January 30, 1995

Mr. Eric Newman  
U.S. EPA Region III  
841 Chestnut Building  
Philadelphia, PA. 19107

ASSISTANCE REQUESTED:  Systemic Toxicity Information for Cobalt (CASRN 7440-48-4), and Thiocyanate (CASRN).  (Halby Chemical/New Castle, DE.)

ENCLOSED INFORMATION:  Risk Assessment Issue Paper for: Provisional RfD for Cobalt (7440-48-4)  
Risk Assessment Issue Paper for: Derivation of a Provisional RfD for Thiocyanate (CASRN see below)

BE ADVISED: 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 Joan Dollarhide at (513) 569-7539.

Attachments

cc:  B. Root (CH2M)  
     R. Kolluru (CH2M)

Support provided by LABAT-ANDERSON, Incorporated under contract 68-W4-0028.
Cobalt has been found to stimulate the production of red blood cells in humans and, therefore, has been used as a treatment for anemia. In 12 anemic, anephric patients undergoing dialysis, treatment with 0.18 mg cobalt/kg/day as cobalt chloride for 12 weeks resulted in a significant rise in hemoglobin (Duckham and Lee, 1976). Taylor et al. (1977) reported similar effects in 8 anephric patients treated with 0.16-0.32 mg cobalt/kg/day as cobalt chloride for 12-32 weeks. In both studies, hemoglobin levels returned to pre-treatment levels following the cessation of treatment. Similar effects were reported in nonanemic humans and animals (Davis and Fields, 1958; Krasovskii and Fridlyand, 1971). Reversible polycythemia was reported in 6 normal male subjects following treatment with 1 mg cobalt/kg/day as cobalt chloride for 25 days (Davis and Fields, 1958). In normal rats, treatment with 0.5 mg cobalt/kg/day, but not 0.05 mg/kg/day, as cobalt chloride resulted in polycythemia and an increase in hemoglobin (Krasovskii and Fridlyand, 1971). An increase in hematocrit and hemoglobin levels was not observed, however, in pregnant women treated with 0.5-0.6 mg cobalt/kg/day for 90 days in an attempt to alleviate the anemia often found during pregnancy (Holly, 1955).

Much of the oral data in humans deals with the cardiomyopathy seen in people who drank large quantities of beer containing cobalt chloride (used to stabilize the foam) (Alexander, 1969, 1972; Morin et al., 1971). The people ingested 0.04-0.14 mg cobalt/kg/day (approximately 8-30 pints of beer daily) over a period of years (Alexander, 1969, 1972; Morin et al., 1971). The cardiomyopathy in the beer-drinkers, termed "beer-cobalt cardiomyopathy", was fatal to 43% of the subjects within several years, with approximately 18% of these deaths occurring within the first several days. The beer-cobalt cardiomyopathy appeared to be similar to alcoholic cardiomyopathy and beriberi, but the onset of the beer-cobalt cardiomyopathy was much more abrupt. The practice of adding cobalt to beer to stabilize the foam has been discontinued. It should be noted, however, that the cardiomyopathy may have also been due to the fact that the beer-drinkers had protein-poor diets and may have had prior cardiac and hepatic damage from alcohol abuse. Treatment of both pregnant and nonpregnant anemic patients with comparable or much higher doses of cobalt (0.09-1 mg cobalt/kg/day) did not result in effects on the heart (Duckham and Lee, 1976; Davis and Fields, 1958; Holly, 1955; Taylor et al., 1977).

Cobalt has been found to be a sensitizer in humans. Individuals are sensitized following dermal or inhalation exposure, but flares of dermatitis may be triggered following cobalt ingestion. One study was located that orally challenged cobalt-exposed workers in order to assess sensitization (Veien et al., 1987). In this study, several patients with eczema of the hands were challenged orally with 1 mg cobalt (0.014 mg cobalt/kg/day as cobalt sulfate) in tablet form once per week for 3 weeks and 28/47 patients had a flare of dermatitis following the oral challenge (Veien et al., 1987). Forty-seven patients had positive patch tests to cobalt (13 to cobalt alone and 34 to nickel and cobalt) and
7 of the 13 patients that patch tested positive to cobalt reacted to the oral challenge. Using both the oral challenge and dermal patch tests, it was determined that the cobalt allergy was systemically induced. The exposure levels associated with sensitization to cobalt following inhalation or dermal exposure were not established.

Interrelationships have been found to exist between cobalt and nickel sensitization (Bencko et al., 1983; Rystedt and Fisher, 1983; Veien et al., 1987). In guinea pigs, nickel and cobalt sensitization appear to be interrelated and mutually enhancing (Lammintausta et al., 1985). Therefore, it is possible that in people sensitized by nickel, exposure to cobalt may result in an allergic reaction. The elicitation of an allergic response in cobalt-sensitized workers was considered for the derivation of an oral RfD. An oral RfD was not derived because a NOAEL for the elicitation of the allergic response in humans was not defined and, because interrelationships exist between cobalt and nickel sensitization, people sensitized by nickel may have an allergic reaction following cobalt exposure. Consequently, it is impossible to certify that an RfD based on this effect would provide sufficient protection for sensitive individuals.

Three studies were located examining the developmental effects of orally administered cobalt (given as cobalt chloride) in rodents (Domingo et al., 1985; Paternain et al., 1988; Seidenberg et al., 1986). Domingo et al. (1985) treated pregnant female rats to 5.4 to 21.8 mg cobalt/kg/day from gestation day 14 through lactation day 21. Fetal effects included stunted growth of the pups at 5.4 mg cobalt/kg/day and decreased survival at 21.8 mg cobalt/kg/day. These effects occurred at levels that were maternally toxic (authors did not specify the effects), therefore, the effects may be a result of maternal toxicity and not cobalt treatment. No teratogenic effects were reported.

No significant effects on fetal growth or survival were found in rats exposed to 6.2 to 24.8 mg cobalt/kg/day during gestation days 6-15 (Paternain et al., 1988), although a nonsignificant increase in the incidence of stunted fetuses was found in the animals treated with 12.4 or 24.8 mg cobalt/kg/day. Maternal effects, however, including reduced body weight and food consumption and altered hematological parameters, were reported. No fetal effects were reported in mice exposed to 81.7 mg cobalt/kg/day during gestation days 8-12 (Seidenberg et al., 1986), but a significant decrease in maternal weight was found.

Several studies reported testicular degeneration and atrophy in rats exposed to 5.7 to 30.2 mg cobalt/kg/day as cobalt chloride for 2-3 months in the diet or in the drinking water (Corrier et al., 1985; Domingo et al., 1984; Mollenhauer et al., 1985; Nation et al., 1983; Pedigo et al., 1988).

Given the database, the most sensitive indicators of cobalt toxicity following oral exposure are the increase in hemoglobin in both humans and animals, and the elicitation of dermatitis in sensitized individuals.

An alternative approach was likewise evaluated based on the hematological effects of cobalt treatment (increase in hemoglobin) in anemic dialysis patients (Duckham and Lee, 1976). The results of this study are supported by a similar study in anephric patients (Taylor et al., 1977). Hematological effects of cobalt were also found in studies in normal humans (Davis and Fields, 1977).
1958) and rats (Krasovskii and Fridlyand, 1971) indicating that the effect is not limited to anephric individuals. The data of Davis and Fields (1958) reported hemoglobin increase of 6-11 % over "normal" in "normal" volunteers given 0.96 mg cobalt/kg/day as cobaltous chloride. However, the data of Duckham and Lee (1976) describes a case of refractory anemia in patients with chronic renal failure that upon treatment with 0.18 mg cobalt/kg/day for 12 weeks responded favorably. The patients hemoglobin levels were increased to levels at or near low "normal" clinical levels from levels clinically described as anemic. The anemia recurred following cessation of treatment. Thus, this effect of cobalt administration in the Duckham and Lee (1976) study (and likewise that of Taylor et al., 1977) cannot be termed adverse, but are actually clinically beneficial to patients with renal disease. Consequently, these data cannot be used to derive an oral RfD.

The only known nutritional, but vital function of cobalt is as a cofactor of vitamin B₁₂. In humans, vitamin B₁₂ is derived from bacterial synthesis and therefore, cobalt is essential for animal species, such as ruminants, that depend totally on their bacterial flora for vitamin B₁₂. There is no evidence that the intake of cobalt is ever limiting in the human diet, and therefore no RDA is deemed necessary for cobalt (NRC, 1989). It should be noted that the average daily intake of cobalt in humans ranges from approximately 0.002-0.008 mg cobalt/kg/day in adults (0.16-0.58 mg cobalt/day ÷ 70 kg; Tipton et al., 1966; Schroeder et al., 1967) and 0.01-0.06 mg cobalt/kg/day in children (0.3-1.77 mg cobalt/day ÷ 28 kg; NRC, 1989; Murthy et al., 1971). Murthy et al. (1971) indicated that the children in this study ranged in age from 9-12 years. Using the average weight of 28 kg for children aged 7-10 years (NRC, 1989), the average daily intake for the children in this study ranged from 0.01-0.06 mg/kg/day. If the default adult weight of 70 kg is used with the Murthy data, then the range of intake would be from 0.004-0.025 mg/kg/day.

The effects of chronic occupational exposure to cobalt on the respiratory system are well documented. Cobalt has been found to be the etiologic agent in hard metal disease. The observed effects include respiratory irritation, wheezing, asthma, pneumonia and fibrosis and have been found to occur at exposure levels ranging from 0.003 to 0.893 mg cobalt/m³ over a period of 2-17 years (Davison et al., 1983; Demedts et al., 1984; Kusaka et al., 1986a,b; Raffn et al., 1988; Shirakawa et al., 1988; Sprince et al., 1988).

Studies have implicated cobalt as a sensitizer in humans. Although the minimum exposure level associated with cobalt sensitization has not been determined, work-related asthma was found in hard metal workers who were occupationally exposed (for greater than 3 years) to levels of cobalt ranging from 0.007 to 0.893 mg cobalt/m³ (Shirakawa et al., 1988). Given the database, the most sensitive indicators of cobalt toxicity by inhalation exposure are the effects on the respiratory system in both humans and animals and allergic responses in cobalt-sensitized individuals.

The data described above does not identify a single study, animal or human, that could be used to properly derive an oral RfD. In unusual circumstances, i.e., excessive beer drinking or through occupational sensitization, cobalt has been shown to manifest toxicological symptomatology. However, these reports provide inadequate data on which to derive an RfD. Furthermore, use of inhalation data to derive an oral RfD is precluded due to portal of entry effects. It is apparent that the upper range of average intake for children (0.06 mg/kg/day) is below the
levels of cobalt needed to induce polycythemia in both renally comprised patients (0.18 mg/kg/day) and normal patients (0.96 mg/kg/day).

Therefore, in lieu of an oral RfD for cobalt and given the ubiquitous nature of cobalt and the relatively well characterized intake of cobalt in food, it is recommended that the intake levels described above be used as guidance for oral exposure to cobalt.

References:


Krasovskii, G.N. and S.A. Fridlyand. 1971. Experimental data for the validation of the maximum


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

Review of the available literature revealed that thiocyanate is an anion normally present in human plasma (0.2–0.7 mg/100 mL) and several foods (0.2 to 100 mg/kg; with beets, cauliflower, and cabbage containing the highest concentrations) (Wood, 1975). Thiocyanate was also a widely used oral antihypertensive medication in the 1920s–1940s. In general, therapeutic doses for potassium or sodium thiocyanate ranged between 130 and 1,000 mg/day (1.1 and 8.6 mg thiocyanate/kg-day for potassium thiocyanate or 1.3 and 10.3 mg thiocyanate/kg-day for sodium thiocyanate) (Barker, 1936; Nichols, 1925; Smith and Rudolf, 1928). Healthy volunteers (6

1Dose conversions obtained by dividing the dose by the reference weight for the average male, 70 kg (U.S. EPA, 1986), and multiplying by the percentage of the dose weight accounted for by the thiocyanate ion.

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persons; sex not specified) receiving daily doses of 325 mg of sodium thiocyanate (3.3 mg thiocyanate/kg-day) for 1 week showed a 15–30 mmHg fall in systolic blood pressure (Smith and Rudolf, 1928). However, because of variability in the rate of excretion of thiocyanate between patients (Domzalski et al., 1953), blood levels, rather than dose, were typically used in clinical practice to monitor drug levels. Doses were titrated as necessary to maintain therapeutic blood levels and avoid toxic side effects. 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 (Barker, 1936; Barker et al., 1941; Domzalski et al., 1953; Russell and Stahl, 1942). Common effects observed after several months of continuous ingestion included fatigue, secondary anemia, and dry scaling skin (Barker et al., 1941). In addition, a number of clinicians reported thyroid toxicity (myxedematous swelling of the tissues of the face, enlargement of the thyroid, decreased metabolic rate, decreased serum protein-bound iodine) in several patients after prolonged thiocyanate therapy (Barker, 1936; Barker et al. 1941; Beamish et al., 1954; Blackburn et al. 1951). In several cases, the thyroid toxicity was observed at blood thiocyanate levels (1.3–5 mg/100 mL) below the therapeutic range (Beamish et al., 1954).

**Chronic oral studies.** No chronic-duration human studies were located that correlated doses of thiocyanate with toxic effects. A single study in animals was located that examined the carcinogenicity of chronic oral exposure to sodium thiocyanate (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)². No LOAEL was determined.

**Subchronic oral studies.** A single study was identified that examined the effects of subchronic ingestion of thiocyanate by normal human volunteers (Dahlberg et al., 1984). However, 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).

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²Dose 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.
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 milk contained 20 mg/L thiocyanate and volunteers consumed 8 mg of thiocyanate/day (0.11 mg/kg-day) in the milk for 12 weeks. Serum levels of thiocyanate increased from 0.4 mg/100 mL to a maximum of 0.78 mg/100 mL in the nonsmokers and from 0.84 mg/100 mL to a maximum of 1.07 mg/100 mL in smokers after 4 weeks of exposure. No significant difference from pretest levels was observed for serum thyroxine, triiodothyronine, or thyrotropic hormone, or the ratio of triiodothyronine:thyroxine. Therefore, the NOAEL in this study is 0.11 mg thiocyanate/kg-day.

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) 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 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) based on thyroid toxicity.

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3Dose conversion obtained by dividing the dose by the reference weight for the average male, 70 kg (U.S. EPA, 1986).

4Dose 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.

5Dose 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.
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)\(^6\) 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)\(^7\) 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 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)\(^8\) 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

\(^6\)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.

\(^7\)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.

\(^8\)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.
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)\(^9\) 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)\(^10\) 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 mammary
development was significantly decreased at 0.3% potassium thiocyanate after 12 weeks exposure.
However, no effect on the weight of the pituitary or adrenals 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)\(^11\). The
LOAEL for reproductive toxicity was 341 mg thiocyanate/kg-day (0.3 g/100 mL x 0.0057 L/day x

\(^9\)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.

\(^10\)Dose conversion obtained by multiplying by the percentage of the dose weight accounted
for by the thiocyanate ion.

\(^11\)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.
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)\(^{12}\) 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 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 were determined to be thyroid toxicity and hematotoxicity. Side effects associated with long-term oral exposure of humans to thiocyanates in the treatment of hypertension include thyroid toxicity, fatigue, anemia, and dry skin (Barker, 1936; Barker et al., 1941; Beamish et al., 1954; Blackburn et al., 1951). Insufficient information was provided regarding quantification of dosing to determine NOAELs or LOAELs for these effects. Thyroid toxicity and hematotoxicity

\(^{12}\)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.
were also observed in subchronic animal studies (Kanno et al., 1990; Lindberg et al., 1941; Nagasawa et al., 1980; Philbrick et al., 1979; Pyska, 1977; Rawson et al., 1944; Taubman and Heilborn, 1930; Wolff et al., 1946). The animal data regarding adverse effects on the hematopoietic system were insufficient to determine a NOAEL or LOAEL for this endpoint. However, several studies in rodents showed LOAELs and/or NOAELs for thyroid toxicity (Kanno et al., 1990; Nagasawa et al., 1980; Philbrick et al., 1979; Pyska, 1977; Rawson et al., 1944; Wolff et al., 1946).

The 10-week study by Pyska (1977) was chosen as the principal study because it demonstrated significant thyroid toxicity at the lowest dose. The lowest dose tested (52 mg thiocyanate/kg-day) was identified as a minimal LOAEL, because plasma protein-bound iodine was decreased at this dose. At higher doses, plasma protein-bound iodine was decreased to a greater extent. Plasma protein-bound iodine is an index of thyroid function. Depression of mammary growth (regulated by thyroid hormones) was also observed at 52 mg thiocyanate/kg-day. The 11.5-month study by Philbrick et al. (1979) was chosen as a co-principal study because it provides supporting information for the critical effect and threshold for toxicity. The LOAEL for thyroid toxicity (decreased plasma thyroxine and increased thyroid weight) was 67 mg thiocyanate/kg-day. No deaths, adverse clinical signs, or adverse effects on body weight gain were observed at this dose. Results from other subchronic studies in rodents (Kanno et al., 1990; Nagasawa et al., 1980; Rawson et al., 1944; Wolff et al., 1946) support the critical effects (thyroid toxicity) identified in the principal and co-principal studies. The report by Heydens (1985) of decreased postnatal growth and development of pups after maternal exposure to 55 mg thiocyanate/kg on gestation days 6–15 was not used to derive the provisional oral RfD for thiocyanate because limited experimental details were provided and the authors conclusions could not be verified because experimental results were not provided. The report by Dahlberg et al. (1984), in which humans were exposed to low levels of sodium thiocyanate in milk was also not used for derivation of the provisional RfD, because the dose used was 500-fold lower than the LOAELs observed in animal studies and use of such a low freestanding NOAEL may have been overprotective.

A provisional RfD of 2E-2 mg thiocyanate/kg-day was determined based on the LOAEL of 52 mg thiocyanate/kg-day from the study by Pyska (1977). A total uncertainty factor of 3,000 was applied to account for the use of a LOAEL (10), the use of a subchronic study (10), inter- and intraspecies variability (10), and insufficient database (3).

Confidence in the principal study is medium-to-low. Confidence is medium because the critical effect identified in the study was supported by the results of several other studies. Appropriate number of animals and statistical analyses were used and the critical effect was assessed using a range of doses. However, confidence is limited because only a single parameter (plasma protein-bound iodine) was examined. Other potential indicators of thyroid toxicity (decreased thyroid iodine uptake, increased thyroid weight, altered thyroid histopathology) were not also examined. Also, other potential target organs were not evaluated, and only one sex was tested.

Confidence in the database is medium. The confidence is not higher because of the uncertainty regarding the critical endpoint. Human data come primarily from reports of clinical experience with thiocyanate as an antihypertensive agent (Barker, 1936; Barker et al., 1941;
Beamish et al., 1954; Blackburn et al., 1951; Domzalski et al., 1953; Gorman et al., 1948; Nichols, 1925; Russell and Stahl, 1942; Smith and Rudolf, 1928). None of the clinical reports that were identified carefully analyzed the relative toxicity of thiocyanate toward a variety of organ systems. For the purpose of this report, the most sensitive target organs in humans were identified by determining those side effects that occurred most frequently as the result of exposure to what was considered safe doses. The animal database is similarly limited. No animal studies were identified that examined a broad spectrum of potential effects. A single chronic-duration study was located which focused almost exclusively on neoplastic effects (Lijinsky and Kovatch, 1989). Several subchronic animal studies were identified that examined thyroid toxicity (Kanno et al., 1990; Nagasawa et al., 1980; Philbrick et al., 1979; Pyska, 1977; Rawson et al., 1944; Wolff et al., 1946). However, these studies did not also examine other potential endpoints. The two references that identified the hematological system as a target organ for thiocyanate toxicity (Lindberg et al., 1941; Taubman and Heilborn, 1930) provided suggestive evidence that hematotoxicity may also have been a sensitive endpoint for prolonged exposure to thiocyanate, but insufficient information was given to determine NOAELs or LOAELs or to determine the relative toxicity toward the blood versus the thyroid. Also, the database is somewhat limited because although developmental toxicity and reproductive toxicity in females have been investigated, the reproductive effects resulting from exposure of males to thiocyanate is unknown. Based on the confidence in the database (medium) and in the principal study (medium-to-low), the overall confidence in the RfD is medium.

The provisional RfD calculated here is preferrable to that obtained by the requestor by dividing the oral LD$_{50}$ by a factor of 1,000. The acute oral LD$_{50}$ for thiocyanate in rats is approximately 500 mg/kg (854 x 58.08/97.18, potassium thiocyanate; 764 x 58.08/81.07, sodium thiocyanate) (RTECS, 1993). Therefore, a value of 5E-1 mg thiocyanate/kg-day is obtained by dividing the oral LD$_{50}$ by a factor of 1,000. Such a method uses a frank effect resulting from an acute exposure to derive an exposure level intended to be protective of populations over a lifetime. Review of the literature regarding thiocyanate toxicity revealed a variety of adverse effects occurring at concentrations lower than those causing death. Therefore, it is more appropriate to use the information available to calculate exposure levels that are intended to protect the population from the toxic effects less serious than death. The provisional RfD calculated in this report is 25-fold lower than that calculated by the requestor.

**REFERENCES**


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13Dose conversion obtained by multiplying by the percentage of the dose weight accounted for by the thiocyanate ion.

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Thiocyanate RfD

<table>
<thead>
<tr>
<th>Study</th>
<th>Species</th>
<th>Effect</th>
<th>Effect Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyska 1977</td>
<td>rats (females only)</td>
<td>Thyroid (decreased plasma protein-bound iodine)</td>
<td>LOAEL = 52 mg/kg-day</td>
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<tr>
<td>10-week study</td>
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<tr>
<td>Philbrick et al. 1979</td>
<td>rats (males only)</td>
<td>Thyroid (decreased plasma thyroxine levels; increased thyroid weight)</td>
<td>LOAEL = 67 mg/kg-day</td>
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<tr>
<td>11.5-month study</td>
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<tr>
<td>Dahlberg et al. 1984</td>
<td>humans</td>
<td>No effects were observed on serum thyroxine, triiodothyronine, or thyroid-stimulating hormone</td>
<td>NOAEL = 0.11 mg/kg-day</td>
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<td>12-week study</td>
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<td>Lijinsky and Kovatch 1989</td>
<td>rats</td>
<td>No effect on mortality, adverse clinical signs, or tumor formation</td>
<td>NOAEL = 75 mg/kg-day (males) 128 mg/kg-day (females)</td>
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<td>112-week study</td>
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<tr>
<td>Kanno et al. 1990</td>
<td>rats (males only)</td>
<td>Thyroid (increased thyroid weight, diffuse hyperplasia and increased colloid, increased serum thyroid-stimulating hormone, decreased serum thyroxine</td>
<td>LOAEL = 418 mg/kg-day</td>
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<td>25-week study</td>
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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>
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<td>12-week study</td>
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<tr>
<td>Wolff et al. 1946</td>
<td>rats</td>
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<td>Study</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>
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<td>Lindberg et al. 1941</td>
<td>dogs</td>
<td>Hematology (decreased erythrocyte count and hematocrit, bone marrow acellularity)</td>
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<td>4-27-week study</td>
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<td>Liver (decreased serum protein, fatty vacuolation, decreased serum cholesterol)</td>
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<td>Taubman and Heilbron 1930</td>
<td>guinea pigs</td>
<td>Hematology (decreased hemoglobin and erythrocytes)</td>
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<td>(duration not specified)</td>
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<td>Nagasawa et al. 1980</td>
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<td>NOAEL (repro.) = 114 mg/kg-day</td>
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<td>No effects on weight of pituitary or adrenals, ovarian histology, fertility, litter size, fetal viability, pup weight</td>
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<td>developmental toxicity</td>
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<td>Heydends 1985</td>
<td>rats (females only)</td>
<td>Developmental (decreased postnatal growth and development)</td>
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