MEMORANDUM

DATE: June 25, 1996

SUBJECT: Systemic Oral Toxicity Information on Thiocyanate for the Stauffer Chemical site in Region IV and the Halby Chemical site in Region III.

FROM: Dr. Harlal Choudhury, Ph.D.

TO: Joanne Benante
U.S. EPA
Region IV

TO: Eric Newman
U.S. EPA
Region III

This memorandum responds to your request for oral toxicity information on Thiocyanate for the Stauffer Chemical and Halby Chemical Superfund site. The attached paper includes changes made by Dr. Harlal Choudhury, PhD.

Attachment I: Risk Assessment Issue Paper for: Derivation of a Provisional RfD for Thiocyanate (CASRN see below)

It is to be noted that the values provided in the Risk Assessment Issue Papers are provisional only, and have not been through the U.S. EPA formal review process. Therefore, they do not represent a U.S. EPA-verified assessment. If you have any questions regarding this information, please contact Harlal Choudhury at (513) 569-7536.

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Risk Assessment Issue Paper for:
Derivation of a Provisional RfD for Thiocyanate (CASRN see below)

INTRODUCTION

The request for derivation for a provisional oral RfD for thiocyanate did not specify a particular thiocyanate compound. Therefore, databases were searched for several simple thiocyanate compounds. No chronic oral RfD or inhalation RfC was available on IRIS (U.S. EPA, 1994a) or HEAST (U.S. EPA, 1993a) for any thiocyanate compound. The RfD/RfC Work Group Monthly Status Report (U.S. EPA, 1994b) did not mention any thiocyanate compound. Also, no documents were listed on the CARA list (U.S. EPA, 1993b) or the updated NTP Status Reports (NTP, 1993) for any thiocyanate, and no drinking water regulations or health advisories (U.S. EPA, 1993c) or ATSDR Toxicological Profiles have been developed for thiocyanates. Based on the lack of governmental reports on thiocyanates, a broad-based literature search was conducted in November 1993 to identify research reports pertinent to the derivation of a provisional oral RfD for thiocyanates. TOXLINE (1965-present), MEDLINE (1966-present), and TOXLIT (1965-present) were searched using CAS numbers for several simple salts of thiocyanate (ammonium thiocyanate [1762-95-4], calcium thiocyanate [2092-16-2], potassium thiocyanate [333-20-0], sodium thiocyanate [540-72-7], and thiocyanic acid [463-56-9]), chemical names, and the MESH heading "thiocyanate". The search strategy covered toxicity by the inhalation, oral, and dermal routes (modified RfC strategy). HSDB and RTECS were searched using CAS numbers and thiocyanate in the name field.

REVIEW OF PERTINENT LITERATURE

Toxicity of Thiocyanate in Humans

There is a large amount of data on the toxicity of thiocyanate in humans. However, most of these data involve the short-term use of thiocyanates to decrease blood pressure in hypertensive patients. Data on the toxicity of thiocyanate in normotensive humans are limited to an acute exposure study conducted by Smith and Rudolf (1928) and a 12-week study conducted by Dalhberg et al. (1984). In the Smith and Rudolf (1928) study, 6 healthy adults (sex not specified) were given oral doses of 324 mg sodium thiocyanate (232 mg thiocyanate; 3.3 mg/kg-day thiocyanate, assuming a reference body weight of 70 kg) for 1 week. A 15-30 mm Hg decrease in systolic blood pressure was observed. Blood pressure was the only endpoint measured; the authors noted that the subjects did not complain of any symptoms.
Dahlberg et al. (1984) tested the effects of sodium thiocyanate-supplemented milk on thyroid function in 37 volunteers (9 men and 28 women) aged 16 to 54 years. The subjects were given the milk providing 8 mg/day thiocyanate (0.11 mg/kg-day) for 12 weeks. No significant differences from pretest levels were observed for serum thyroxine, triiodothyronine, or thyrotropic hormone, or the ratio of triiodothyronine: thyroxine. Serum thiocyanate levels increased from 0.4 mg/100 ml to a maximum of 0.78 mg/200 ml in non-smokers and from 0.84 mg/100 ml to a maximum of 1.07 mg/100 ml in smokers after 4 weeks of exposure. This study only assessed the effect of thiocyanate on thyroid toxicity and did not measure blood pressure.

In the first half of the 1900's, thiocyanate, in particular sodium thiocyanate and potassium thiocyanate, was used to treat hypertension. A number of papers have been published which report the effectiveness of thiocyanate in reducing blood pressure; some also discuss the adverse effects associated with this treatment. However, in general, these studies mainly focused on blood pressure and did not examine other endpoints. The reported effectiveness of thiocyanate in reducing blood pressure varies greatly from study to study. As reviewed by Andersen and Chen (1940), decreases in blood pressure have been observed in 12-100% of patients treated with thiocyanate. This large between study variation in the effectiveness of thiocyanate in decreasing blood pressure is partly due to the criteria used to determine a significant decrease in systolic blood pressure and the underlying cause of the hypertension (i.e., essential hypertension, hypertension secondary to renal failure). The magnitude of the decrease in blood pressure typically ranged from 10 to 50 mm Hg. Although decreases of 100 mm Hg have been reported. The decrease in blood pressure was often seen within several weeks of treatment initiation. Typically, blood pressure would return to pre-treatment levels shortly after termination of the thiocyanate treatment. Ayman (1931) noted that the magnitude of the decrease in blood pressure, as well as the onset of the decrease were dose-related. However, large individual variations in blood pressure makes a determination of the dose-dependency of the magnitude of change and the duration of onset difficult to determine.

The most commonly reported adverse effects in hypertensive patients treated with thiocyanate were weakness, fatigue, and nausea/vomiting. Other observed effects include thyroid toxicity (enlarged thyroid, myxedema, decreased basal metabolic rate), dermatitis (pruritus, exfoliative dermatitis, and maculopapular eruption), neurotoxicity, and angina. Some of these effects may have been secondary to the rapid decrease in blood pressure. As noted early, most of these studies were not designed to adequately assess toxicity.

An in-depth review of the studies examining the effects of thiocyanates is beyond the scope of this issue paper. Below is a summary of the results following treatment with some of the more commonly used doses. When thiocyanate treatment was first introduced in the early 1900's, high doses of thiocyanates were used resulting in “toxic psychosis” deaths (Domzalski et al., 1953). When thiocyanate treatment was reintroduced in 1925, lower doses were used, and many physicians followed similar treatment regimes, administering 97.2-324 mg potassium
thiocyanate or sodium thiocyanate 1-5 times per day. In the papers reviewed during the preparation of this issue paper, the lowest dose tested was 97.2 mg potassium thiocyanate (58.1 mg thiocyanate) administered 3 times per day for the first week, 2 times per day for the second week, and 1 time per day for 1-2 weeks (TWA dose of 1.5-1.7 mg/kg-day thiocyanate, assuming a reference body weight of 70 kg) (Palmer et al., 1929a,b). In this study, 42.4% of the 59 hypertensive subjects had a decrease in systolic blood pressure of 30 mm Hg or higher. Adverse effects (weakness, angina, and precordial distress) were observed in 6 subjects.

Several studies used moderate dose levels (2.6-2.8 mg/kg-day). Ayman (1931) treated patients with 100 mg potassium thiocyanate (59.8 mg thiocyanate) administered 3 times per day for 42-109 days (2.6 mg/kg-day thiocyanate); Barker et al. (1941) administered 0.3 g/day potassium thiocyanate (0.18 g/day thiocyanate; 2.6 mg/kg-day thiocyanate) 2-10 years (although it is not clearly reported, there may have been interruptions in the dosing schedule); and Goldring and Chasis (1931) used 0.326 g/day potassium thiocyanate or sodium thiocyanate (0.19 g/day thiocyanate assuming all was in the form of potassium thiocyanate; 2.8 mg/kg-day) for 14-78 days. Ayman (1931) found a 10-30 mm Hg and 5-20 mm Hg decrease in systolic and diastolic blood pressure, respectively, in 10 of 13 hypertensive patients. Adverse effects (weakness, fatigue, "laziness", drowsiness, and/or diarrhea) were reported by five of the patients. Decreases in systolic blood pressure (magnitudes of response not reported) were observed in 67% of the subjects in the Barker et al. (1941) study, and 32.4% of the subjects in the Goldring and Chasis (1931) study had a decrease in blood pressure of at least 45 mm Hg systolic and 31 mm Hg diastolic. In the Barker et al. (1941) and Goldring and Chasis (1931) studies, neurological effects (depression, aphasia, slurring speech, mental confusion, disorientation, hallucinations of sight and hearing and unsteady gait) were observed. Signs of thyroid toxicity (enlarged thyroid and myxedematous facies with decreased basal metabolic rate) were also observed in some of the subjects in the Barker et al. (1941) study. Barker et al. (1941) noted that "it is not unusual to see fatigue, secondary anemia, and a dry scaling skin appear after many months of continuous ingestion of cyanates"; it is not known if this statement is referring to results of the study or general observations in patients being treated with thiocyanate. The incidence of adverse effects was 18/246 in the Barker et al. (1941) and 13/50 in the Goldring and Chasis (1931) study. Two subjects in the Goldring and Chasis (1931) study died. Although the daily dose in the Ayman (1931) study was similar to doses used in the Barker et al. (1941) and Goldring and Chasis (1931) studies, a marked difference in the severity of effects was observed. A possible explanation for this difference may be that the subjects in the Ayman (1931) study received the 2.6 mg/kg-day dose in 3 smaller doses, compared to the larger, single dose used in the other two studies.

Ayman (1931) also treated a group of 14 patients with 0.2 g potassium thiocyanate (0.08 g thiocyanate) 4-5 times per day (4.6-5.8 mg/kg-day thiocyanate) for 4-89 days. Decreases of 30-40 mm Hg systolic and 10-30 mm Hg diastolic were observed in 12/14 patients. The decrease in blood pressure occurred after 2-4 weeks in patients given the thiocyanate 4 times per day and after 1-2 weeks in patients treated 5 times per day. The author noted that the marked
toxic symptoms precluded continuation of the treatment. Adverse effects (weakness, fatigue, "laziness", drowsiness, diarrhea, abdominal cramps, tremors, numbness in upper body) were observed in 12/14 patients.

As reviewed by Gorman et al. (1948), the large within study variability in the effectiveness of thiocyanate in decreasing blood pressure and the incidence of adverse effects may be due to individual differences in the excretion of thiocyanate. The differences in individual average daily excretion rates of thiocyanate can vary as much as 500%. Because of the large potential differences in thiocyanate excretion, a number of physicians advocated monitoring blood thiocyanate levels, and adjusting dosages to maintain therapeutic blood levels. Blood levels between 5 and 14 mg/100 mL were considered optimal for reduction of blood pressure (Barker, 1936; Domzalski et al., 1953; Gorman et al., 1948), with toxicity (muscular fatigue, nausea and vomiting, dermatitis, disorientation, mental confusion, motor aphasia, hallucinations, delirium, convulsions, and death) believed to occur at blood levels above 14-20 mg/100 mL. Although maintenance of a blood level of 5-14 mg/100 mL is advocated as a "safe" blood level, Beamish et al. (1954) observed thyroid toxicity (decreases in protein-bound plasma iodine concentration and thyroid uptake of iodine) in subjects with blood thiocyanate levels (1.3-5 mg/100 mL) below the therapeutic range. Normal blood thiocyanate levels are 0.2-0.7 mg/100 mL (Wood, 1975).

There are a number of limitations to the human database. With the exception of the Smith and Rudolf (1928) and Dahlberg et al. (1984) studies, hypertensive subjects were used, and no control group was used. All of these studies (Palmer et al., 1929a; Goldring and Chasis, 1931; Barker et al., 1941; Ayman, 1931) showed decreases in blood pressure, the magnitude of the change was 10-50 mm Hg. The decrease in blood pressure observed in the human studies was considered a beneficial effect of oral exposure to thiocyanate because the subjects were hypertensive. If oral exposure to thiocyanate also resulted in a 30 mm Hg or higher decrease in systolic blood pressure in normotensive as well as hypertensive individuals, the effect would be considered adverse. In the Palmer et al. (1929a) study, over 40% of the subjects had a decrease in systolic blood pressure of 30 mm Hg or greater; the subjects were orally exposed to a TWA dose of 1.5-1.8 mg/kg-day for 3-4 weeks. It is not known if normotensive subjects were exposed to similar doses, if the magnitude of decrease in systolic blood pressure would be the same. Smith and Rudolf (1928) demonstrated a 15-30 mm Hg drop in systolic blood pressure in normotensive subjects treated with 3.3 mg/kg-day for 1 week. If the assumption is made that a similar magnitude decrease in blood pressure would be observed in normotensive and hypertensive individuals, then the TWA dose of 1.5-1.7 mg/kg-day used in the Palmer et al. (1929a) study is a LOAEL.

Toxicity of Thiocyanate in Animals

Chronic oral studies. Data on the chronic toxicity of thiocyanate in animals is limited to a carcinogenicity study conducted by Lijinsky and Kovatch (1989).
Lijinsky and Kovatch (1989) exposed Fischer 344 rats (20-24/sex/dose) to 0% or 0.32% sodium thiocyanate in the drinking water 5 days/week for 112 weeks. The study authors determined that the total dose of sodium thiocyanate ingested was approximately 1 mole/kg in males and 1.7 mole/kg in females. The authors estimated that this was roughly equivalent to a daily dose of 250 mg/kg of sodium thiocyanate in females (147 mg/kg of sodium thiocyanate in males, by extrapolation). No increase in mortality, noticeably adverse effects, or tumor formation was reported in the treated rats. It is unclear from the report whether the incidence of any nonneoplastic lesions was increased in treated rats. The NOAEL for this study was 75 mg thiocyanate/kg in males (147 x 5/7 x 58.08/81.07) and 128 mg thiocyanate/kg in females (250 x 5/7 x 58.08/81.07)\(^1\). No LOAEL was determined.

Subchronic oral studies. Several studies in animals examined the effects of subchronic oral exposure to thiocyanate (Kanno et al., 1990; Lindberg et al., 1941; Nagasawa et al., 1980; Philbrick et al., 1979; Pyska, 1977; Rawson et al., 1944; Wolff et al., 1946).

Philbrick et al. (1979) exposed male weanling rats (10/group; strain not specified) to control casein diets (supplemented with 0.3% DL-methionine, potassium iodide, and vitamin B12) or similarly supplemented casein diets containing 2,240 ppm potassium thiocyanate for 11.5 months. No deaths, clinical signs, or adverse effects on body weight gain were observed in the potassium thiocyanate-treated rats. However, potassium thiocyanate-treated rats had significantly decreased plasma thyroxine and thyroxine secretion rates after 4 months and significantly increased thyroid weight and decreased plasma thyroxine after 11 months of exposure. Histopathological analysis showed no effects on the thyroid, optic nerve, sciatic nerve, or other neural tissues. No NOAEL was determined in this study. The LOAEL for this study was 67 mg thiocyanate/kg-day (2,240 ppm x 0.05 kg diet/kg body weight/day x 58.08/97.18)\(^2\) based on thyroid toxicity.

Kanno et al. (1990) exposed male Fischer 344/DuCrj rats (30/group) to 0.5% potassium thiocyanate in the drinking water for 25 weeks. Controls received drinking water without added potassium thiocyanate. Treated rats showed a significant increase in thyroid weight. Histopathologic analysis of the thyroids showed slight diffuse hyperplasia and increased colloid so that the percent area occupied by the follicular cells was decreased relative to controls. Treated rats had significantly increased serum levels of thyroid stimulating hormone and triiodothyronine and decreased serum levels of thyroxine. No neoplasia were observed in the

\(^1\)Dose conversion obtained by correcting the dose for less than a 7 day/week exposure and multiplying by the percentage of the dose weight accounted for by the thiocyanate ion.

\(^2\)Dose conversion obtained by multiplying the dietary level by the reference food factor for rats, 0.05 kg diet/kg body weight/day (U.S. EPA, 1986), and multiplying by the percentage of the dose weight accounted for by the thiocyanate ion.
thyroids of control or treated rats. No NOAEL was determined in this study. The LOAEL for this study was 418 mg thiocyanate/kg-day (0.5 g/100 mL x 0.049 L/day x 1/0.35 kg x 58.08/97.18)\(^3\) based on thyroid toxicity.

Nagasawa et al. (1980) exposed female SHN mice (18/group) to 0.1% or 0.3% potassium thiocyanate in the drinking water for 12 weeks. Controls received tap water. Statistically significant decreases in plasma thyroxine were observed in females at both doses of potassium thiocyanate. Plasma triiodothyronine was also significantly decreased in females at 0.3% potassium thiocyanate. No NOAEL was determined in this study. The LOAEL was 114 mg thiocyanate/kg-day (0.1 g/100 mL x 0.0057 L/day x 1/0.03 kg x 58.08/97.18)\(^4\) based on thyroid toxicity.

Pyska (1977) exposed 3-week-old female Wistar rats (17–19/group) to 0.1% potassium thiocyanate for approximately 10 weeks (until the rats were 3 months old) and pregnant Wistar rats (12–27/group) to 0.1%, 0.3%, or 0.5% potassium thiocyanate during pregnancy and 14 days of lactation. Controls received tap water without added thiocyanate. Daily intake of drinking water was estimated at 20–30 mL. Both the developing and pregnant rats had significantly decreased plasma protein-bound iodine at 0.1% potassium thiocyanate. The extent of the decrease increased with dose. The plasma protein-bound iodine was used as an index of thyroid activity. No NOAEL was determined in this study. The LOAEL was 52 mg thiocyanate/kg-day (0.1 g/100 mL x 20 mL/day x 1/0.23 kg [actual maternal weight] x 58.08/97.18)\(^5\) based on thyroid toxicity.

Wolff et al. (1946) exposed rats (4-6/group; sex and strain not specified) to 0.5% potassium thiocyanate in the diet for 18–21 days. Controls received basal diet. Treated rats had increased thyroid weights and decreased thyroxine iodine and total iodine in the thyroid. Protein-bound iodine in the plasma was also decreased in the treated rats. No NOAEL was

\(^3\)Dose conversion obtained by multiplying the concentration in the drinking water by the reference value for volume of water consumed/day by rats, 0.049 L/day (U.S. EPA, 1986), dividing the result by the reference value for rat weight, 0.35 kg (U.S. EPA, 1986), and multiplying by the percentage of the dose weight accounted for by the thiocyanate ion.

\(^4\)Dose conversion obtained by multiplying the concentration in the drinking water by the reference value for the volume of water consumed/day by mice, 0.0057 L/day (U.S. EPA, 1986), dividing by the reference value for the weight of mice, 0.03 kg (U.S. EPA, 1986), and multiplying by the percentage of the dose weight accounted for by the thiocyanate ion.

\(^5\)Dose conversion obtained by multiplying the concentration in the drinking water by the lower end estimate of the actual daily drinking water intake (20 mL/day), dividing by the actual average weight (0.23 kg), and multiplying by the percentage of the dose weight accounted for by the thiocyanate ion.
determined in this study. The LOAEL was 149 mg thiocyanate/kg-day (0.5 g/100 g diet x 0.05 kg diet/kg body weight/day x 58.08/97.18)\(^6\) based on thyroid toxicity.

Rawson et al. (1944) exposed male Sherman rats (25/group) to 0.25% potassium thiocyanate in the drinking water for 28 days. Controls received drinking water without added potassium thiocyanate. The diet and drinking water supplements provided a borderline-deficient intake of iodine. Thyroid weight was increased in the potassium thiocyanate-treated rats. At necropsy, the thyroids of treated rats were dark red, highly vascularized, and grossly enlarged and histopathology revealed marked hyperplasia and loss of colloid. No NOAEL was determined in this study. The LOAEL was 209 mg thiocyanate/kg-day (2.5 g/L x 0.049 L/day x 1/0.35 kg x 58.08/97.18)\(^7\) based on thyroid toxicity.

Lindberg et al. (1941) gave 12 dogs (sex not specified) potassium thiocyanate orally (300 mg doses; dosage regimen not reported) and examined effects on erythrocyte count, hematocrit, serum proteins, and plasma cholesterol. Exposure for 4–27 weeks resulted in blood thiocyanate levels as high as 75 mg/100 mL and decreases in serum cholesterol, total protein, erythrocyte count, and hematocrit. Histopathological analyses showed bone marrow acellularity and fatty vacuolation of the liver. Insufficient information was provided to determine a NOAEL or LOAEL for these effects.

Taubman and Heilborn (1930; as cited in Lindberg et al., 1941; study not available for review) reported that administration of 2 doses of 200 mg/kg potassium thiocyanate (120 mg thiocyanate/kg)\(^8\) to 15 guinea pigs (sex and strain not specified) resulted in a 25% decrease in hemoglobin and erythrocytes. Smaller doses given over longer periods resulted in greater decreases in these parameters (dosing regimen not specified). Insufficient information was provided to determine a NOAEL or LOAEL for these changes.

**Developmental and reproductive toxicity studies.** Nagasawa et al. (1980) exposed female 8-week-old SHN (18/group) or 5-week-old GR/A (32/group) mice to 0.1% or 0.3% potassium thiocyanate in the drinking water. Controls received tap water. In the SHN mice, normal

\(^6\)Dose conversion obtained by multiplying the dietary level by the reference value for the food factor in rats, 0.05 kg diet/kg body weight/day (U.S. EPA, 1986), and multiplying by the percentage of the dose weight accounted for the thiocyanate ion.

\(^7\)Dose conversion obtained by multiplying the concentration in the drinking water by the reference value for daily water intake for rats, 0.049 L/day (U.S. EPA, 1986), dividing by the reference value for average rat weight, 0.35 kg (U.S. EPA, 1986), and multiplying by the percentage of the dose weight accounted for by the thiocyanate ion.

\(^8\)Dose conversion obtained by multiplying by the percentage of the dose weight accounted for by the thiocyanate ion.
mammary development was significantly decreased at 0.3% potassium thiocyanate after 12 weeks exposure. However, no effect on the weight of the pituitary or adrenal or ovarian histology were observed. In the GR/A mice, exposure for 5 weeks prior to mating and then for 4 additional weeks had no effect on fertility, litter size, fetal viability, or pup weight. In addition, maternal pituitary levels of prolactin and growth hormone were unaffected. The NOAEL for reproductive toxicity in this study was 114 mg thiocyanate/kg-day (0.1 g/100 mL x 0.0057 L/day x 1/0.03 kg x 58.08/97.18)\(^9\). The LOAEL for reproductive toxicity was 341 mg thiocyanate/kg-day (0.3 g/100 mL x 0.0057 L/day x 1/0.03 x 58.08/97.18)\(^{11}\) based on decreased mammary development. The NOAEL for developmental toxicity was 341 mg thiocyanate/kg-day. No LOAEL for developmental toxicity was determined.

Pyska (1977) exposed 3 week-old female Wistar rats (17–19/group) to 0.1% potassium thiocyanate in the drinking water for approximately 10 weeks (until the rats were 3 months old). Controls received tap water. High mortality was reported at doses higher than 0.1%, but the doses at which the increased mortality were observed was not reported. Mammary weight and DNA content were significantly decreased in the treated rats. Female rats (12–27/group) were also exposed to 0.1%, 0.3%, or 0.5% potassium thiocyanate in the drinking water during pregnancy and 14 days of lactation. Daily intake of drinking water was estimated at 20–30 mL. Mammary gland weight, DNA, and RNA content were significantly decreased at all doses. The authors suggested that the depressed mammary growth was associated with depressed thyroid activity also observed at this dose (see above). In addition, the weight of 14-day-old litters was significantly decreased at 0.3% and 0.5% and maternal weight was significantly decreased at 0.5% potassium thiocyanate. It is unclear whether the effects on litter weight were due to pre- or postnatal exposure to the thiocyanate. No NOAEL for reproductive toxicity was determined in this study. The LOAEL for reproductive toxicity was 52 mg thiocyanate/kg-day (0.1 g/100 mL x 20 mL/day x 1/0.23 kg x 58.08/97.18)\(^{10}\) based on depressed mammary development. The NOAEL for developmental toxicity was 52 mg thiocyanate/kg-day. The LOAEL for developmental toxicity was 156 mg thiocyanate/kg-day (0.3 g/100 mL x 20 mL x 1/0.23 kg x 58.08/97.18)\(^{12}\) based on decreased litter weight.

Heydens (1985) exposed female rats (number/dose and strain not specified) to 55 or 220 mg/kg of thiocyanate on gestation days 6–15 or to 150 mg/kg of thiocyanate throughout gestation (route of exposure not specified). No teratogenicity was observed, but postnatal growth

\(^9\)Dose conversion obtained by multiplying the concentration in the drinking water by the reference value for daily water intake by mice, 0.0057 L/day (U.S. EPA, 1986), dividing by the reference value for mouse weight, 0.03 kg (U.S. EPA, 1986), and multiplying by the percentage of the dose weight accounted for by the thiocyanate ion.

\(^10\)Dose conversion obtained by multiplying the concentration in the drinking water by the lower end estimate for daily water intake (20 mL/day), dividing by the average rat weight (0.23 kg), and multiplying by the percentage of the dose weight accounted for by the thiocyanate ion.
and development were reported to have been retarded. Continued exposure throughout the period of lactation did not result in substantially greater growth retardation, indicating that the effects observed were caused primarily during gestation. Limited experimental details and results were presented in this report. No NOAEL was reported. Based on the information provided, the LOAEL for this study was 55 mg thiocyanate/kg-day based on developmental retardation.

DERIVATION OF PROVISIONAL CHRONIC RfD

Based on the available information in humans and animals, the critical effects of orally administered thiocyanate are decreased blood pressure and thyroid toxicity. Data from the Lindberg et al. (1941) and Taubman and Heilborn (1930) animal studies and the statement in the Barker et al. (1941) human study that secondary anemia is a frequently observed effect in patients treated with thiocyanate for a long period of time suggest that anemia may also be a sensitive effect. Several other effects have been reported in hypertensive patients taking thiocyanate, including weakness, fatigue, dermatitis, and neurotoxicity. Some of these effects may be due to the rapid decrease in blood pressure or thyroid toxicity. Several authors have noted that the dermatitis observed after exposure to thiocyanate is similar to the dermatitis observed in individuals undergoing iodide treatment, presumably for hypothyroidism. Muscular weakness is often seen in individuals with hypothyroidism. It is also possible that the low-dose thiocyanate studies of blood pressure effects in humans did not measure thyroid parameters, a determination of the most sensitive effect cannot be made. Thus, it is assumed that the thyroid and blood pressure endpoints are equally sensitive.

There are a number of human and animals studies, but most of these studies are limited in scope. No human or animal studies examining a wide range of potential endpoints were located, and most of the human studies used hypertensive patients and no control group. Although, there are limitations to the human and animal studies, collectively they identify a NOAEL of 0.11 mg/kg-day for thyroid toxicity in humans (Dahlberg et al., 1984) and a LOAEL of 1.5-1.7 mg/kg-day for decreased systolic blood pressure (Palmer et al., 1929a). The Palmer et al. (1929a) study did not adequately examine for thyroid toxicity. A LOAEL of 2.6 mg/kg-day for thyroid toxicity (enlarged thyroid and myxedema) was identified in the Barker et al. (1941) study. The lowest LOAEL identified in the animal studies was 52 mg/kg-day in the Pyska study for thyroid toxicity (decreased plasma-bound iodine); a NOAEL was not identified. The animal studies did not examine the effect of thiocyanate on blood pressure.

The Linjinsky and Kovatch (1989) chronic study was selected as the principal study for the derivation of an oral RfD. The dose level of 128 mg/kg/day shows thyroid hyperplasia in female rats. This is suggestive of thiocyanate-target organ effect because of its effect on iodine uptake by the thyroid. Although, this effect falls short of statistical significance, it has some relevancy to the biological significance of the known toxic effects of thiocyanate. In the absence
of appropriate control data on histopathology of the target organs and in view of the fact that thyroid effects have been observed in another study (Phillbrick et al., 1979 subchronic study), we consider the above dose as “minimal” LOAEL.

\[
RfD = \frac{LOAEL}{UF \times MF}
\]

where:

\[
LOAEL = 128/\text{kg/day}
\]

\[
UF = 1000. \text{ An uncertainty factor of 1000 reflects 10 for animal to human extrapolation, 10 for human sensitive population, 3 for database deficiency, 3 for minimal LOAEL}
\]

\[
MF = 1
\]

\[
RfD = \frac{(128 \text{ mg/kg/day})}{1000 \times 1}
\]

\[
= 1.28 \times 10^{-1} \text{ mg/kg/day}
\]

\[
= 1 \times 10^{-1} \text{ mg/kg/day} \text{ (rounded to the nearest one)}
\]

Confidence in the principal study is low. Only one dose was tested and the number of animals tested were inadequate for appropriate toxicological evaluations and the histopathological evaluations did not include control animals. The database lacks a well-conducted chronic study and reproductive/developmental studies. Because of the presence of cyanides in the ground water at the site, possible thiocyanate dissociation to cyanide and the cyanide-related target effect need to be evaluated; thus resulting in medium to low confidence in the database. Reflecting the low confidence in the principle study and the database, the overall confidence in the RfD is low.

**REFERENCES**


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<tr>
<td>Nagasawa et al. 1980</td>
<td>mice (females only)</td>
<td>Thyroid (decreased plasma thyroxine)</td>
<td>LOAEL = 114 mg/kg-day</td>
</tr>
<tr>
<td>12-week study</td>
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<tr>
<td>Wolff et al. 1946</td>
<td>rats</td>
<td>Thyroid (increased thyroid weight, decreased thyroxine iodine and total iodine in the thyroid, decreased plasma protein-bound iodine)</td>
<td>LOAEL = 149 mg/kg-day</td>
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<tr>
<td>18–21 day study</td>
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<tr>
<td>Study</td>
<td>Species</td>
<td>Effect</td>
<td>Effect Level</td>
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<tr>
<td>Rawson et al. 1944</td>
<td>rats (males only)</td>
<td>Thyroid (increased weight, dark red, highly vascularized, and enlarged at necropsy, marked hyperplasia and loss of colloid)</td>
<td>LOAEL = 209 mg/kg-day</td>
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<tr>
<td>28-day study</td>
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<tr>
<td>Lindberg et al. 1941</td>
<td>dogs</td>
<td>Hematology (decreased erythrocyte count and hematocrit, bone marrow acellularity) Liver (decreased serum protein, fatty vacuolation, decreased serum cholesterol)</td>
<td>NOAEL and LOAEL could not be determined</td>
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<tr>
<td>4–27-week study</td>
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<tr>
<td>Taubman and Heilbron 1930</td>
<td>guinea pigs</td>
<td>Hematology (decreased hemoglobin and erythrocytes)</td>
<td>NOAEL and LOAEL could not be determined</td>
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<tr>
<td>(duration not specified)</td>
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<tr>
<td>Nagasawa et al. 1980</td>
<td>mice (females only)</td>
<td>Reproductive (decreased mammary gland development) No effects on weight of pituitary or adrenals, ovarian histology, fertility, litter size, fetal viability, pup weight</td>
<td>NOAEL (repro.) = 114 mg/kg-day</td>
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<tr>
<td>reproductive and</td>
<td></td>
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<td>LOAEL (repro.) = 341 mg/kg-day</td>
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<td>developmental toxicity</td>
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<td></td>
<td>NOAEL (devel.) = 341 mg/kg-day</td>
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<tr>
<td>Pyska 1977</td>
<td>rats (females only)</td>
<td>Reproductive (decreased mammary gland weight and DNA content) Developmental (decreased weight of 14-day-old litters)</td>
<td>LOAEL (repro.) = 52 mg/kg-day</td>
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<td>reproductive and</td>
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<td>NOAEL (devel.) = 52 mg/kg-day</td>
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<td>developmental toxicity</td>
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<td>LOAEL (devel.) = 156 mg/kg-day</td>
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<td>Heydens 1985</td>
<td>rats (females only)</td>
<td>Developmental (decreased postnatal growth and development)</td>
<td>LOAEL (devel.) = 55 mg/kg-day</td>
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<td>developmental toxicity</td>
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