Hydrogen Cyanide and Cyanide Salts; CASRN Various

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR HYDROGEN CYANIDE AND CYANIDE SALTS

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	09/28/2010
Inhalation RfC (I.B.)	yes	09/28/2010
Carcinogenicity Assessment (II.)	yes	09/28/2010

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Substance Name —Hydrogen Cyanide and Cyanide Salts
CASRN — 74-90-8; 143-33-9; 151-50-8; 506-61-6; 460-19-5
Last Revised — 09/28/2010

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of

substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

The previous oral RfD for cyanide (posted on the IRIS database in 1985) was 2×10^{-2} mg/kg-day, based on coprincipal studies (Philbrick et al., 1979; Howard and Hanzal, 1955). The no-observed-adverse-effect level (NOAEL) was identified as 10.8 mg/kg-day based on the lack of effects at the highest dose (Howard and Hanzal, 1955) and the lowest-observed-adverse-effect-level (LOAEL) was identified as 44 mg/kg-day, based on myelin degeneration in the central nervous system (CNS) and increased thyroid gland weight (Philbrick et al., 1979). The RfD of 2×10^{-2} mg/kg-day was calculated by applying an uncertainty factor (UF) of 500 (including a factor of 10 each for extrapolation from animals to humans and intraspecies variability, and a modifying factor of 5 to account for the apparent tolerance to cyanide when it is ingested with food compared with administration by gavage or by drinking water) to the NOAEL of 10.8 mg/kg-day.

I.A.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD
Decreased cauda epididymis weight in male F344/N rats **13-Week drinking water study** **NTP, 1993**	$BMDL_{1SD}$: 1.9 mg/kg-day	3,000	0.0006 mg/kg-day

*Conversion Factors and Assumptions – The BMD_{1SD} associated with a 1 standard deviation (SD) change in the control mean for decreased cauda epididymis weight was 3.5 mg/kg-day, and its 95% lower confidence limit ($BMDL_{1SD}$ shown above) was 1.9 mg/kg-day.

I.A.2. PRINCIPAL AND SUPPORTING STUDIES

A study by NTP (1993) examined the toxicity of CN^- over a wide range of doses. NTP administered NaCN in drinking water to rats and mice (10/sex/group) at concentrations of 0, 0.16, 0.48, 1.4, 4.5, and 12.5 mg/kg-day CN^- in male rats; 0, 0.16, 0.53, 1.7, 4.9, and 12.5 mg/kg-day in female rats; 0, 0.26, 0.96, 2.7, 8.6, and 24.4 mg/kg-day CN^- in male mice;

and 0, 0.32, 1.1, 3.3, 10.1, and 28.8 mg/kg-day in female mice. Reproductive effects were observed in male animals of both species, although rats appeared to be the more sensitive species. In rats, a statistically significant decrease in cauda epididymis weight (7%) was seen at doses ≥1.4 mg/kg-day. A 7% decrease in whole epididymis weight (as compared to cauda epididymis weight) was seen at 12.5 mg/kg-day. At the highest dose tested, 12.5 mg/kg-day, epididymis and cauda epididymis weights were decreased by 7 and 13%, respectively. Dose-related decreases in testis weight (8%), number of spermatid heads (14%), and spermatid concentration (14%) were also found to be significant at doses ≥12.5 mg/kg-day. No change in epididymal sperm count was observed at any dose; however, a statistically significant decrease in epididymal sperm motility was observed at doses ≥1.4 mg/kg-day CN^-, although it did not appear to increase in severity with dose.

In consideration of the available studies reporting low-dose effects of chronic and subchronic oral exposure to cyanide in animals, the NTP (1993) study was chosen as the principal study. This study was well designed, with five dose groups of 10 animals per group per sex and species. Numerous tissues and endpoints were assessed, and methods and observed effects were thoroughly reported. This study identified statistically significant male reproductive effects in rats and mice that increased in severity in a dose-dependent manner. The observed effects included decreased cauda and whole epididymis weights, decreased testes weight, and altered sperm parameters.

The reproductive effects observed by NTP (1993) are consistent with an effect on male reproductive endpoints, including organ weights and sperm parameters, although the magnitude of the effects alone may be insufficient to decrease fertility in rats. However, human males have markedly lower rates of sperm production and sperm counts compared with rats; thus, the potential impact of decrements in sperm quality in humans is considered to be greater than that of rats (U.S. EPA, 1996; Working, 1988). Furthermore, the cyanide database contains limited additional support for the specific endpoint of reproductive toxicity (Kamalu, 1993). Therefore, for the above reasons, NTP (1993) was chosen as the principal study.

EPA has selected decreased cauda epididymis weight as the critical effect because it was determined that this effect represents the most sensitive endpoint indicative of male reproductive toxicity. The cauda epididymis is one of the three primary subsections of the epididymis (along with the caput and corpus) and functions as the site of sperm storage and maturation.

The available models for continuous data in the EPA Benchmark Dose Software (BMDS version 1.4.1) were fit to the male rat data for cauda epididymis weight. A benchmark response (BMR) level was selected corresponding to a change in the mean response equal to 1 SD from the control mean for cauda epididymis weight. Information regarding the degree of

change in this endpoint that is considered biologically significant was not available in the literature. Therefore, the BMR for continuous data of 1 SD change in the control mean was selected under the assumption that it represents a minimally biologically significant response level. The polynomial model provided the best fit to the data for decreased cauda epididymis weight and resulted in a BMD_{1SD} and $BMDL_{1SD}$ of 3.5 and 1.9 mg/kg-day, respectively.

I.A.3. UNCERTAINTY FACTORS

UF = 3,000

A default 10-fold UF was used to account for uncertainties in extrapolating from laboratory animals to humans. Humans and laboratory animals have qualitatively similar absorption, distribution, metabolism, and excretion of cyanide. However, quantitative comparisons of toxicokinetic parameters are lacking. Additionally, a wide range of sensitivity to effects of cyanide has been observed between different species of experimental animals. The available data do not provide quantitative information on the difference in susceptibility to cyanide between rats and humans.

A default 10-fold UF was used to account for variation in susceptibility among members of the human population (i.e., interindividual variability). Insufficient information is available to quantitatively estimate variability in human susceptibility to cyanide.

A 10-fold UF was applied for the extrapolation of subchronic-to-chronic exposure duration. The 91-day study by NTP (1993) falls well short of a lifetime duration. In addition, there is a lack of data on male reproductive parameters following chronic administration of cyanide, and the mode of action of the reproductive effects observed in this study is unclear. Therefore, it is unknown whether effects would be more severe or would be observed at lower doses with a longer exposure duration. For these reasons, the UF of 10 to extrapolate from a study with a subchronic duration was applied.

A 3-fold UF was applied to account for deficiencies in the cyanide toxicity database, including the lack of a multigenerational reproductive toxicity study and a sensitive neurodevelopmental toxicity study. The database includes limited human data from epidemiological studies of workers exposed by inhalation to HCN (Chatgtopadhyay et al., 2000; Banerjee et al., 1997; Blanc et al., 1985; El Ghawabi et al., 1975). The database also includes studies in laboratory animals, including chronic and subchronic dietary exposure studies and developmental studies. The database includes oral toxicity studies in various animal species, including rats, mice, rabbits, dogs, pigs, and goats. A developmental study with skeletal and visceral examination has not been conducted for cyanide; however, developmental studies exist in rats and goats evaluating the thyroid, kidney, liver, pancreas, brain, and CNS of gestationally

and/or lactationally exposed offspring (Imosemi et al., 2005; Malomo et al., 2004; Soto-Blanco and Gorniak, 2004, 2003; Tewe and Maner, 1981). External or overt developmental effects with cyanide exposure have not been noted at doses up to 1.2 mg/kg-day in goats (Soto-Blanco and Gorniak, 2004. 2003) and 21.6 mg/kg-day in rats (Imosemi et al., 2005; Malomo et al., 2004; Tewe and Maner, 1981). However, due to the mode of action of thiocyanate involving competitive iodine uptake inhibition and implications for neurotoxicity in the developing animal, the lack of a sensitive neurodevelopmental toxicity study to assess endpoints sensitive to thyroid disruption is a weakness in this database. The cyanide database is also lacking an appropriately designed multigenerational reproductive toxicity study, although an assessment of reproductive organs was included as a component of the 13-week NTP (1993) studies in rats and mice, and testicular histology was also assessed in dogs (Kamalu, 1993). These studies in adult animals demonstrated low-dose reproductive effects. The observance of these effects reinforces the need for a multigenerational assessment of reproductive endpoints. Therefore, in consideration of the above data gaps, a 3-fold UF to account for deficiencies in the database was applied.

The UF for LOAEL-to-NOAEL extrapolation was not used because the current approach is to address this factor as one of the considerations in selecting a benchmark response (BMR) for benchmark dose (BMD) modeling. In this case, a BMR of a 1 SD change from the control mean in epididymis weight was selected under an assumption that it represents a minimally biologically significant response level.

The oral RfD for CN^- was calculated as follows:

$$RfD = BMDL_{10} \div UF$$
$$= 1.9 \text{ mg/kg-day} \div 3{,}000$$
$$= 6.3 \times 10^{-4} \text{ mg/kg-day (rounded to } 6 \times 10^{-4} \text{ mg/kg-day)}$$

The RfDs for simple cyanide salts like NaCN and KCN, which freely dissociate into cyanide, are calculated from the RfD for CN^- by adjusting for molecular weight (i.e., the RfD is multiplied by the ratio of the total molecular weight of the compound to the molecular weight of the CN^-):

RfD for aqueous HCN [HCN(aq)] = $6.3 \times 10^{-4} \times 27/26 = 7 \times 10^{-4}$ mg/kg-day
RfD for NaCN = $6.3 \times 10^{-4} \times 49/26 = 1 \times 10^{-3}$ mg/kg-day
RfD for KCN = $6.3 \times 10^{-4} \times 65/26 = 2 \times 10^{-3}$ mg/kg-day
RfD for calcium cyanide[1] [$Ca(CN)_2$] = $6.3 \times 10^{-4} \times 92/(2 \times 26) = 1 \times 10^{-3}$ mg/kg-day
RfD for potassium silver cyanide[2] [$KAg(CN)_2$] = $6.3 \times 10^{-4} \times 199/26 = 5 \times 10^{-3}$ mg/kg-day
RfD for cyanogen[2] $(CN)_2$ = $6.3 \times 10^{-4} \times 52/26 = 1 \times 10^{-3}$ mg/kg-day

Use of the RfD for free cyanide to calculate RfDs of other cyanide compounds may be merited, but the ability of the individual cyanogenic species to dissociate and release free cyanide in aqueous solution (and at physiological pHs) should be taken into consideration. If dissociation of the compound is expected, then liberated cations should be considered for potential toxicity independent of CN^-. Also, some metallocyanides, such as copper cyanide, have chemical-specific data and are not included in this analysis.

[1]Two molar equivalents of free CN^- released in water.
[2]One molar equivalent of free CN^- released in water.

I.A.4. ADDITIONAL STUDIES/COMMENTS

Manzano et al. (2007) treated 6 or 10 pigs per group (sex not specified and number of animals unclear due to inconsistencies in reporting) with KCN administered in the diet at 0, 1.4, 2.8, or 4.3 mg/kg-day for 10 weeks. An increase of 24% in thyroid weight was seen at 4.3 mg/kg-day. Histologic alterations were reported in the thyroid, liver, kidney, and CNS in all dosed animals. However, no incidence data or statistical analyses were provided for these histologic findings, precluding a characterization of the dose response for these effects. This study identified a LOAEL of 4.3 mg/kg-day and a NOAEL of 2.8 mg/kg-day for a statistically significant increase in thyroid weight. This study is limited by poor reporting of study design and observed histologic effects.

Jackson (1988) evaluated the effects of gavage administration of KCN on behavior and thyroid function in miniature pigs. Doses of 0, 0.4, 0.7, or 1.2 mg/kg-day KCN were administered by gavage to three pigs per group (mixed sexes) for 24 weeks. Both triiodothyronine (T_3) and thyroxine (T_4) demonstrated a dose-related decrease (23 and 13%, respectively) that was statistically significant by week 18 of the study. Changes in thyroid hormones were portrayed graphically as means, without reporting variance or data for individual animals. The author concluded that the overall pattern of behavioral changes, characterized as an increased ambivalence and slower response to stimuli, was different in the highest dose group compared to control animals. Based on behavioral changes and decreased thyroid hormones, the LOAEL and NOAEL values are 1.2 and 0.7 mg/kg-day CN^-, respectively. The biological significance of the behavioral changes observed in this study is unclear. In addition, the utility of this study is limited by the use of bolus dosing. In comparison to relatively steady intake throughout the day via dietary administration, bolus dosing produces higher peak blood levels as the entire daily dose is rapidly absorbed. This difference is especially important considering that the toxicity of cyanide is highly rate dependent. Thus, the findings from bolus exposure to cyanide are considered less relevant to subchronic or chronic exposure conditions in humans.

Soto-Blanco et al. (2002a) treated Wistar rats (six to seven per group) with 0, 0.06, 0.12, or 0.24 mg/kg-day by gavage for 12 weeks and reported histopathologic changes in the CNS. The same authors also conducted a 5-month drinking water study in female goats (six to eight per group) with concentrations ranging from 0 to 1.2 mg/kg-day (Soto-Blanco et al., 2002b). In these studies, the authors reported a variety of histopathologic changes in the CNS described as spheroids on the spinal cord, neuronal loss in the hippocampus, damaged Purkinje cells, gliosis, and loss of cerebellar white matter. However, the authors provided no quantitative data, precluding a dose-response characterization of the reported effects.

Kamalu (1993) evaluated the toxicity of NaCN administered to 22-week-old mongrel dogs (six males per group) for 14 weeks. The diet was supplemented with NaCN corresponding to 0 or 1.04 mg/kg-day CN^-. Lesions in the kidneys and adrenal gland were reported at the only dose tested; however, no quantitation of these lesions was provided. In the testes, a specialized morphologic analysis indicated that the treated dogs had a significantly decreased percentage of tubules in stage VIII of the spermatogenic cycle, as compared with controls ($p < 0.01$). An evaluation of the thyroid of animals in this study was published by Kamalu and Agharanya (1991). Serum T_3 was significantly decreased (55%) and thyroid weight was significantly increased (23%) in the cyanide-exposed group. Based on thyroid enlargement and histopathologic changes in the kidneys, testes, and adrenal glands, the only dose tested, 1.04 mg/kg-day, was considered to be the LOAEL. The authors reported that the animals suffered from recurring parasitic infestations that required treatment with pharmaceuticals throughout the study. Therefore, the use of the data from the Kamalu (1993) and Kamalu and Agharanya (1991) studies are limited by the use of dogs of compromised health status.

An unpublished study by Leuschner and Neumann (1989) administered KCN to male Sprague-Dawley rats (26–40/group) in drinking water for 13 weeks. Administered doses were 0, 40, 80, or 160 mg KCN/kg-day or 0, 16, 32, or 64 mg CN^-/kg-day. Early mortality was observed at the high dose with 11 animals dying prematurely. Body weight was statistically significantly decreased 42% at the high dose and 15% in the mid dose. Organ weight changes were not observed at the lowest dose level tested (16 mg CN^-/day). Absolute thymus weight was statistically significantly decreased (20%) at the mid-dose level (32 mg CN^-/day). Statistically significant relative and absolute organ weight changes were seen at the highest dose level (64 mg CN^-/kg-day), although these changes were inconsistent. At the highest dose, absolute heart, liver, spleen, kidney, and brain weights were statistically significantly decreased compared to the controls. However, when relative weights were calculated, all organs showed increased weight compared to controls (except for the thymus, which was decreased). A LOAEL of 32 mg/kg-day was identified based on decreased body weight.

Studies observing low-level developmental effects were also considered in the selection of the principal study and critical effect (Soto-Blanco and Gorniak, 2004, 2003). Soto-Blanco and Gorniak (2004) administered gavage doses of CN^- equivalent to 0, 0.4, 0.8, or 1.2 mg/kg-day throughout gestation (gestation day 24 to birth) to pregnant goats (six per group) and observed elevated T_3 (but not T_4) levels in dams and offspring tested at birth in the highest dose group. Another publication by the same authors (Soto-Blanco and Gorniak, 2003) treated goats with 0, 0.4, 0.8, or 1.2 mg/kg-day during lactation (postnatal days 0–90) and identified vacuolation of kidney epithelial cells and hepatocytes in offspring and dams at unspecified doses. Incidence or severity of the reported histologic lesions was not provided, precluding any characterization of dose response. These studies are limited by the use of bolus doses and the lack of dose-response characterization.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF)

I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD

Study — Medium
Database — Low to Medium
RfD — Low to Medium

The overall confidence in the RfD is low to medium. Confidence in the principal study (NTP, 1993) is medium. This study was well conducted, involved a sufficient number of animals per group (including both sexes of two species), used several dose levels, and assessed a wide range of tissues and endpoints. However, this study did not evaluate thyroid endpoints and was only 90 days in duration. Confidence in the database is low to medium. The cyanide database includes occupational inhalation exposure studies in humans, chronic and subchronic dietary exposure studies in laboratory animals, and several developmental studies in laboratory animals. However, the database is lacking a multigenerational reproductive toxicity study, a sensitive neurodevelopmental study, and a chronic study evaluating noncancer endpoints. Therefore, reflecting low to medium confidence in the database and medium confidence in the principal study, the overall confidence in the RfD is low to medium.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document — U.S. EPA (2010)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Hydrogen Cyanide and Cyanide Salts* (U.S. EPA, 2010). **To review this appendix, exit to the Toxicological Review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF).**

Agency Completion Date — 09/28/2010

I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Substance Name — Hydrogen Cyanide and Cyanide Salts
CASRN — 74-90-8; 143-33-9; 151-50-8; 506-61-6; 460-19-5
Section I.B. Last Revised — 09/28/2010

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

The previous inhalation RfC for HCN was 3×10^{-3} mg/m^3 (posted on the IRIS database in 1994) based on the same occupational study (El Ghawabi et al., 1975) used to derive the current RfC. The LOAEL of 7.07 mg/m^3 was identified based on findings of thyroid effects and neurological symptoms in workers (El Ghawabi et al., 1975). The RfC of 3×10^{-3} mg/m^3 was calculated by applying an UF of 1,000 (comprised of UFs of 10 each to account for the lack of a NOAEL and intrahuman variability and UFs of 3 each to account for the use of a study of less-than-chronic duration and deficiencies in the database) to the $LOAEL_{ADJ}$ of 2.5 mg/m^3 (adjusted for daily continuous exposure).

I.B.1. Inhalation RfC Summary

Critical Effect	Point of Departure*	UF	Chronic RfC
Thyroid enlargement and altered iodide uptake **Epidemiology study** **El Ghawabi et al., 1975**	NOAEL: None LOAEL: 7.07 mg HCN/m^3 $LOAEL_{ADJ}$: 2.5 mg HCN/m^3	3,000	0.0008 mg/m^3

* Conversion Factors and Assumptions - El Ghawabi et al. (1975) did not report daily exposure durations for exposed workers; therefore, an 8-hour/day, 5-day/week exposure scenario was assumed. The LOAEL of 7.07 mg HCN/m^3 was adjusted for daily exposure duration using a default occupational ventilation rate of 10 m^3/8-hour day and a default ventilation rate for continuous ambient exposure of 20 m^3/24-hour day. The LOAEL was also adjusted for continuous exposure from 5 days/week to 7 days/week. $LOAEL_{(ADJ)}$ = 7.07 mg/m^3 HCN × 10/20 × 5 days/7 days = 2.5 mg/m^3 HCN.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES

El Ghawabi et al. (1975) reported statistically significantly altered rates of iodide uptake by the thyroid, thyroid enlargement, and CNS symptoms (e.g., self-reported increased incidence of headache, weakness, and sensory changes for taste and smell) in workers (n = 36) exposed to HCN for 5–15 years in three electroplating factories. Individual breathing zone measurements of HCN were collected from each worker. The mean concentrations across factories ranged from 7.07 to 11.5 mg/m^3 HCN and the values for individual workers ranged from 4.6 to 13.7 mg/m^3 HCN. Urine SCN^- levels, an indicator of internal dose, collected from workers were highly correlated with individual HCN exposure concentrations. Twenty of the exposed workers (56%) were identified with mild to moderate thyroid

enlargement. Radioactive iodine uptake measured following a 2-day break in HCN exposure indicated statistically significantly elevated iodide uptake after 4 hours (38.7 compared to 22.4%) and 24 hours (49.3 compared to 39.9%) as compared to controls.

Increased 24-hour uptake of radioactive iodide by the thyroid has been reported to occur in hyperthyroidism, iodine deficiency, and goiter (NLM, 2008; Ravel, 1995). The study authors concluded that the increased iodine uptake observed in the workers following the 2-day cessation in exposure was a postexposure response to depletion of iodine in the thyroid. A similar increase in iodide uptake has been seen with perchlorate (ClO_4^-), another competitive inhibitor of iodide uptake, following cessation of exposure. Lawrence et al. (2000) measured iodine uptake in volunteers administered doses of ClO_4^- at baseline, at 2 weeks of dosing, and then 2 weeks postexposure cessation. The authors reported that iodide uptake decreased 10–38% in the low- and high-dose groups (compared to baseline) at 2 weeks of dosing. Two weeks after exposure was discontinued, iodide uptake was statistically significantly increased 22 and 25%, indicating a rebound effect in iodide accumulation postexposure.

The lowest mean concentration of HCN recorded in the three factories, 7.07 mg/m^3, is designated as a LOAEL for thyroid enlargement and altered iodide uptake. The study authors also indicated some coexposure of the workers to gasoline, alkali, and acid during the electroplating process, although the magnitudes of these exposures were not quantified and it is unclear if these exposures would impact the observed thyroid effects.

Considering the availability of studies in the HCN database, El Ghawabi et al. (1975) was chosen as the principal study. The results of this study indicate that chronic, low-level exposure to cyanide was associated with thyroid enlargement and altered iodine uptake in humans. This study examined workers exposed to HCN for extended durations (5–15 years). Although this study is limited by small sample size, it used matched controls and is not confounded by smoking since all workers and controls were nonsmokers. The authors collected individual breathing zone measurements of HCN exposure, which were strongly correlated with urinary SCN^-, a measure of internal exposure. Mean individual HCN concentrations reported from all three plants were close (6.4–10.4 ppm) and the range among the 36 individuals was also relatively small (4.2–12.4 ppm), indicating similar magnitude of exposure for exposed workers. Thyroid enlargement was strongly associated with HCN exposure, with 56% of the exposed workers diagnosed with mild to moderate thyroid enlargement. This observation is supported by an increased radioactive iodide uptake in workers ($p < 0.001$). Increased uptake of radioactive iodide has been reported to occur in hyperthyroidism, iodine deficiency, recovery from thyroid suppression, and goiter (NLM 2008a; Spencer 2008; Ravel 1995;). The increase in iodide uptake may have resulted from temporary weekend cessation of exposure. A similar phenomenon of post-inhibitory response

was also seen in an occupational study by Blanc et al. (1985), which noted significantly increased T_3 uptake observed in workers several months following HCN exposure.

The thyroid alterations reported in El Ghawabi et al. (1975) are believed to be biologically significant effects. These effects, particularly thyroid enlargement, are consistent with those observed in oral exposure animal studies (Manzano et al., 2007; Jackson, 1988; Philbrick et al., 1979). Additionally, other human inhalation studies have indicated thyroid effects in exposed workers (Banerjee et al., 1997; Blanc et al., 1985). The thyroid effects observed in El Ghawabi et al. (1975) are also supported by mode-of-action data for cyanide, indicating competitive iodide uptake. The thyroid enlargement observed in the HCN-exposed workers likely indicates antagonism of iodine uptake by the cyanide metabolite, SCN^-. This biological response indicates a stress on the homeostatic mechanisms of the thyroid, which is of concern to populations that include individuals with iodine deficiency, individuals with clinical or subclinical hypothyroidism, and the developing fetus.

I.B.3. UNCERTAINTY FACTORS

UF= 3,000

A 1-fold UF for extrapolation across species was applied because the RfC is based on thyroid enlargement and altered iodide uptake reported in an occupational study.

A 10-fold UF was used to account for variation in susceptibility to cyanide among members of the human population. Although some information is available on potential sensitive populations, there are insufficient quantitative data to inform the UF for human variability with chemical-specific data.

A 10-fold UF was used for extrapolating from a LOAEL to a NOAEL (UF_L) because the POD was a LOAEL.

A 3-fold UF was applied to account for extrapolation from what is assumed to be a largely subchronic exposure to chronic exposure duration. The workers in the principal study were exposed to cyanide for 5–15 years. Of the 36 workers, 14 had been exposed for 5 years, 14 for 5–10 years, 7 for 10–15 years, and 1 for >15 years. The mean and median exposure times for the worker population were not reported. Twenty of the 36 exposed workers had thyroid enlargement; however, the authors found no correlation between duration of exposure and either incidence or magnitude of thyroid enlargement in the workers. A lack of an association could be related to the low sample size and/or the failure of the authors to consider iodine status of the workers. In addition, following continued administration of cyanide in rats, thyroid effects were less prominent at 11 months of exposure compared to 4 months of

exposure (Philbrick et al., 1979), which provides some indication (although limited), that increased duration of exposure may not lead to an increase in thyroid effects. Therefore, it is not clear whether greater alteration in thyroid function or increased incidence of the effect would be observed with longer exposure duration. In the absence of information indicating the effects of HCN would not progress in incidence or severity, a subchronic to chronic UF of 3 was applied.

A 10-fold UF was applied to account for deficiencies in the cyanide inhalation database. The database includes limited human data from epidemiologic studies of inhalationally exposed workers (Blanc et al., 1985; El Ghawabi et al., 1975). Inhalation studies on acetone cyanohydrin (ACH) evaluated limited male and female reproductive endpoints and were negative for impacts on fertility (Monsanto Co., 1985a, b). Oral studies of cyanide exposure in rodents have suggested that the male reproductive tract is a sensitive target of cyanide toxicity following subchronic exposure (NTP, 1993). However, the database lacks developmental and multigenerational reproductive toxicity studies. New data are available which evaluate potential health effects following perturbations of thyroid function in pregnant women and their offspring (see Section 4.8.1). These studies indicate increased pregnancy complications and decrements in learning and memory in offspring of women with subclinical hypothyroidism (Kooistra et al., 2006; Casey et al., 2005; Pop et al., 2003; Haddow et al., 1999). Due to the proposed cyanide mode of action of thyroid disruption (through the metabolite thiocyanate), developmental neurotoxicity studies or developmental studies assessing maternal and fetal thyroid function are also considered data insufficiencies. Thus, a database UF of 10 was applied in this assessment to account for the lack of developmental and multigenerational reproductive toxicity studies.

The RfC for HCN was calculated as follows:

$$RfC = LOAEL_{(ADJ)} \div UF$$
$$= 2.5 \text{ mg/m}^3 \div 3{,}000$$
$$= 0.00083 \text{ mg/m}^3 \text{ (rounded to } 8 \times 10^{-4} \text{ mg/m}^3\text{)}$$

It is recommended that the RfC for HCN should not be used to estimate an RfC for cyanide salts due to inhalation considerations. Specifically, exposure to HCN occurs as a gas, whereas the extremely high boiling points and vapor pressures of cyanide salts predict that inhalation exposure would occur as aerosols. Different dosimetric approaches would apply to the aerosol (or particle) exposures that would result from exposure to cyanide salts, compared with exposure to HCN gas.

I.B.4. ADDITIONAL STUDIES/COMMENTS

Blanc et al. (1985) conducted a study of silver-reclamation workers (n = 36) examined an average of 11 months following exposure. The median length of employment was 8.5 months and mean exposure duration was 11 months. Workers were categorized into low-, moderate-, or high-exposure groups based on their primary job activities. Information on exposure was limited, as the plant had been shut down following the death of one worker from cyanide overexposure. Environmental monitoring conducted the day after the plant was shut down found that the 24-hour time-weighted average (TWA) HCN exposure was 16.6 mg/m^3. Serum thyroid stimulating hormone (TSH) levels in workers were significantly elevated relative to laboratory controls. The authors noted a significant positive trend with increasing exposure level for self-reported weight loss and several symptoms, including dizziness, syncope, and nausea and vomiting. Serum TSH levels in workers were reported as being significantly elevated in workers relative to laboratory controls. T_3 uptake in the highest exposed workers (n = 9) was statistically significantly elevated compared to laboratory controls. The authors reported that this elevation may reflect a post-inhibitory response. Because there were multiple possible routes of cyanide exposure, including dermal exposure and contamination of food, and because earlier air levels were likely higher than the measured TWA concentration, the environmental monitoring data do not allow for the selection of a LOAEL. Additionally, this study examined workers an average of 11 months post-occupational HCN exposure and may therefore have missed effects that have the potential to regress following cessation of exposure. The observation of significant effects on the thyroid almost 1 year after cessation of exposure indicates that these observed thyroid effects are not transient.

An unpublished study by Leeser et al. (1990) compared the health of 63 male cyanide salt production workers with a control group of 100 British workers in a cross-sectional study. Cyanide workers were exposed for periods ranging from 1 to 32 years with a mean duration of 12.6 years and mean breathing zone concentrations of cyanide up to 1 mg/m^3. Several hematological parameters in cyanide workers were statistically significantly elevated including hemoglobin (adjusted mean 15.57 vs. 15.08 g/dL), ratios associated with hemoglobin, such as MCH and MCHC, and lymphocyte count (adjusted mean 2.87 compared to 2.55×10^9/L). However, the biological significance of these slight elevations in hematological parameters is unclear. Serum T_4 levels in cyanide-exposed workers were decreased in controls, but the difference was not reported as statistically significant by the study authors (85.13 ± 2.51 vs. 89.04 ± 1.81 nmol/L). Additionally, serum T_4 was below the clinical reference range (60–160 nmol/L) in 3 cyanide-exposed workers. Other commonly administered, and more sensitive, tests for thyroid function, including TSH, free T_4, or iodide uptake, were not measured. It is unclear whether a NOAEL for thyroid effects can be established by this study as only one, relatively insensitive indicator of thyroid function was measured. A LOAEL of 1 mg/m^3 cyanide for increased lymphocyte count and increased

hemoglobin concentration was identified. A NOAEL for thyroid effects was not identified from this study based on the lack of measurement of sensitive thyroid parameters, although overt hypothyroidism was not observed.

In another occupational study of electroplating workers exposed to HCN, workers (n = 35) exposed for 5 years had significantly decreased T_3 (48%) and T_4 (37%) and significantly increased TSH (142%) as compared to controls (Banerjee et al., 1997). Serum SCN^- was elevated in workers compared to controls. A significant negative correlation between serum T_4 and SCN^- concentrations and a significant positive correlation between TSH and SCN^- concentrations were observed. However, no information was provided on exposure levels; therefore, no NOAEL or LOAEL could be identified from this study.

Chandra et al. (1980) reported on a group of 23 electroplating workers chronically exposed to average breathing zone concentrations of 0.15 mg/m^3 HCN. The authors noted that the workers complained of symptoms typical of cyanide poisoning but provided no additional information on specific symptoms or further analysis. In the absence of information on measured effects, no NOAEL or LOAEL could be identified from this study.

Chatgtopadhyay et al. (2000) found some indication of decreased pulmonary function in workers at a metal-tempering plant. Specifically, the authors observed decreased pulmonary function in 24 workers exposed for a mean duration of 24 years. This study provided no information regarding the environmental exposure levels of the workers, and thus, no NOAEL or LOAEL could be identified.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF)

I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC

Study — Medium
Database — Low to medium
RfD — Low to medium

El Ghawabi et al. (1975) was chosen as the principal study. The results of this study indicate that chronic, low-level exposure to cyanide was associated with thyroid enlargement and altered iodine uptake in humans. This study examined workers exposed to HCN for extended durations (5–15 years). Although this study is limited by small sample size, it used matched controls and is not confounded by smoking since all workers and controls were nonsmokers. The authors collected individual breathing zone measurements of HCN exposure, which were strongly correlated with urinary SCN^-, a measure of internal

exposure. The range of mean individual HCN concentrations reported from all three plants was 6.4–10.4 ppm and the range among the 36 individuals was 4.2–12.4 ppm, indicating a similar magnitude of exposure for exposed workers. The database includes limited human data from epidemiologic studies of inhalationally exposed workers (Blanc et al., 1985; El Ghawabi et al., 1975). The database lacks developmental and multigenerational reproductive toxicity studies. Reflecting medium confidence in the principal study (El Ghawabi et al., 1975) and low to medium confidence in the inhalation database, the overall confidence in the cyanide RfC is low to medium.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC

Source Document — U.S. EPA (2010)

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Hydrogen Cyanide and Cyanide Salts* (U.S. EPA, 2010). **To review this appendix, exit to the Toxicological Review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF).**

Agency Completion Date – 09/28/2010

I.B.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name — Hydrogen Cyanide and Cyanide Salts
CASRN — 74-90-8; 143-33-9; 151-50-8; 506-61-6; 460-19-5
Section II. Last Revised — 09/28/2010

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the U.S. EPA (2005a) *Guidelines for Carcinogen Risk Assessment*, there is "inadequate information to assess the carcinogenic potential" of cyanide. Studies examining cancer incidence in occupationally exposed cyanide workers are not available. Studies of cancer in populations exposed to thiocyanate via diet were limited to examinations of thyroid cancer and results are generally not positive (Bosetti et al., 2002; Kolonel et al., 1990), although one recent case control study has associated high consumption of goitrogenic food and low iodine intake with increased incidence of thyroid cancer in women (Truong et al., 2010). The currently available data indicate that cyanide is not genotoxic. Bacterial mutagenicity assays, with and without activation, are predominantly negative (NTP, 1993; De Flora et al., 1984; De Flora, 1981). The only available chronic animal study of cyanide that analyzed a wide variety of tissues is an oral study in rats (Howard and Hanzal, 1955), in which tumors or lesions were not associated with either dose group following dietary administration of cyanide at doses up to 10.8 mg/kg-day for 2 years. This study is limited by small sample sizes (n = 10), histopathologic assessment of only a subset of potential target organs of carcinogenicity, and uncertainty regarding dose due to HCN volatility issues. Therefore, the available data for cyanide are inadequate to assess the carcinogenic potential of cyanide.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.8 (PDF)

II.A.2. HUMAN CARCINOGENICITY DATA

Not applicable.

II.A.3. ANIMAL CARCINOGENICITY DATA

Not applicable.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Not applicable.

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

II.B.1. SUMMARY OF RISK ESTIMATES

Not applicable.

II.B.2. DOSE-RESPONSE DATA

Not applicable.

II.B.3. ADDITIONAL COMMENTS

Not applicable.

II.B.4. DISCUSSION OF CONFIDENCE

Not applicable.

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not applicable.

II.C.1. SUMMARY OF RISK ESTIMATES

Not applicable.

II.C.2. DOSE-RESPONSE DATA

Not applicable.

II.C.3. ADDITIONAL COMMENTS

Not applicable.

II.C.4. DISCUSSION OF CONFIDENCE

Not applicable.

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

Source Document – U.S. EPA (2010)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Hydrogen Cyanide and Cyanide Salts)* (U.S. EPA, 2010). **To review this appendix, exit to the Toxicological Review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF).**

Agency Completion Date – 09/28/2010

II.D.2. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202) 566-1676 (phone), (202) 566-1749 (fax), or hotline.iris@epa.gov (email address).

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name —Hydrogen Cyanide and Cyanide Salts
CASRN —74-90-8; 143-33-9; 151-50-8; 506-61-6; 460-19-5

VI.A. ORAL RfD REFERENCES

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VII. REVISION HISTORY

Substance Name — Hydrogen Cyanide and Cyanide Salts
CASRN — 74-90-8; 143-33-9; 151-50-8; 506-61-6; 460-19-5
File First On-Line 01/31/1987

Date	Section	Description
09/01/1994	I.B.	Inhalation RfC on-line
09/28/2010	I., II., VI	RfD and RfC assessment updated; cancer assessment added.

VIII. Synonyms

Substance Name — Hydrogen Cyanide and Cyanide Salts
CASRN — 74-90-8; 143-33-9; 151-50-8; 506-61-6; 460-19-5
Section VIII Last Revised — 09/28/2010

- Prussic acid
- hydrocyanic acid
- Cyclone B
- Cyanogran
- Cymag
- Cyanobrik
- white cyanide
- Calcyanide
- Calcyan, cyanogas
- black cyanide
- Potassium dicyanoargentate
- dicyanogen
- ethanedinitrile
- oxalonitrile
- 74-90-8
- 143-33-9
- 151-50-8
- 506-61-6
- 460-19-5