United States
Environmental Protection
Agency

EPA/690/R-12/031F
Final
12-10-2012

Provisional Peer-Reviewed Toxicity Values for

Thiocyanic Acid
(CASRN 463-56-9, 80864-27-3)

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

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHEMICAL MANAGER

Q. Jay Zhao, PhD, MPH, DABT, National Center for Environmental Assessment, Cincinnati, OH

DRAFT DOCUMENT PREPARED BY

National Center for Environmental Assessment, Cincinnati, OH

This document was externally peer-reviewed under contract to
Eastern Research Group, Inc.
110 Hartwell Avenue
Lexington, MA 02421-3136

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).

TABLE OF CONTENTS

COMMONLY USED ABBREVIATIONS

BMC	benchmark concentration
BMCL	benchmark concentration lower bound 95% confidence interval
BMD	benchmark dose
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
POD	point of departure
p-OSF	provisional oral slope factor
p-RfC	provisional reference concentration (inhalation)
p-RfD	provisional reference dose (oral)
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 THIOCYANIC ACID (CASRN 463-56-9, 80864-27-3)

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 (http://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

Thiocyanic acid, also known as hydrogen thiocyanate or hydrogen rhodanide, belongs to a class of chemicals called Thiocyanates (S-C≡N). Thiocyanates are a group of compounds formed from a combination of sulfur, carbon, and nitrogen (ATSDR, 2006). They occur naturally in various foods and plants such as spinach, radish, celery, and cabbage (RIVM, 2001) and are produced primarily from the reaction of free cyanide with sulphur (ATSDR, 2006). This reaction occurs in the environment (for example, in industrial waste streams that contain cyanide) and in the human body after cyanide is swallowed or absorbed (thiocyanate is the main metabolite of free cyanide). Thiocyanates are known to affect the thyroid gland, reducing iodine uptake and thereby reducing the ability of the gland to produce hormones that are necessary for the normal function of the body (U.S. EPA, 2006). In the past, thiocyanate was used therapeutically to treat severe hypertension, but the results of this therapy were inconsistent from clinic to clinic, and even within a single study. Thiocyanate is believed to play a role in an endogenous antibacterial system (lactoperoxidase/thiocyanate/hydrogen peroxide system) present in milk. It has been added commercially to some milk preparations as an antibacterial agent (U.S. EPA, 2006).

Table 1. Physicochemical Properties
Thiocyanic Acid (CASRN 463-56-9, 80864-27-3)[a]

Property (unit)	Value
Boiling point (ºC)	146ºC at 760 mm Hg
Melting point (ºC)	5
Density (g/cm^3)	1.126
Vapor pressure (mmHg at 25ºC)	4.73
pH (unitless)	N/A
Solubility in water (g/100 mL at 25ºC)	Good
Relative vapor density (air = 1)	2.0
pKa (20ºC)	1.1
Molecular weight (g/mol)	59.1

[a]Values from NIOSH (2006) and ChemSpider (2010).

No Reference Dose (RfD), Reference Concentration (RfC), or cancer assessment for thiocyanic acid is included on the United States Environmental Protection Agency (U.S. EPA) Integrated Risk Information System (IRIS) database (U.S. EPA, 2011a) or on the Drinking Water Standards and Health Advisories List (U.S. EPA, 2011b). No RfD or RfC values are reported in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 2011c). The Chemical Assessments and Related Activities (CARA) list does not include any EPA documents for thiocyanic acid (U.S. EPA, 1994). The toxicity of thiocyanic acid has not been reviewed by the Agency for Toxic Substances and Disease Registry (ATSDR, 2011) or the World Health

Organization (WHO, 2011). However, some aspects of thiocyanate toxicity were discussed in the ATSDR profile of cyanide because it is the main metabolite of cyanide (ATSDR, 2006). The California Environmental Protection Agency (CalEPA, 2008, 2012) has not derived toxicity values for exposure to thiocyanic acid. No occupational exposure limits for thiocyanic acid have been derived by the American Conference of Governmental Industrial Hygienists (ACGIH, 2011), the National Institute of Occupational Safety and Health (NIOSH, 2011), or the Occupational Safety and Health Administration (OSHA, 2011).

The HEAST (U.S. EPA, 2011c) does not report any cancer values for thiocyanic acid. The International Agency for Research on Cancer (IARC, 2011) has not reviewed the carcinogenic potential of thiocyanic acid. Thiocyanic acid is not included in the *12th Report on Carcinogens* (NTP, 2011). CalEPA (2012) has not derived a quantitative estimate of carcinogenic potential for thiocyanic acid.

There are available data on thiocyanate salts (such as sodium, potassium, and ammonium thiocyanate) that can potentially serve as suitable surrogates for thiocyanic acid. Most of the relevant data on thiocyanate salts have been reviewed in a Provisional Peer Reviewed Toxicity Value (PPRTV) document on the thiocyanates (U.S. EPA, 2006), which reports provisional subchronic and chronic reference doses for thiocyanates of 0.0006 and 0.0002 mg/kg-day, respectively. These provisional values are based on significant changes in thyroid function (thyroxine concentration, triiodothyronine, and thyroid stimulating hormone in blood serum) observed in a group of women exposed to thiocyanate in cow's milk for 5 years (Banerjee et al., 1997). In calculating both the subchronic and chronic p-RfD values, the lowest-observed-adverse-effect level (LOAEL) of 0.19 mg/kg-day from Banerjee et al. (1997) was used as the point-of-departure for both the subchronic and chronic p-RfD values, with a cumulative uncertainty factor of 300 and 1000 applied to the LOAEL, respectively. Confidence in the principal study is low (U.S. EPA, 2006). The carcinogenic potential of thiocyanates has not been reviewed (U.S. EPA, 2006). New toxicological studies on thiocyanates have been identified which were published after the PPRTV publication date.

The Netherlands National Institute of Public Health and the Environment, Research for Man and Environment (RIVM, 2001) established a Tolerable Daily Intake (TDI) of 0.011 mg/kg-day for thiocyanate (SCN^-). This was based on the NOAEL from a 90-day human study in which volunteers were exposed to milk containing SCN^- as sodium thiocyanate, using a UF of 10 (Dahlberg et al., 1984).

Literature searches were conducted on sources published from 1900 through September 2011 for studies relevant to the derivation of provisional toxicity values for thiocyanic acid (CAS No. 463-56-9 and 80864-27-3). Searches were conducted using 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 relevant health information: ACGIH, ATSDR, CalEPA, EPA IRIS, EPA HEAST, EPA HEEP, EPA OW, EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (CANCER AND NONCANCER)

The literature search revealed no human or animal studies, either acute, short term, or chronic, for thiocyanic acid.

DERIVATION OF PROVISIONAL VALUES

No subchronic and chronic p-RfD values can be derived because the literature search revealed no human or animal studies, either acute, short term, or chronic, for thiocyanic acid. However, there are available data on thiocyanate salts (such as sodium, potassium and ammonium thiocyanate) which can potentially serve as suitable surrogates for thiocyanic acid. Thiocyanic acid is a moderately strong acid, with a pKa of 1.1. In physiological conditions, it would be mostly dissociated, and thus, exposure to thiocyanic acid is presumably comparable to exposure to the thiocyanate anion. Thus, screening subchronic and chronic p-RfDs based on previous PPRTV assessment on thiocyanates are provided in Appendix A.

Limitations in the available data preclude development of inhalation RfC and cancer toxicity values.

CANCER WEIGHT-OF-EVIDENCE (WOE) DESCRIPTOR

Limitations in the available data preclude development of a WOE descriptor.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2011) Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: ACGIH. As cited in HSDB (Hazardous Substances Data Bank). Available online at http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB. Accessed on 12/29/2011.

ATSDR (Agency for Toxic Substances and Disease Registry). (2006) Toxicological profile for cyanide. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. Available online at http://www.atsdr.cdc.gov/ToxProfiles/tp8.pdf. Accessed on 12/29/2011.

ATSDR (Agency for Toxic Substances and Disease Registry). (2011) Toxicological profile information sheet. U.S. Department of Health and Human Services, Public Health Service, Atlanta, GA. Available online at http://www.atsdr.cdc.gov/toxprofiles/index.asp. Accessed on 12/29/2011.

Banerjee, KK; Marimuthu, P; Bhattacharyya, P; et al. (1997) Effect of thiocyanate ingestion through milk on thyroid hormone homeostasis in women. *Brit J Nutr* 78(5):679−681. (as cited in U.S. EPA, 2006).

CalEPA (California Environmental Protection Agency). (2012) All OEHHA acute, 8-hour and chronic reference exposure levels (chRELs) as on February2012. Office of Environmental Health Hazard Assessment, Sacramento, CA. Available online at http://www.oehha.ca.gov/air/allrels.html. Accessed on 11/28/2012.

CalEPA (California Environmental Protection Agency). (2011) OEHHA toxicity criteria database. Office of Environmental Health Hazard Assessment, Sacramento, CA. Available online at http://www.oehha.ca.gov/risk/\ChemicalDB/index.asp. Accessed on 12/29/2011.

ChemSpider. (2010) Thiocyanic acid. The Royal Society of Chemistry (RSC). Available online at http://www.chemspider.com/Chemical-Structure.760.html?rid=e8084690-3764-4230-ba9f-d5b49f467818. Accessed on 11/04/2010.

Dahlberg, PA; Bergmark, A; et al. (1984) Intake of thiocyanate by way of milk and its possible effect on thyroid function. *Am J Clin Nutr* 39(3):416−420. (as cited in U.S. EPA, 2006).

Dahlberg, PA; Bergmark, A; Eltom, M; et al. (1985) Effect of thiocyanate levels in milk on thyroid function in iodine deficient subjects. *Am J Clin Nutr* 41(5):1010−1014. (as cited in U.S. EPA, 2006).

de Sousa, AB; Maiorka, PC; Goncalves, ID; et al. (2007) Evaluation of effects of prenatal exposure to the cyanide and thiocyanate in wistar rats. *Repro Toxicol* 23(4):568−577

IARC (International Agency for Research on Cancer). (2011) Monographs on the evaluation of carcinogenic risks to humans. Lyon, France: IARC. Available online at http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php. Accessed on 12/29/2011.

NIOSH (National Institute for Occupational Safety and Health). (2006) Thiocyanic acid. International Chemical Safety Cards. ICSC 1671. Available online at http://www.cdc.gov/niosh/ipcsneng/neng1671.html.

NIOSH (National Institute for Occupational Safety and Health). (2011) NIOSH pocket guide to chemical hazards. Index of chemical abstracts service registry numbers (CAS No.). Center for Disease Control and Prevention, U.S. Department of Health, Education and Welfare, Atlanta, GA. Available online at http://www.cdc.gov/niosh/npg/npgdcas.html. Accessed on 12/29/2011.

NTP (National Toxicology Program). (2011) 12th Report on carcinogens. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC.

OSHA (Occupational Safety and Health Administration). (2011) Air contaminants: occupational safety and health standards for shipyard employment, subpart Z, toxic and hazardous substances. U.S. Department of Labor, Washington, DC; OSHA Standard 1915.1000. Available online at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10286. Accessed on 12/29/2011.

RIVM (National Institute of Public Health and the Environment). (2001) Re-evaluation of human-toxicological maximum permissible risk levels. RIVM report no. 711701025. Bilthoven, The Netherlands: RIVM; pp. 86−95. Available online at http://www.rivm.nl/bibliotheek/rapporten/711701025.pdf.

Soto-Banco, B; Stegelmeier, BL; Pfister, JA; et al. (2008) Comparative effects of prolonged administration of cyanide, thiocyanate and chokecherry (*Prunus virginiana*) to goats. *J Appl Toxicol* 28(3):356−363

U.S. EPA (Environmental Protection Agency). (1994) Chemical assessments and related activities (CARA). Office of Health and Environmental Assessment, Washington, DC; EPA/600/R-94/904. Available online at http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=60001G8L.txt.

U.S. EPA (Environmental Protection Agency). (2006) Provisional peer reviewed toxicity values for thiocyanates. Office of Research and Development, National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (STSC), Cincinnati, OH. Available online at http://hhpprtv.ornl.gov/quickview/pprtv.php?chemical=Thiocyanate. Accessed on 10/06/2010.

U.S. EPA (Environmental Protection Agency). (2011a) Integrated risk information system (IRIS). Office of Research and Development, National Center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris/. Accessed on 12/29/2011.

U.S. EPA (Environmental Protection Agency). (2011b) 2011 Edition of the drinking water standards and health advisories. Office of Water, Washington, DC; EPA 820-R-11-002. Available online at http://water.epa.gov/action/advisories/drinking/upload/dwstandards2011.pdf. Accessed on 12/29/2011.

U.S. EPA (Environmental Protection Agency). (2011c) Health effects assessment summary tables (HEAST). Prepared by the Office of Research and Development, National Center for Environmental Assessment, Cincinnati OH for the Office of Emergency and Remedial Response, Washington, DC. Available online at http://epa-heast.ornl.gov/. Accessed on 12/29/2011.

WHO (World Health Organization). (2011) Online catalogs for the Environmental Health Criteria series. Available online at http://www.who.int/ipcs/publications/ehc/en/. Accessed on 12/29/2011.

APPENDIX A. PROVISIONAL SCREENING VALUES

For reasons noted in the main PPRTV document, it is not possible to derive provisional toxicity values for thiocyanic acid. However, information is available for this chemical 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 an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an Appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an Appendix 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 Health Risk Technical Support Center.

DERIVATION OF SCREENING PROVISIONAL ORAL REFERENCE DOSE

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

Due to its low pKa value, thiocyanic acid would be likely dissociated in physiological conditions. Therefore, it acts similarly as a thiocyanate anion. The screening subchronic p-RfD is based on the subchronic p-RfD derived for thiocyanates (U.S. EPA, 2006). Appendix B presents a detailed derivation of the p-RfDs for thiocyanates.

For thiocyanates, the available human data clearly identify both decreased blood pressure and changes in thyroid function as sensitive effects of oral exposure to thiocyanates. However, the effects on blood pressure were reported at doses generally ranging from 1.3−4.3 mg (SCN)/kg-day (U.S. EPA, 2006), while effects on the thyroid occurred at exposure levels of ≥0.19 mg (SCN)/kg-day in healthy subjects (Banerjee et al., 1997). Animal studies likewise indicate that the thyroid is the most sensitive target of thiocyanate toxicity. However, the effect levels are considerably greater in animal studies (on the order of 15−100 mg/kg-day) than in the available human studies based on U.S. EPA (2006), even though an updated literature search identified some lower effective doses (summarized below).

An updated literature review identified two new animal studies that evaluated thiocyanate toxicity (Soto-Blanco et al., 2008; de Sousa et al., 2007) since 2006 to August 2011. Soto-Blanco et al. (2008) reported that after 4 weeks of treatment with 4.5-mg potassium thiocyanate (KSCN)/kg-day (equivalent to 2.6 mg [SCN]/kg-day) by gavage, female goats (4 animals/group) had an increased number of vacuoles in the colloid of thyroid glands. In a developmental (Trial A) and reproductive (Trial B) study (de Sousa et al., 2007), female Wister rats received daily doses of 0.8, 2.4, or 24 mg (KSCN)/kg-day (equivalent to 0.48, 1.4, or 14 mg [SCN]/kg-day) in drinking water from GDs 6−21 (Trial A), or GD 6 to 1 day after weaning (PND 21). Dams and pups were examined for comprehensive developmental (Trial A) and reproductive endpoints (Trial B), respectively. The most sensitive response observed in this study was an increase in the number of mild reabsorption vacuoles in follicular colloid in the thyroid of dams exposed to thiocyanate (≥0.48 mg [SCN]/kg-day) during gestation. Although these two studies identified animal effective doses lower than those in the database reported in the PPRTV assessment for thiocyanates (U.S. EPA, 2006), they are still higher than the LOAEL

of 0.19 mg (SCN)/mg-day in humans (Banerjee et al., 1997), which served as the basis for deriving the thiocyanate p-RfDs.

The study of Banerjee et al. (1997) evaluated a group of women exposed to an average of 0.19-mg thiocyanate (SCN)/kg-day for 5 years, relative to a matched control group. In addition to elevated serum thiocyanate levels, a significant increase in serum TSH and a significant decrease in serum T4 were observed in thiocyanate-exposed women. While the change in TSH was statistically significant ($p < 0.01$) from the controls, the mean value of the treated group (2.49 μU/mL) was within the normal range of the assay (0.2−4.0 μU/mL). Serum T4 was both statistically different from controls and altered to a level outside of the normal assay range. The 0.19-mg (SCN)/kg-day exposure level is, therefore, identified as a LOAEL for changes in thyroid endpoints.

The Dahlberg et al. (1985) study identified a lowest LOAEL of 0.018 mg (SCN)/kg-day for decreased serum TSH, T3, and T4 in iodine-deficient subjects exposed to thiocyanate for 4 weeks. However, concerns over the design of this study, including the age of the study group (13−17 years), the comparatively short duration (4 weeks), and the fact that the subjects were goiterous in Stage I or II (and, therefore, already had an existing thyroid condition) prior to the start of the study, preclude its selection as the principal study for derivation of the subchronic or chronic p-RfD for thiocyanates. Another study by the same investigators (Dahlberg et al., 1984) identified a NOAEL of 0.11 mg (SCN)/kg-day for effects on thyroid function in healthy volunteers exposed for 12 weeks, but concerns regarding the comparatively short study duration and the lack of identification of a LOAEL preclude its selection as the principal study for p-RfD derivation for thiocyanates.

The LOAEL of 0.19 mg (SCN)/kg-day reported by Banerjee et al. (1997) is supported by a LOAEL of 0.018 mg(SCN)/kg-day in sensitive subjects reported by Dahlberg et al. (1985), which is approximately an order of magnitude lower than that of healthy subjects, as would be expected from a standard UF approach. The Banerjee et al. (1997) study was, therefore, selected as the principal study for p-RfD derivation for thiocyanates.

A subchronic p-RfD of 6×10^{-4} mg/kg-day was derived previously for thiocyanates (U.S. EPA, 2006) based on the LOAEL of 0.19 mg/kg-day divided by a composite UF of 300 (10 to protect sensitive individuals, 10 for use of a LOAEL, and 3 for deficiencies in the database, specifically the limited evaluations of dose response available for humans, because effects in animals appear to occur at higher doses).

Considering thiocyanic acid would mostly dissociate and act as a thiocyanate anion in biological conditions, a screening subchronic p-RfD for thiocyanic acid is derived based on a molecular weight (MW) conversion from the subchronic p-RfD for thiocyanates as follows:

Screening Subchronic p-RfD = Thiocyanate Subchronic p-RfD × [MW (HSCN) ÷ MW (SCN)]
= 6×10^{-4} mg/kg-day × (59.1 g/mol ÷ 58.1 g/mol)
= **6×10^{-4} mg/kg-day**

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

Similar to the Screening Subchronic p-RfD, the screening chronic p-RfD is based on the chronic p-RfD derived previously for thiocyanates (U.S. EPA, 2006). The chronic p-RfD of 2×10^{-4} mg(SCN)/kg-day for thiocyanates was derived by applying an additional UF of 3 for extrapolation from subchronic (in the principal study) to chronic duration. A full factor of 10 was not applied because while the Banerjee et al. (1997) study ran for less than 10% of the total expected lifespan, the study duration of 5 years was likely sufficient to establish an equilibrium of thiocyanate levels within the body, based on an estimated serum half-life of approximately 3 days. The composite UF for the chronic p-RfD for thiocyanates is, therefore, 1000 (3 for extrapolation from subchronic to chronic duration, 10 to protect sensitive individuals, 10 for use of a LOAEL, and 3 for deficiencies in the database).

A screening chronic p-RfD of 2×10^{-4} mg/kg-day for thiocyanic acid is derived based on a MW conversion from the chronic p-RfD for thiocyanates as follows:

Screening Chronic p-RfD = Thiocyanate Chronic p-RfD × [MW (HSCN) ÷ MW (SCN)]
= 2×10^{-4} mg/kg-day × (59.1g/mol ÷ 58.1 g/mol)
= **2×10^{-4} mg/kg-day**

APPENDIX B. PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR THIOCYANATES

3-15-2006

Provisional Peer Reviewed Toxicity Values for

Thiocyanates
(Multiple CASRNs)

Derivation of Subchronic and Chronic Oral RfDs

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

ACRONYMS AND ABBREVIATIONS

Bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit

NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose
PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR THIOCYANATES (MULTIPLE CASRNs)
Derivation of Subchronic and Chronic Oral RfDs

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

Neither a subchronic nor a chronic reference dose (RfD) for thiocyanates is listed on the Integrated Risk Information System (IRIS) (U.S. EPA, 2006), in the Health Effects Assessment Summary Tables (HEAST) (U.S. EPA, 1997), or in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2004). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1991, 1994) does not report any relevant documents for thiocyanates. The Agency for Toxic Substances and Disease Registry (ATSDR) (2005), International Agency for Research on Cancer (IARC) (2005), National Toxicology Program (NTP) (2005) and the World Health Organization (WHO) (2005) have not published documents for thiocyanates. Literature searches were conducted from 1965 to September, 2002 in TOXLINE, MEDLINE, CANCERLIT, CCRIS, TSCATS, HSDB, RTECS, GENETOX, DART/ETICBACK and EMIC/EMICBACK. Update literature searches were conducted from September, 2002 to August, 2005 in MEDLINE, TOXLINE (NTIS), TOXCENTER (BIOSIS), TSCATS, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS and Current Contents. Searches were conducted for the following thiocyanates: sodium thiocyanate (CASRN 540-72-7), potassium thiocyanate (CASRN 333-20-0), calcium thiocyanate (CASRN 2092-16-2), ammonium thiocyanate (CASRN 1762-95-4) and thiocyanic acid (CASRN 463-56-9).

REVIEW OF THE PERTINENT LITERATURE

Human Studies

In the past, thiocyanate was used therapeutically to treat severe hypertension. A number of early reports describe the efficacy of thiocyanate therapy, with 45-78% of treated patients responding favorably to the treatment (Barker, 1936; Barker et al., 1941; Palmer et al., 1929). Dose levels ranged from 0.09-0.3 g/day (1.3-4.3 mg/kg-day, assuming a 70 kg reference body weight) with a general lowering of blood pressure of 20-40 mm Hg. However, the results of thiocyanate therapy were inconsistent from clinic to clinic, and even within a single study two patients rarely responded similarly to equivalent treatment regimens (Barker, 1936). Numerous adverse effects were noted in treated patients, including weakness, swollen face, somnolence, enlarged thyroid, and death (Barker, 1936; Barker et al., 1941; Palmer et al., 1929; Russel and Stahl, 1942). These effects were unpredictable in occurrence, even when blood thiocyanate levels were monitored to control the dose. The mechanism of the antihypertensive effects of thiocyanate is not presently known.

Of particular note were the reports of effects of thiocyanate exposure on the thyroid. While the reported incidence of thyroid-related effects was generally less than 10% (Barker et al., 1941; Taylor, 1945), the studies typically noted only gross changes, with no discussion of possible alterations in functional status. Thiocyanate has since been shown to produce a marked, reversible depression of thyroid iodine uptake, which is exacerbated by iodine deficiency and can be reduced or eliminated by co-exposure to iodide (Beamish et al., 1954; Thilly et al., 1980). Later studies (Banerjee et al., 1997; Dahlberg et al., 1984, 1985; Delange et al., 1980a; Thilly et al., 1980) have reported that elevated thiocyanate levels in serum can have effects on the histologic structure and function of the thyroid.

Thiocyanate is believed to play a role in an endogenous antibacterial system (lactoperoxidase/ thiocyanate/ hydrogen peroxide system) present in milk. It has been added commercially to some milk preparations as an antibacterial agent. Dahlberg et al. (1984) exposed 37 volunteers (9 males and 28 females) affiliated with University departments in Uppsala (Sweden), ages 16-54, to milk containing 20 mg SCN (thiocyanate)/L as sodium thiocyanate. The human subjects research ethics of this study were reviewed and approved by the Human Subjects Committee of the University of Upsala, Sweden. Of the subjects, 32 were nonsmokers and 5 were smokers; smokers and nonsmokers were analyzed separately. All subjects had normal dietary habits, were of normal health status and had no early incidence of goiter or thyroid dysfunction. Each subject consumed 200 mL of milk twice daily, for a total intake of 8 mg SCN/day, for 12 weeks; assuming a reference body weight of 70 kg, the average daily dose was 0.11 mg SCN/kg-day. Serum thiocyanate levels were significantly increased at 4, 8 and 12 weeks of exposure in nonsmokers and at 4 weeks in smokers. No changes were seen in urinary iodine levels in either group at any evaluated time point. No significant changes were reported in serum concentrations of thyroxine (T_4), triiodothyronine (T_3) or thyroid-stimulating hormone (TSH) in either the smokers or the nonsmokers. Effects on other endpoints were not evaluated.

Dahlberg et al. (1985) examined the effect of 4 weeks of exposure to thiocyanate on 55 iodine-deficient subjects (31 males, 24 females) between 13 and 17 years of age. The subjects

were volunteers from four different secondary schools in western Sudan, where goiter is endemic, reportedly as a consequence of dietary iodine deficiency. The human subjects research ethics of this study were reviewed and approved by the Human Subjects Committee of the University of Upsala, Sweden and by the University of Kartoum, Sudan. All subjects were goiterous in stage I and II based on the size of the thyroid gland, but otherwise had a normal health status and were clinically euthyroid. Subjects consumed 250 mL of milk containing either 3.6 mg SCN/L (n=19) or 19 mg SCN/L (n=18) per day; an additional group received milk containing 19 mg SCN/L together with an iodine supplement. Using an estimated mean body weight of 50 kg for the Sudanese teenagers (which appears reasonable based on average body weights of 53 to 65 kg for U.S. teenagers of the same ages [U.S. EPA, 2002]), average daily doses were 0.018 mg/kg-day and 0.095 mg/kg-day for the 3.6 mg/L and 19 mg/L groups, respectively. Day 0 readings for each group served as reference values for statistical analysis. Serum thiocyanate levels were significantly elevated in both groups receiving 19 mg SCN/L, but not in the 3.6 mg SCN/L group. In all groups, an increase in urinary iodine was seen following thiocyanate exposure; the magnitude of the change was greatest in the iodine-supplemented subjects and lowest in the unsupplemented 19 mg/L group. Thiocyanate exposure resulted in significantly decreased serum TSH in all groups (14%, 17% and 25% decreases in the 3.6 mg/L, 19 mg/L and 19 mg/L+iodine groups, respectively), as well as decreased T_3 (12.5% and 15% decrease in the 3.6 and 19 mg/L groups, respectively) and T_4 (13% and 11% decrease in the 3.6 and 19 mg/L groups, respectively) in groups without iodine supplementation. Iodine supplementation reversed the decrease in serum T_3 and T_4 levels seen in the 19 mg/L group. Other endpoints were not evaluated in this study.

Banerjee et al. (1997) evaluated the chronic effects of oral thiocyanate on women in Calcutta. Thirty five women who had consumed ~250 mL/day of a commercially-available cow's milk containing 30-50 mg SCN/L (average level of 45 mg SCN/L) for the previous 5 years were selected as the exposed group, while an equal number of women matched for age and dietary habits, aside from consumption of thiocyanate-treated milk, were designated as the control group. Review of the publication does not provide information on the human subjects research ethics procedures undertaken in this study, but there is no evidence that the conduct of the research was fundamentally unethical or significantly deficient. Women from both groups had similar dietary patterns, did not use tobacco products and had no prior history of thyroid disease. Blood was taken from each subject and analyzed for serum levels of SCN, TSH, T_3, and T_4, and a urine sample was taken for iodine determination. Other endpoints were not evaluated. Based on the average milk concentration of 45 mg SCN/L, an estimated milk consumption of 0.25 L/day, and a reference body weight for women of 60 kg, average daily consumption of thiocyanate was 0.19 mg/kg-day. No differences in urinary iodine elimination were noted between groups. The results of the thyroid hormone evaluations are presented in Table 1, below. Women who consumed SCN-containing milk had significantly lower levels of serum T_4 and significantly greater levels of serum TSH than controls; serum T_3 levels were elevated, but not significantly. The decrease in serum T_4 went below normal levels, as described by the assay manufacturer. Significant correlations were found between serum thiocyanate concentrations and serum T_4 (negative correlation) and TSH levels (positive correlation) in the exposed group; similar correlations were not found in the control group. Although the data in Table 1 suggest that levels of serum thiocyanate in controls were above normal, the researchers noted that a previous analysis conducted on non-smokers from the same geographic region as the current

study found serum thiocyanate levels in non-smokers for this region in the range of 80-100 µmol/L, which is consistent with results of this study.

Table 1 – Results of Banerjee et al. (1997) Evaluations of Thyroid Endpoints

	Control Subjects		Thiocyanate Subjects		Normal Range
	Mean	SE	Mean	SE	
SCN (umol/L)	90.8	9.0	230.0[a]	10.0	34-69[b]
T_4 (nmol/L)	125.4	11.5	87.8[a]	6.6	110-270[c]
T_3 (nmol/L)	1.71	0.16	2.39	0.32	0.93-3.12[c]
TSH (µU/mL)	1.09	0.28	2.49[a]	0.20	0.2-4.0[c]

[a] significantly different ($p<0.01$) from the control group
[b] Pechacek et al., 1985
[c] reported by the assay manufacturer

Studies of humans who consume heavy amounts of cassava, consisting of up to 80% of the total diet in some cases (Dorea et al., 2004), have provided suggestive evidence of effects of thiocyanate on the thyroid of both adults and the developing child. Cassava contains high levels of cyanide, which, when consumed orally, is metabolized to thiocyanate; considerable increases (up to 5-fold or more) in blood thiocyanate levels have been reported following exposure to cyanide-rich cassava (Cliff et al., 1986; Delange et al., 1980b).

Delange et al. (1980b) reported that pregnant women in Zaire who regularly consumed cassava had statistically significantly elevated blood thiocyanate levels relative to a control group of pregnant Belgian women (0.68 mg SCN/dL in the Zairian women, relative to 0.21 mg SCN/dL in the Belgian women), as well as significantly elevated TSH (14.0 µU/mL in the Zairian women and 3.9 µU/mL in the Belgian women) and significantly decreased serum concentrations of T_4 (8.6 µg/dL in the Zairian women and 15.3 µg/dL in the Belgian women) and T_3 (191 ng/dL in the Zairian women and 220 ng/dL in the Belgian women). In newborns of these women, significantly greater serum SCN levels were noted (0.62 mg/dL in the Zairian newborns and 0.19 mg/dL in the Belgian newborns), as well as significantly increased serum TSH (50.9 µU/mL in the Zairian newborns and 6.8 µU/mL in the Belgian newborns) and T_3 (106 ng/dL in the Zairian newborns and 60 ng/dL in the Belgian newborns) and significantly decreased serum T_4 (7.5 µg/dL in the Zairian newborns and 12.0 µg/dL in the Belgian newborns). Similar results were seen in infants (aged 2 weeks to 15 months), with significantly increased serum SCN (0.55 mg/dL in the Zairian infants and 0.38 mg/dL in the Belgian infants) and TSH (52.6 µU/mL in the Zairian infants and 3.5 µU/mL in the Belgian infants) and significantly decreased T_4 (6.9 µg/dL in the Zairian infants and 8.7 µg/dL in the Belgian infants); serum levels of T_3 were not affected in infants. Maternal serum concentrations of thiocyanate at delivery were linearly correlated with those in the umbilical cord blood. Concentrations of thiocyanate in the milk were not significantly different between Zairian and Belgian mothers.

Animal Studies

In an early study of the subchronic toxicity of thiocyanate, Anderson and Chen (1940) exposed groups of 10 female rats (strain unspecified) by gavage to 100 mg sodium thiocyanate/kg-day (~71.6 mg SCN/kg-day), 100 mg potassium thiocyanate/kg-day (~59.8 mg SCN/kg-day) or vehicle 5 days/week for 12 weeks. Prior to study termination, four control rats, four sodium thiocyanate rats and two potassium thiocyanate rats died due to gavage errors. Neither thiocyanate compound resulted in growth inhibition; effects on other endpoints were not reported. A follow-up experiment was conducted, exposing groups of 10 rats to 200 mg of sodium or potassium thiocyanate (143 or 120 mg SCN/kg-day, respectively) 5 days/week for 8 weeks. As with the previous experiment, no changes in growth were seen as a result of thiocyanate treatment and other endpoints were not evaluated. In the third portion of the study, groups of dogs (n=4-5) were exposed to approximately 100 mg/kg-day of sodium (~71.6 mg SCN/kg-day) or potassium (~59.8 mg SCN/kg-day) thiocyanate, as enterically-coated capsules, 5 days/week for up to 3 months. Repeated ingestion of 100 mg/kg-day of sodium or potassium thiocyanate resulted in severe clinical effects, including progressive weight loss, apathy, head-droop and ataxia; all animals but one at this exposure level died, despite discontinuation of exposure (cause of death could not be determined). Another group of three animals, one of which had been previously exposed to higher levels of thiocyanate, was exposed to 20-25 mg/kg-day; these animals showed no evidence of toxicity (further details not reported). A single dog exposed to 31 mg sodium thiocyanate/kg-day died following 7 weeks of treatment during which the dog showed progressive body weight decrease; a precise cause of death was not determined.

Lindberg et al. (1941) exposed 12 dogs to 300 mg potassium thiocyanate/day (75 mg SCN/kg-day, assuming a reference body weight [U.S. EPA, 1988] of 2.4 kilograms) for 3 months. Body weight and clinical signs were not evaluated. Thiocyanate exposure resulted in an abrupt fall in blood cholesterol, followed by a slow decline over time. There was a rough parallel between elevation of blood thiocyanate levels and decreased cholesterol level once the initial decrease had stabilized. A similar effect was noted for total plasma protein levels. Thiocyanate exposure resulted in a fall in erythrocyte numbers, as well as decreased hematocrit and hemoglobin; no changes were seen in white cell numbers. Histologic sections of bone marrow revealed an essentially acellular bone marrow in treated animals, and examination of the livers of treated animals revealed a diffuse intracellular vacuolization with no evidence of hyperplasia or regeneration; no changes were seen in the adrenal glands of treated animals.

Nagasawa et al. (1980) exposed groups of 18 weanling SHN female mice (a strain with a high background mammary tumor incidence) to 0, 0.1 or 0.3% potassium thiocyanate in the drinking water for 12 weeks. Using the allometric equations and mean body weights presented in U.S. EPA (1988), mean thiocyanate doses were estimated at 0, 153 and 457 mg SCN/kg-day for the 0, 0.1 and 0.3% groups, respectively. No differences between groups were noted in body weight or body weight gain, estrous cycle pattern, pituitary or adrenal weight or ovarian histology. Dose-related decreases in serum T_3 (significant in the 0.3% group) and T_4 (significant in the 0.1 and 0.3% groups) were reported. Development of the lobulo-alveolar system of the mammary gland was significantly inhibited in the 0.3% group. Dose-related decreases in preneoplastic mammary hyperplastic alveolar nodules and mammary tumor incidence were reported; these decreases attained statistical significance in the 0.3% animals.

In a second experiment, Nagasawa et al. (1980) exposed groups of 19-22 female GR/A mice to 0, 0.1 or 0.3% potassium thiocyanate in the drinking water for 5 weeks prior to and for 10 weeks following mating; exposure was discontinued for the 3 days during which mating occurred. Using the allometric equations and mean body weights presented in U.S. EPA (1988), mean thiocyanate doses were estimated at 0, 155 and 470 mg SCN/kg-day for the 0, 0.1 and 0.3% groups, respectively. At the end of exposure, the animals were sacrificed and examined for changes in reproductive parameters (number of pregnancies, litter size, pup weight, percent stillborn pups) and the presence of pregnancy-dependent mammary tumors (PDMT). On day 4 of lactation, plasma prolactin levels were evaluated in the dams. No changes in maternal body weight, evaluated reproductive parameters or plasma prolactin levels were noted following thiocyanate treatment. Treatment with thiocyanate resulted in a significantly decreased number of PDMT (16/22, 7/20, 5/19 PDMT in the 0, 0.1 and 0.3% groups, respectively). No other endpoints were evaluated in the study.

Ermans et al. (1980) exposed groups of rats (n=9-25) to 0.1-10 mg thiocyanate/day (~0.6-56 mg/kg-day, based on a reference body weight of 180 g) in the diet for 2-5 weeks; the diet was intentionally iodine-deficient. Treated rats showed a dose-related depletion of thyroid iodine content, reaching 40-50% of the control value. Exposure to 10 mg/day resulted in a significant decrease in T_4 levels, while T_3 levels were not altered. Effects on organs other than the thyroid were not reported.

Philbrick et al. (1979) exposed groups (n=10) of male rats to 0 or 2240 ppm potassium thiocyanate (KSCN) in the diet for 11.5 months. Both iodine-supplemented and iodine-deficient diets were provided, with appropriate controls. Using a reference body weight of 380 grams and reference food consumption of 30 g/day (U.S. EPA, 1988), an average daily dose of 106 mg SCN/kg-day can be estimated. At 4 and 11 months, five animals per group were evaluated for plasma T_4, T_4 secretion rates and urinary thiocyanate concentrations. At terminal sacrifice, weights of whole brain, heart, liver and thyroid were obtained. Brain, optic nerves, spinal cord and thyroid glands were fixed for light microscopy and sections of spinal cord were prepared for electron microscopic evaluation. No changes in body weight gain were seen as a result of KSCN treatment and no adverse clinical effects were reported. Treatment with thiocyanate resulted in significant decreases in plasma T_4 and T_4 secretion rate at 4 months and decreased thyroid weight and plasma T_4 at 11 months; T_4 secretion rate was not different from controls after 11 months of thiocyanate exposure. No definitive histological changes in the thyroid gland, optic or sciatic nerves or neural tissues were seen in animals receiving iodine supplementation along with KSCN treatment. However, it appeared that KSCN treatment resulted in an alteration of the vacuolization in spinal cord tissues that was seen in control animals fed an iodine-deficient diet. This vacuolization, which was accompanied by a mild-to-moderate astrogliosis (no quantification was provided), was seen at both the light and electron microscopic level.

Bala et al. (1996) exposed groups of 8-week old female Wistar/NIN rats to 0 or ~15 mg SCN/kg-day, as potassium thiocyanate, for varying times throughout conception and lactation. After 8 weeks of exposure, the animals were mated with control males and monitored throughout gestation, parturition and lactation. In one group, the effect of exposure of the offspring was also examined, using the same dietary exposure level, with a parallel group that was exposed during gestation and weaning but not post-weaning. Exposure to KSCN did not affect the body weight

or the ratio of brain-to-body weight of any group of dams. Animals exposed to KSCN from the beginning of the experiment through weaning showed a significantly increased urinary excretion of iodine, as well as increased thyroid weight and decreased levels of serum T_4. In the pups of animals exposed to SCN, a significant decrease in serum T_4 levels was noted; this decrease was present whether the dams had been exposed from the beginning of the study, were exposed from conception through weaning or were exposed only after giving birth. Pup body weights at weaning were decreased in animals exposed beginning at conception through weaning, but not in those exposed throughout the experiment or those only exposed postpartum. Exposure to SCN did not result in a significant change in the uptake of sucrose, leucine, tyrosine or 2-deoxy-D-glucose, regardless of time of exposure. Offspring not exposed during gestation, but exposed in the diet post-weaning showed significant decreases in serum T_4 and significant increases in brain weight, as did offspring exposed during gestation and lactation, but not exposed post-weaning. The paper did not report on the presence or lack of malformations in the offspring of treated dams.

In a subsequent report, Raghunath and Bala (1998) examined the offspring of Wistar/NIN rat dams exposed either prior to mating throughout weaning, from conception through weaning or from parturition through weaning (offspring of the dams from Bala et al., 1996) to ~15 mg SCN/kg-day in the diet, as potassium thiocyanate, for 8 weeks. At weaning (the start of the follow-up study), the offspring in all three treated groups already had lower serum T_4 levels, relative to untreated controls. Further treatment with SCN did not result in an additional lowering of serum T_4 levels. Offspring of animals exposed continuously from weaning, through pregnancy and lactation, showed a decreased brain uptake of 2-deoxy-D-glucose relative to controls; this change was not noted in the offspring of animals treated from conception onward or in those whose dams were only exposed during weaning.

In a second portion of the manuscript (Raghunath and Bala, 1998), the authors describe a continuous 2-generation exposure to ~15 mg SCN/kg-day, as potassium thiocyanate, in Wistar/NIN rats. F_0 animals were exposed from weaning (8 weeks of age) throughout gestation and lactation. At weaning, the F_1 pups were exposed to an identical diet for 8 weeks, then mated and exposed throughout gestation, parturition and weaning. F_2 pups showed no changes in body weight at birth or weaning and brain weight was not affected. Serum levels of T_4 were significantly decreased in F_2 pups; this decrease was greater than the decrease seen in their F_1 counterparts. Treated F_2 rats showed a significant decrease in the brain uptake of 2-deoxy-D-glucose, leucine and tyrosine; brain uptake of sucrose was not affected. Effects on other endpoints were not evaluated.

Delange et al. (1980a) exposed pregnant Wistar rats to 0 or 10 mg thiocyanate/day from the second day of pregnancy through weaning (postnatal day 16). Based on body weights provided in the manuscript, the average daily dose was calculated to be 45-56 mg/kg-day. Additional groups received 25 or 100 µg of potassium iodide by intraperitoneal injection 2 days prior to delivery. Exposure to SCN had no effect on body weights of the dams at birth or at the end of exposure. Maternal thyroid weights were increased, but not significantly. At both delivery and weaning, hyperplasia of the thyroid was noted in SCN-exposed dams; treatment with iodide resulted in a dose-related reduction in the severity of the hyperplastic effect. A significant decrease in T_4 was noted only at delivery and a decrease in T_3 was noted only at

weaning; treatment with iodide completely reversed these effects. Weights of the pups were not affected by exposure with the exception of the group that received 25 μg of iodide prior to delivery (pup weights in 100 μg iodide group were not different from controls). Effects in pups at weaning, relative to controls, were significantly increased thyroid weights, hyperplasia of the thyroid and decreased levels of serum T_4; administration of iodide prior to birth did not ameliorate these effects.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC RfDs FOR THIOCYANATES

The available human data clearly identify both decreased blood pressure and changes in thyroid function as sensitive effects of oral exposure to thiocyanates. However, the effects on blood pressure were reported at doses generally ranging from 1.3-4.3 mg/kg-day (Barker, 1936; Barker et al., 1941; Palmer et al., 1929), while effects on the thyroid occurred at exposure levels of 0.19 mg/kg-day in healthy subjects (Banerjee et al., 1997). Animal studies likewise indicate that the thyroid is the most sensitive target of thiocyanate toxicity, although the effect levels are considerably greater in animal studies (on the order of 15-100 mg/kg-day) than in the available human studies.

The Dahlberg et al. (1985) study was considered for use as the principal study in p-RfD derivation because it identified the lowest LOAEL in exposed humans, 0.018 mg/kg-day for decreased serum TSH, T_3 and T_4 in iodine-deficient subjects exposed to thiocyanate for 4 weeks. However, concerns over the design of this study, including the age of the study group (13-17 years), the comparatively short duration (4 weeks) and the fact that the subjects were goiterous in stage I or II (and therefore already had an existing thyroid condition) prior to the start of the study, preclude its selection as the principal study for derivation of the subchronic or chronic p-RfD. Another study by the same investigators (Dahlberg et al., 1984) identified a NOAEL of 0.11 mg/kg-day for effects on thyroid function in healthy volunteers exposed for 12 weeks, but concerns regarding the ages of the study population, the comparatively short study duration and the lack of identification of a LOAEL preclude its selection as the principal study for p-RfD derivation.

The study of Banerjee et al. (1997) evaluated a group of women exposed to an average of 0.19 mg thiocyanate/kg-day for 5 years, relative to a matched control group. In addition to elevated serum thiocyanate levels, a significant increase in serum TSH and a significant decrease in serum T_4 were observed in thiocyanate-exposed women. While the change in TSH was statistically significant ($p<0.01$) from the controls, the mean value of the treated group (2.49 μU/mL) was within the normal range of the assay (0.2-4.0 μU/mL). Serum T_4 was both statistically different from controls and altered to a level outside of the normal assay range. The 0.19 mg/kg-day exposure level is therefore identified as a LOAEL for changes in thyroid endpoints. The LOAEL is supported by the LOAEL of 0.018 mg/kg-day in sensitive subjects reported by Dahlberg et al. (1985), which is approximately an order of magnitude lower than that of healthy subjects, as would be expected from a standard uncertainty factor (UF) approach. The Banerjee et al. (1997) study was therefore selected as the principal study for p-RfD derivation.

To derive the subchronic p-RfD, the LOAEL of 0.19 mg/kg-day is divided by an UF of 300 (10 to protect sensitive individuals, 10 for use of a LOAEL and 3 for deficiencies in the database, specifically the limited evaluations of dose-response available for humans, since effects in animals appear to occur at considerably higher doses). The **subchronic p-RfD of 6E-4 mg/kg-day** is derived as follows:

$$\begin{aligned} \text{Subchronic p-RfD} &= \text{LOAEL} \div \text{UF} \\ &= 0.19 \text{ mg/kg-day} \div 300 \\ &= 0.0006 \text{ or } 6\text{E-}4 \text{ mg/kg-day} \end{aligned}$$

To derive the chronic p-RfD, an additional UF of 3 was applied for extrapolation from subchronic to chronic duration. A full factor of 10 was not applied because while the Banerjee et al. (1997) study ran for less than 10% of the total expected lifespan, the study duration of 5 years was likely sufficient to establish an equilibrium of thiocyanate levels within the body, based on an estimated serum half-life of approximately 3 days (Schulz, 1984). The total UF for the chronic p-RfD is therefore 1000 (3 for extrapolation from subchronic to chronic duration, 10 to protect sensitive individuals, 10 for use of a LOAEL and 3 for deficiencies in the database, specifically the limited evaluations of dose-response available for humans, since effects in animals appear to occur at considerably higher doses). The **chronic p-RfD of 2E-4 mg/kg-day** is derived as follows:

$$\begin{aligned} \text{p-RfD} &= \text{LOAEL} \div \text{UF} \\ &= 0.19 \text{ mg/kg-day} \div 1000 \\ &= 0.0002 \text{ or } 2\text{E-}4 \text{ mg/kg-day} \end{aligned}$$

Confidence in the principal study is low. While the study evaluated the most sensitive known endpoints for thiocyanate exposure, it did so at only one time point, non-thyroid endpoints were not evaluated and a NOAEL was not identified. Confidence in the database is medium. The available human data support the choice of critical effect and considerable animal data exist supporting thyroid effects as a sensitive endpoint of thiocyanate; however, only limited dose-response data on the effects of oral thiocyanate in humans are available and the effects seen in animal studies appear to occur at considerably greater levels (~100-1000-fold) than those in humans. Low confidence in the provisional subchronic and chronic RfD values results.

REFERENCES

Anderson, R.C. and K.K. Chen. 1940. Absorption and toxicity of sodium and potassium thiocyanates. J. Am. Pharm. Assoc. 6:152-161.

ATSDR (Agency for Toxic Substances and Disease Registry). 2005. Internet HazDat Toxicological Profile Query. U.S. Department of Health and Human Services, Public Health Service. Atlanta, GA. Available at http://www.atsdr.cdc.gov/gsql/toxprof.script.

Bala, T.S., M.K. Janardanasarma and M. Raghunath. 1996. Dietary goitrogen-induced changes in the transport of 2-deoxy-D-glucose and amino acids across the rat blood-brain barrier. Int. J. Dev. Neurosci. 14(5):575-583.

Banerjee, K.K., P. Marimuthu, P. Bhattacharyya and M. Chatterjee. 1997. Effect of thiocyanate ingestion through milk on thyroid hormone homeostasis in women. Brit. J. Nutr. 78(5):679-681.

Barker, M.H. 1936. The blood cyanates in the treatment of hypertension. J. Am. Med. Assoc. 106:762-767.

Barker, M.H., H.A. Lindberg and M.H. Wald. 1941. Further experiences with thiocyanates. J. Am. Med. Assoc. 117:1591-1594.

Beamish, R.E., W.F. Perry and V.M. Storrie. 1954. Observations on thyroid function in hypertensive patients treated with potassium thiocyanate. Am. Heart. J. 48:433-438.

Cliff, J., P. Lundquist, H. Rosling, B. Sorbo and L. Wide. 1986. Thyroid function in a cassava-eating population affected by epidemic spastic paraparesis. Acta Endocrin. 113:523-528.

Dahlberg, P.A., A. Bergmark, L. Bjorck et al. 1984. Intake of thiocyanate by way of milk and its possible effect on thyroid function. Am. J. Clin. Nutr. 39(3):416-420.

Dahlberg, P.A., A. Bergmark, M. Eltom et al. 1985. Effect of thiocyanate levels in milk on thyroid function in iodine deficient subjects. Am. J. Clin. Nutr. 41(5):1010-1014.

Delange, F., N. Van Minh, L. Vanderlinden et al. 1980a. Influence of goitrogens in pregnant and lactating rats on thyroid function in the pups. In: Role of cassava in the etiology of endemic goitre and cretinism. A.M. Ermans, N.M. Mbulamoko, F. Delange and A. Ahluwalia, Eds. pp. 127-134.

Delange, F., P. Bourdoux, R. Lagasse et al. 1980b. Effects of thiocyanate during pregnancy and lactation on thyroid function in infants. In: Role of assava in the etiology of endemic goitre and cretinism. A.M. Ermans, N.M. Mbulamoko, F. Delange and A. Ahluwalia, Eds. pp. 121-126.

Dorea, J.D. 2004. Maternal thiocyanate and thyroid status during breast-feeding. J. Am. Col. Nutr. 23(2):97-101.

Ermans, A.M., J. Kinthaert, M. van der Velden and P. Bourdoux. 1980. Studies of the antithyroid effects of cassava and of thiocyanate in rats. In: Role of cassava in the etiology of endemic goitre and cretinism. A.M. Ermans, N.M. Mbulamoko, F. Delange and A. Ahluwalia, Eds. pp. 93-110.

IARC (International Agency for Research on Cancer). 2005. IARC Agents and Summary Evaluations. Available at http://www-cie.iarc.fr/htdig/search.html.

Lindberg, H.A., M.H. Wald and M.H. Barker. 1941. Observations on the pathologic effects of thiocyanate: An experimental study. Am. Heart. J. 21:605-616.

Nagasawa, H., R. Yanai, Y. Nakajima et al. 1980. Inhibitory effects of potassium thiocyanate on normal and neoplastic mammary development in female mice. Eur. J. Cancer. 16:473-480.

NTP (National Toxicology Program). 2005. Management Status Report. Available at http://ntp-server.niehs.nih.gov/cgi/iH_Indexes/Res_Stat/iH_Res_Stat_Frames.html.

Palmer, R.S., L.S. Silver and P.D. White. 1929. Clinical use of potassium sulfocyanate in hypertension: A preliminary report of 59 cases. New Engl. J. Med. 201:709-714.

Pechacek, T.F., A.R. Folsom, R. de Gaudermaris et al. 1985. Smoke exposure in pipe and cigar smokers: Serum thiocyanate measures. JAMA. 254:3330-3332.

Philbrick, D.J., J.B. Hopkins, D.C. Hill et al. 1979. Effects of prolonged cyanide and thiocyanate feeding in rats. J. Toxicol. Environ. Health. 5:579-592.

Raghunath, M. and T.S. Bala. 1998. Diverse effects of mild and potent goitrogens on blood-brain barrier nutrient transport. Neurochem. Int. 33:173-177.

Russel, W.O. and W.C. Stahl. 1942. Fatal poisoning from potassium thiocyanate treatment of hypertension. J. Am. Med. Assoc. 119:1177-1181.

Schulz, V. 1984. Clinical Pharmacokinetics of Nitroprusside, Cyanide, Thiosulphate and Thiocyanate. Clin. Pharmacokinet. 9:239-251.

Taylor, R.D. 1945. Experience with potassium thiocyanate as a therapeutic agent in arterial hypertention. Proc. Am. Federation. Clin. Res. 2:10 (Cited in Beamish et al., 1954)

Thilly, C.H., G. Roger, R. Lagasse et al. 1980. Fetomaternal relationship, fetal hypothyroidism, and psychomotor retardation. In: Role of cassava in the etiology of endemic goitre and cretinism. A.M. Ermans, N.M. Mbulamoko, F. Delange and A. Ahluwalia, Eds. pp. 111-120.

U.S. EPA. 1988. Recommendations for and Documentation of Biological Values for Use in Risk Assessment. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH. EPA/600/6-87/008. NTIS PB 88-17874.

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

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

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

U.S. EPA. 2002. Child-Specific Exposure Factors Handbook. Interim Report. Office of Research and Development, Washington, DC. EPA/600/P-00/002B.

U.S. EPA. 2004. 2004 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. EPA/822/R-02/038. Available at http://www.epa.gov/waterscience/drinking/standards/dwstandards.pdf.

U.S. EPA. 2006. Integrated Risk Information System (IRIS). Online. Office of Research and Development, National Center for Environmental Assessment, Washington, DC. www.epa.gov/iris

WHO (World Health Organization). 2005. Online Catalogs for the Environmental Criteria Series. Available at http://www.inchem.org/pages/ehc.html.