United States
Environmental Protection
Agency

EPA/690/R-06/023F
Final
3-15-2006

Provisional Peer Reviewed Toxicity Values for

Thiocyanates
(Multiple CASRNs)

Derivation of Subchronic and Chronic Oral RfDs

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ACRONYMS AND ABBREVIATIONS

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

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

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR 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:

Subchronic p-RfD = LOAEL ÷ UF
= 0.19 mg/kg-day ÷ 300
= 0.0006 or 6E-4 mg/kg-day

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:

p-RfD = LOAEL ÷ UF
= 0.19 mg/kg-day ÷ 1000
= 0.0002 or 2E-4 mg/kg-day

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.

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01-26-05

Provisional Peer Reviewed Toxicity Values for

Thiocyanates
(Multiple CASRNs)

Derivation of Subchronic and Chronic Inhalation RfCs

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

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-RfD - provisional Oral Reference Dose
p-RfC - provisional Inhalation Reference Concentration
p-OSF - provisional Oral Slope Factor
p-IUR - provisional Inhalation Unit Risk
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
RGDR - Regional deposited dose ratio (for the indicated lung region)
REL - relative exposure level
RGDR - Regional gas dose ratio (for the indicated lung region)
RfD - Oral Reference Dose
RfC - Inhalation Reference Concentration
s.c. - subcutaneous
SCE - sister chromatid exchange
SDWA - Safe Drinking Water Act
sq.cm. - square centimeters
TSCA - Toxic Substances Control Act
UF - uncertainty factor
ug - microgram
umol - micromoles
VOC - volatile organic compound

01-26-05

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR THIOCYANATES (Multiple CASRNs)
Derivation of Subchronic and Chronic Inhalation RfCs

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 chronic RfC for thiocyanates is listed on IRIS (U.S. EPA, 2003) or in the HEAST (U.S. EPA, 1997). The CARA list (U.S. EPA, 1991, 1994) does not report any relevant documents for thiocyanates. ATSDR (2002), IARC (2002) and WHO (2002) have not published review documents for thiocyanates. Occupational exposure limits for thiocyanates have not been established by ACGIH (2002), NIOSH (2002), or OSHA (2002a,b). Literature searches were conducted from 1965 to September, 2002 for the following thiocyanates: sodium thiocyanate (CASRN 540-72-7), potassium thiocyanate (CASRN 333-20-0), calcium thiocyanate (2092-16-2), ammonia thiocyanate (CASRN 1762-95-4), and thiocyanic acid (CASRN 463-56-9). The databases searched were TOXLINE, MEDLINE, CANCERLIT, CCRIS, TSCATS, HSDB, RTECS, GENETOX, DART/ETICBACK, and EMIC/EMICBACK. The NTP (2002)

status report was also searched for relevant information. An updated literature search was conducted through April 2004 and no relevant information was found.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

No studies were located regarding inhalation exposure of humans to thiocyanates.

Animal Studies

No studies were located regarding inhalation exposure of animals to thiocyanates.

FEASIBILITY OF DERIVING PROVISIONAL SUBCHRONIC AND CHRONIC RfCs FOR THIOCYANATES

In the absence of subchronic or chronic inhalation data on the toxicity of thiocyanates, derivation of a provisional subchronic or chronic RfC is precluded.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2002. 2002 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIH, Cincinnati, OH.

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01-26-05

Provisional Peer Reviewed Toxicity Values for

Thiocyanates
(Multiple CASRNs)

Derivation of a Carcinogenicity Assessment

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

bw - body weight
cc - cubic centimeters
CD - Caesarean Delivered
CERCLA - Comprehensive Environmental Response, Compensation, and Liability Act of 1980
CNS - central nervous system
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DWEL - Drinking Water Equivalent Level
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PBPK - physiologically based pharmacokinetic
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s.c. - subcutaneous
SCE - sister chromatid exchange
SDWA - Safe Drinking Water Act
sq.cm. - square centimeters
TSCA - Toxic Substances Control Act
UF - uncertainty factor
ug - microgram
umol - micromoles
VOC - volatile organic compound
SRC TR-03-026/ 05-21-04

01-26-05

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR THIOCYANATES (Multiple CASRNs)
Derivation of a Carcinogenicity Assessment

Background

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INTRODUCTION

A carcinogenicity assessment for thiocyanates is not available on IRIS (U.S. EPA, 2003), in the HEAST (U.S. EPA, 1997), or in the Drinking Water Standards and Health Advisories List (U.S. EPA, 2002). The CARA list (U.S. EPA, 1991, 1994) does not report any relevant documents for thiocyanates. IARC (2002), ACGIH (2002), and NTP (2002) have not assessed the carcinogenicity of thiocyanates. ATSDR (2002) and WHO (2002) have not published review documents for thiocyanates. Literature searches were conducted from 1965 to September, 2002 for the following thiocyanates: sodium thiocyanate (CASRN 540-72-7), potassium thiocyanate (CASRN 333-20-0), calcium thiocyanate (2092-16-2), ammonia thiocyanate (CASRN 1762-95-4), and thiocyanic acid (CASRN 463-56-9). The databases searched were TOXLINE, MEDLINE, CANCERLIT, CCRIS, TSCATS, HSDB, RTECS, GENETOX, DART/ETICBACK,

and EMIC/EMICBACK. An updated literature search was conducted through April 2004 and no relevant information was found.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

No studies examining the potential carcinogenic effects of thiocyanates in humans were located.

Animal Studies

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 presented in U.S. EPA (1988) and mean body weights presented in the manuscript, 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 T3 (significant in the 0.3% group) and T4 (significant in the 0.1 and 0.3% groups) were reported. Mammary rating as an index of development was significantly reduced 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 presented in U.S. EPA (1988) and mean body weights presented in the manuscript, 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 the presence of pregnancy-dependent mammary tumors (PDMT). 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 examinations of neoplastic endpoints were reported in the study. No other examinations of the carcinogenic effects of thiocyantes were located.

Other Studies

Only limited evaluations of the genotoxicity of thiocyanates are available. Yamaguchi (1980) reported that methyl, ethyl, phenyl, and ammonium thiocyanates were not mutagenic in *S.*

typhimurium strain TA100. Kihlman (1957) reported that exposure to thiocyanate did not result in chromosomal aberrations in the root tip of *Vicia faba*. Exposure of *Tetrahymena pyriformis* to sodium thiocyanate resulted in an increased synthesis of both DNA and RNA (Volm et al., 1970).

A mechanism that may be related to possible carcinogenesis by the oral route involves the production of nitrosoamines within the stomach. Thiocyanate, which occurs endogenously in the stomach (Ruddell et al., 1977), is a potent catalyst of the reaction of nitrite and naturally-occurring amines to nitrosoamines, which are carcinogenic. However, whether this mechanism might influence a possible carcinogenic response to exogenous thiocyanate is questionable, as Mirvish et al. (1975) found that co-exposure of sodium thiocyanate and the combination of morpholine (a cyclic amine) and sodium nitrite did not result in a significant increase in the formation of pulmonary adenomas.

PROVISIONAL WEIGHT-OF-EVIDENCE CLASSIFICATION

No carcinogenicity data for thiocyanates are available in humans. Animal data were limited to one study that found no evidence of a neoplastic or preneoplastic effect of short-term drinking water exposure to potassium thiocyanate (up to 470 mg SCN/kg-day) in mice (Nagasawa et al., 1980). Limited genotoxicity data were negative for mutagenicity in bacteria (Yamaguchi, 1980) and clastogenicity in the root tip of *Vicia faba* (Kihlman, 1957). Under the proposed guidelines (U.S. EPA, 1999), data are inadequate for an assessment of the human carcinogenic potential of thiocyanates.

QUANTITATIVE ESTIMATES OF CARCINOGENIC RISK

Derivation of quantitative estimates of cancer risk for thiocyanates is precluded by the lack of data demonstrating carcinogenicity associated with thiocyanate exposure.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2002. 2002 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIH, Cincinnati, OH.

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