 mg/kg	LD_{50} (females) = 1250 mg/kg (confidence limits, 984−1588 mg/kg) LD_{50} (males) = 1275 mg/kg (confidence limits, 931−1747 mg/kg)	Hazleton Labs (1992)
Metabolism/toxicokinetic	ND			
Mode of action/ mechanistic	ND			
Immunotoxicity	ND			
Neurotoxicity	ND			

ND = No data.

Tests Evaluating Carcinogenicity, Genotoxicity, and/or Mutagenicity

The genotoxicity of 3-nitro-4-chlorobenzotrifluoride has been studied using several prokaryotic, nonmammalian eukaryotic, and mammalian in vitro test systems (Benigni et al., 1982; Haworth et al., 1983; Mazza et al., 1986). Table 3A summarizes these genotoxicity studies. With the exception of the finding that 3-nitro-4-chlorobenzotrifluoride caused unscheduled DNA synthesis in cultured epithelial-like human cells (Benigni et al., 1982), these studies indicate that 3-nitro-4-chlorobenzotrifluoride is not mutagenic, genotoxic, or clastogenic in vitro. Benigni et al. (1982) observed unscheduled DNA synthesis at concentrations of 1.0 and 2.0 μL/mL 3-nitro-4-chlorobenzotrifluoride, but not 10.0 μL/mL. Studies investigating the in vivo genotoxic potential of 3-nitro-4-chlorobenzotrifluoride were not identified.

Carcinogenicity (Exposures Other Than Oral or Inhalation)

No studies were identified.

Other Toxicity Studies (Exposures Other Than Oral or Inhalation)

One unpublished, acute study was identified that examined the effects of 3-nitro-4-chlorobenzotrifluoride through routes of exposure other than oral or inhalation (Hazleton Labs, 1992). Table 3B summarizes this and other studies on 3-nitro-4-chlorobenzotrifluoride. In an acute dermal toxicity study, Hazleton Labs (1992) exposed four New Zealand White rabbits (sex not reported, initial body weights of 2.4−3.1 kg) to 316, 1000, 3160, or 10,000 mg/kg of 3-nitro-4-chlorobenzotrifluoride for 24 hours. In two of the animals per exposure group, the skin was clipped and left intact while in the other two animals the skin was abraded prior to the application of 3-nitro-4-chlorobenzotrifluoride. Binders were applied to the exposed area and the animals were fitted with collars to avoid ingestion of the test material. Following exposure, the researchers observed the animals for up to 14 days. One animal in the 10,000-mg/kg exposure group did not produce feces and died 8 days after exposure. An LD_{50} of ≥10,000 mg/kg was assigned by the study authors based on this death.

Short-term Studies

In addition to the study on acute dermal toxicity, Hazleton Labs (1992) also conducted an unpublished, acute oral toxicity study in rats. Five male and five female Sprague-Dawley rats (initial body weights of 150−212 g for males and 142−182 g for females) were administered a single dose of 460, 613, 791, 1025, 1319, or 1706 mg/kg 3-nitro-4-chlorobenzotrifluoride (purity assumed to be 100% by study authors) via gavage in corn oil. There was no indication of a concurrent control group. The animals were examined for mortality and signs of any clinical effects immediately after dosing, after 1, 4, and 24 hours, and once daily thereafter for up to 14 days. Depression and labored respiration were observed at ≥613 mg/kg at 1 hour after dosing. At 791 mg/kg, convulsions were observed in 1/5 males. At all dose levels necropsy revealed dark red lungs, mottled liver, pale spleen, a dark zone between the cortex and medulla of the kidney, and moderate-to-severe autolysis. The raw incidence data of these findings were not provided. It was stated that some body-weight loss was observed. At a dose of 1706 mg/kg the cardiac portion of the stomach had thickened, was white in color, and had adhered to the liver in an unspecified number of animals. Other effects to the stomach included blanching at 1025 mg/kg and distention with thin walls at 1319 and 1706 mg/kg. LD_{50}s of 1250 mg/kg for females and 1275 mg/kg for males were estimated from this study.

Metabolism/Toxicokinetic Studies

No studies were identified.

Mode of Action/Mechanistic Studies

No studies were identified.

Immunotoxicity

No studies were identified.

Neurotoxicity

No studies were identified.

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 Noncancer Reference Values for 3-Nitro-4-chlorobenzotrifluoride (CASRN 121-17-5)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Screening subchronic p-RfD (mg/kg-day)	Rat/M	Decreased relative brain weight and increased triglycerides	1×10^{-4}	LOAEL	1	10,000[a]	Bucchi et al. (1983)
Chronic p-RfD (mg/kg-day)	None	None	None	None	None	None	None
Subchronic p-RfC (mg/m^3)	None	None	None	None	None	None	None
Chronic p-RfC (mg/m^3)	None	None	None	None	None	None	None

[a]The maximum allowed total composite uncertainty factor is 10,000.

Table 5. Summary of Cancer Reference Values for 3-Nitro-4-chlorobenzotrifluoride (CASRN 121-17-5)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
p-OSF	None	None	None	None
p-IUR	None	None	None	None

DERIVATION OF ORAL REFERENCE DOSES

Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

No subchronic p-RfD can be derived because doing so would require the application of a composite uncertainty factor of 10,000, which is greater than the maximum allowable uncertainty factor of 3000. However, a screening subchronic p-RfD is provided in Appendix A. The Bucchi et al. (1983) subchronic study in male rats is the only study available to consider for derivation of the subchronic p-RfD.

Derivation of Chronic Provisional RfD (Chronic p-RfD)

No chronic p-RfD can be derived because doing so would require the application of a composite uncertainty factor in excess of 10,000.

DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No subchronic or chronic p-RfC values can be derived because there are no human or animal inhalation studies currently available.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 6 identifies the cancer weight-of-evidence descriptor for 3-nitro-4-chlorobenzotrifluoride.

Table 6. Cancer Weight of Evidence (WOE) Descriptor for 3-Nitro-4-chlorobenzotrifluoride

Possible WOE Descriptor	Designation	Route of Entry (Oral, Inhalation, or Both)	Comments
"Carcinogenic to Humans"	ND	ND	No comments
"Likely to Be Carcinogenic to Humans"	ND	ND	No comments
"Suggestive Evidence of Carcinogenic Potential"	ND	ND	No comments
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**Both**	**No carcinogenic studies are available that analyze either route of exposure.**
"Not Likely to Be Carcinogenic to Humans"	ND	ND	No comments

ND = No data

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

The lack of data on the carcinogenicity of 3-nitro-4-chlorobenzotrifluoride precludes the derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure.

APPENDIX A. PROVISIONAL SCREENING VALUES

For the reasons noted in the main document, it is inappropriate to derive a provisional subchronic p-RfD for 3-nitro-4-chlorobenzotrifluoride. However, information is available which, although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in a supplemental appendix and develops a screening value. Appendices receive the same level of internal and external scientific peer review as the main document to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in a supplement to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of a supplemental screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Heath Risk Technical Support Center.

DERIVATION OF SCREENING PROVISIONAL ORAL REFERENCES DOSES

Derivation of Screening Subchronic Provisional RfD (Subchronic p-RfD)

There is a single repeated dose study (Bucchi et al., 1983) available on 3-nitro-4-chlorobenzotrifluoride. The study by Bucchi et al. (1983) is selected as the principal study for derivation of the screening subchronic p-RfD. The critical endpoints are decreased relative brain weight (no changes in body weight were noted) and increased triglycerides in male rats. This study was published in a foreign language; however, the journal is peer reviewed and EPA had the study translated on February 1, 2011. The study does not provide a GLP compliance statement. Although numerous endpoints were examined, histopathology was only preliminary at the time of publication. The preliminary histopathology results indicate that generalized vascular damage occurred at the dose selected for POD; however, neither incidence nor severity data were provided. The study is limited in that only male rats were examined and limited data are available for review. Details are provided in the "Review of Potentially Relevant Data" section. BMD analysis is not possible with these data because the data are presented only graphically and as percent change from controls. As the only available and acceptable study, this study represents the lowest POD for developing a subchronic p-RfD.

The POD in this study is a LOAEL of 1 mg/kg-day for decreased relative brain weight and increased serum triglycerides.

No dosimetric adjustments were required because the doses in the principal study were administered via gavage in mg/kg-day, presumably for 7 days per week for the entire study duration.

The screening subchronic p-RfD for 3-nitro-4-chlorobenzotrifluoride, based on 1 mg/kg-day in male rats, is derived as follows:

$$\textbf{Screening Subchronic p-RfD} = LOAEL_{ADJ} \div UF$$
$$= 1 \text{ mg/kg-day} \div 10{,}000$$
$$= \mathbf{1 \times 10^{-4} \text{ mg/kg-day}}$$

Table A.1 summarizes the uncertainty factors for the screening subchronic p-RfD for 3-nitro-4-chlorobenzotrifluoride.

Table A.1. Uncertainty Factors for the Screening Subchronic p-RfD of 3-Nitro-4-chlorobenzotrifluoride

UF	Value	Justification	Notes
UF_A	10	A UF_A of 10 is applied for interspecies extrapolation to account for potential toxicokinetic and toxicodynamic differences between rats and humans.	No notes
UF_D	10	A UF_D of 10 is selected because there are no acceptable two-generation reproduction studies or developmental studies by this route.	No notes
UF_H	10	A UF_H of 10 is applied for intraspecies differences to account for potentially susceptible individuals in the absence of information on the variability of response in humans.	No notes
UF_L	10	A UF_L of 10 is applied for using a POD based on a LOAEL because a NOAEL cannot be determined from the available database.	No notes
UF_S	1	A UF_S of 1 is applied because a subchronic study was utilized.	No notes
UF_C $\leq$3000	10,000	Composite of the five uncertainty factors.	This value is a screening value. The composite UF maximum is 10,000.

APPENDIX B. DATA TABLES

Table B.1. Changes in organ Weights, Clinical Chemistry, and Hematology in Rats Exposed to 3-Nitro-4-chlorobenzotrifluoride by Gavage for 28 Days

Parameter	Exposure Group (mg/kg-day)			
	1	10	100	100 + 300[a]
Relative Organ Weights				
Liver	NS	+11.6%[b]	+12.1%	+22.4%
Brain	−11.9%	−11.7%	NS	−24.7%
Thymus	NS	+33%	NS	+26.6%
Testes	NS	−13.2%	NS	NS
Spleen	NS	NS	NS	−15.1%
Clinical Chemistry				
Blood glucose	NS	NS	+24.5%	+41.1%
Triglycerides	+27.8%	+39.8%	+34.1%	NS
Cholesterol	NS	NS	NS	+22.9%
ALT & γGT[c]	NS	NS	NS	+51.4%
Hematology				
Erythrocyte count	NS	−18.5%	NS	NS
Leukocyte count	NS	NS	+80.6%	NS
Hemoglobin	NS	NS	NS	+6.6%

[a]This group received 100 mg/kg-day for 28 days and then 300 mg/kg-day for an additional 10 days.
[b]Data presented are percent difference from controls as reported in study (actual values and variance were not reported).
[c]These parameters were reported together by the study authors.

NS = Not significantly different from controls (0 mg/kg-day in dietary milk gavage for 28 days).

APPENDIX C. BMD OUTPUTS

There are no BMD outputs to report.

APPENDIX D. REFERENCES

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