Background Documentation for the Development of an "Available Cyanide" Benchmark Concentration

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Text modified slightly 8/98 to refer to current regulation.
This document was the basis for the
Cyanide Imminent Hazard concentration (310 CMR 40.0321(2)(b))
and the MCP Method 1 soil standards (310 CMR 40.0975).

I. SUMMARY OF DOCUMENT

A. PURPOSE

This document provides documentation for the development of criteria to be used for deciding when *immediate* action is necessary to protect the public health from exposures to soils contaminated with *available* cyanide. This document does not focus on cyanides from any one particular industrial or manufacturing category, such as coal gasification or metal plating.

This document develops an exposure scenario which involves accessible surface soils which might be found in residential, recreational or other "open" areas. It does not address inaccessible soils which might be found in industrial or commercial areas, and it does not address construction situations. Such circumstances will continue to be considered on a *site-by-site* basis.

The benchmark concentration for *available* cyanide in surface soil is used to evaluate acute soil-related exposures only. The benchmark soil concentration may not be sufficient, *by itself*, to evaluate the need for immediate action if exposures to cyanides may be occurring via other media (drinking water, for example).

While *available* cyanide (as measured by the Available Cyanide Method) is considered to be extremely toxic, the toxicity of other cyanides and the potential for their environmental transformation must also be fully evaluated.

B. METHOD

For the purposes of this document, the benchmark soil concentration is defined as a concentration of *available* cyanide in soil *at or below which* adverse human health effects would not be expected following an acute exposure. Such a benchmark is consistent with existing DEP regulatory practices and its mandate to be protective of the public health.

The term *available* cyanide used throughout this policy refers to those species of cyanide which are capable of releasing Hydrogen Cyanide (HCN) or the cyanide anion (CN^-) under reasonably anticipated human gastric conditions. This term may include, but is not limited to, hydrogen cyanide (HCN), simple cyanide salts, nitriles, cyanogens and more complexed forms of cyanide.

The derivation of the benchmark concentration for *available* cyanide in soil is described in two steps:

> Available toxicological information and current health risk assessment techniques are used to estimate an *absorbed dose* resulting from an acute exposure to *available*

cyanide which would not cause any adverse health effects in humans.

This absorbed dose is used in conjunction with a soil exposure scenario to derive the benchmark soil concentration of hydrogen cyanide.

Hydrogen cyanide (HCN), considered one of the most toxic of the cyanide compounds, is used as a surrogate in this document for the *available* cyanide compounds. Much of the available literature focuses upon hydrogen cyanide, either as the administered toxin or a product formed in the hydrolysis of simple cyanide salts (typically potassium cyanide or sodium cyanide). Cyanide species which are capable of forming HCN under environmental or physiological conditions have the potential to cause severe health effects, including death in humans after a single exposure.

As *available* cyanide is associated with potentially fatal effects, a reasonable *worst case* soil exposure scenario is used in this evaluation to insure that the approach is protective of health. Briefly, this scenario involves a child who might ingest a quantity (1 gram) of soil in a relatively short period of time.

Cyanides are detoxified rapidly by the body, and a large acute dose which overwhelms the detoxification mechanism is potentially more toxic than the same dose distributed over a period of hours. As noted by the U.S. EPA (1988), *the intermittent ingestion of low doses over a day would allow for sufficient detoxification* [to prevent lethal effects and allow sublethal health effects to be seen]. Hayes (1967) noted the same phenomenon and concluded that an animal's ability to tolerate higher chronic doses in food at levels 25 times the one-dose LD_{50} *indicates the ability of the body, and especially the liver, to detoxify these materials provided there is time in which to accomplish this task.*

Although a child might also be exposed by soil/skin contact and by inhalation of airborne dust from soil, the magnitude of the soil ingestion exposure far outweighs those other exposures. Therefore, for this acute exposure scenario, only the soil ingestion exposure event is quantified, and a soil concentration which corresponds to the no effect dose is derived.

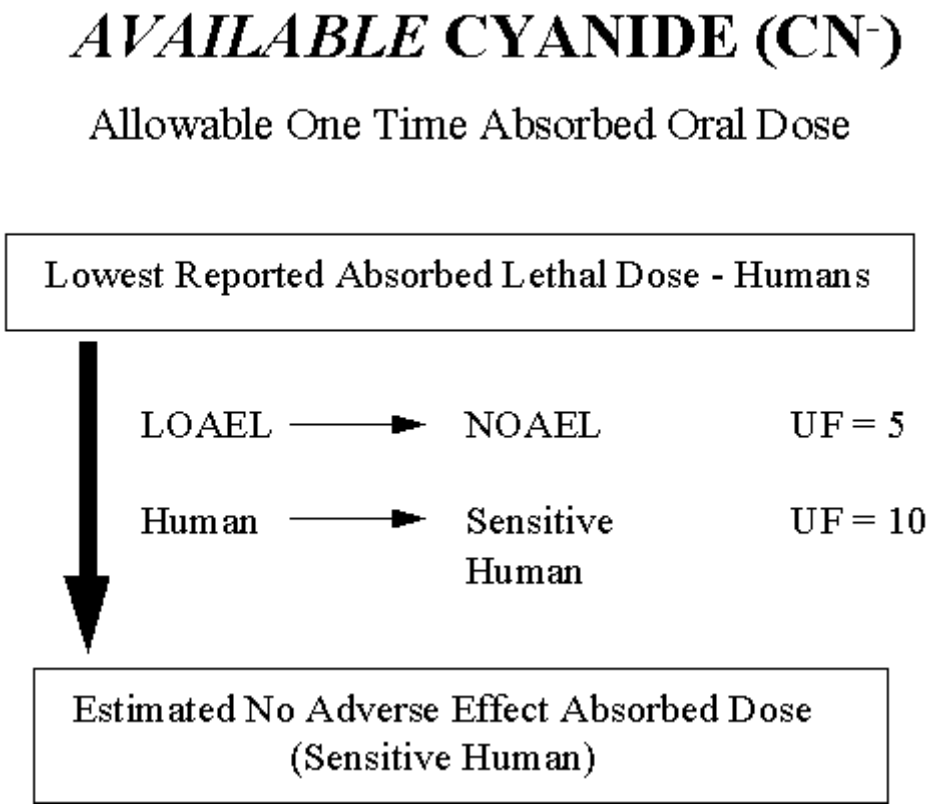
The soil concentration associated with the allowable one-time absorbed dose is the benchmark soil concentration for *available* cyanide. The benchmark soil concentration for *available* cyanide is 100 mg/kg.

A detailed presentation of the estimation of a "safe" one-time dose and the corresponding soil concentration of *available* cyanide follows.

II. DERIVATION OF BENCHMARK SOIL CONCENTRATION FOR *AVAILABLE CYANIDE*

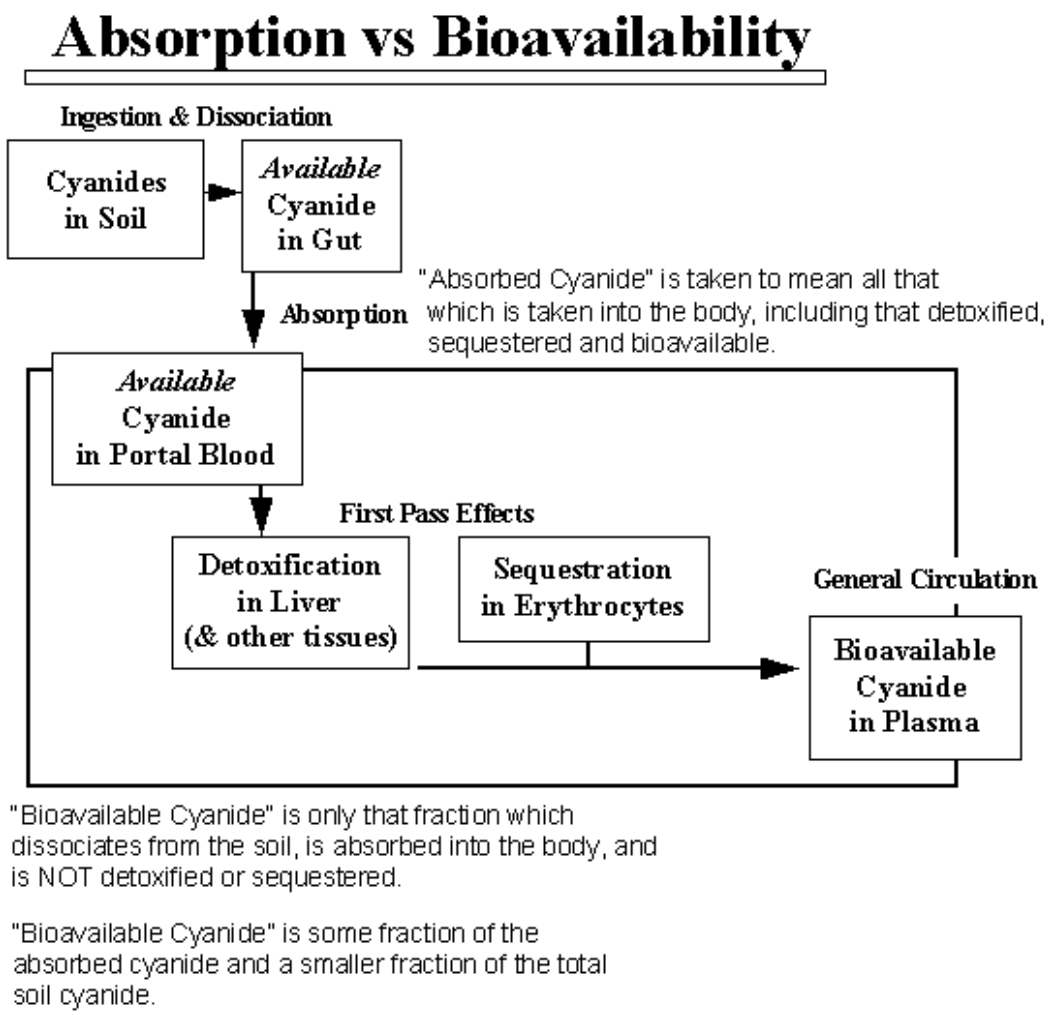
A two step process was used to derive the benchmark soil concentration. In the *first step* (FIGURE 1.), the allowable one-time absorbed dose (AOTAD) of cyanide for humans was derived by applying uncertainty factors to the lowest one-time absorbed dose observed to cause an adverse effect in humans. The lowest one-time absorbed dose which has been observed to cause an adverse effect in humans is called the lowest observed adverse effect level (LOAEL). In this case, the LOAEL happens to be the lowest reported absorbed lethal dose.

Figure 1.



Note that a distinction is made between an "applied" (or "administered") dose and the absorbed dose (FIGURE 2.). Absorption is defined (Klassen, 1986) as the process by which toxicants cross body membranes and enter the bloodstream. For oral intakes, the amount of a substance which is actually absorbed in the gastrointestinal tract is some fraction (ranging from 0 to 100%) of the amount which is initially swallowed, eaten, applied or administered.

Figure 2.



Factors which potentially alter absorption (either positively or negatively) include the presence of other substances in the gastrointestinal tract, starvation and age. Once absorption occurs in the gastrointestinal tract, the substance can be biotransformed by the gastrointestinal cells, extracted by the liver and excreted into bile, biotransformed by the liver or biotransformed by the lung. The phenomenon of removing chemicals after oral absorption before entering the general circulation is referred to as presystemic elimination, or *first-pass effect*. Thus, the "bioavailable" dose is dependent upon the administered amount of the substance, the percentage absorbed and the percentage prevented from reaching general circulation. Though they are often used interchangeably, the terms "absorption" and "bioavailability" are not equivalent.

In the *second step*, the allowable one-time absorbed dose for *available* cyanide is used in conjunction with the reasonable worst case one-time exposure scenario to derive the benchmark soil concentration for *available* cyanide. This methodology is shown in FIGURE 3.

Figure 3.

AVAILABLE CYANIDE BENCHMARK SOIL CONCENTRATION

Acute Exposure Scenario - Accessible Soils

$$[\text{AV-CN}]_{\text{Soil}} = \frac{0.01\,\text{mg/kg} \times 10\,\text{kg} \times 10^3\,\text{g/kg}}{1\,\text{g} \times 1}$$

Where:

[AV-CN]	=	Available Cyanide Concentration in Soil
0.01 mg/kg	=	Allowable One-Time Absorbed Oral Dose
10 kg	=	Bodyweight of Child
10^3 g/kg	=	Units Conversion Factor
1 gram	=	Mass of Soil Ingested
1	=	Absorption Efficiency of 100%

[AV-CN] = 100 mg/kg

a. CYANIDE BACKGROUND INFORMATION

The estimation of the allowable one-time absorbed human dose (AOTAD) is based upon a DEP review of the available hazard identification and dose-response information for cyanides. A brief summary of this information follows.

SUMMARY - HAZARD IDENTIFICATION AND DOSE RESPONSE FOR CYANIDES.

Forms of Cyanides (reproduced from Marrs & Ballantyne in Ballantyne and Marrs, 1987)

Cyanides may be divided into five general categories:

Free Cyanide: can be used to describe toxicologically available cyanide, and refers to the summation of molecular HCN and cyanide anion (CN-) (usually in aqueous media) irrespective of their origin.

Simple Cyanide: is a compound that dissociates directly into the cyanide ion (CN-) and a cation (e.g. H+, Na+, K+, Ca++) with no intermediates. Examples include NaCN, KCN, Ca(CN)2.

Complex Cyanide: is a compound in which the cyanide anion is incorporated into a molecular inorganic or organic complex or complexes. Examples include ferric ferrocyanides.

Nitrile: is an organic compound containing the cyanide group. Examples include acrylonitrile and toluene diisocyanate

Cyanogen: is a nitrile which can liberate free cyanide under appropriate chemical or physiological conditions, and hence is capable of causing signs and symptoms characteristic of acute cyanide poisoning. Examples include cyanogenic glycosides in food (cassava, bitter almonds, lima beans) and in laetrile (an anti-cancer agent).

The term *available* cyanide, as used in this document, could theoretically include cyanides from each of the five categories described above.

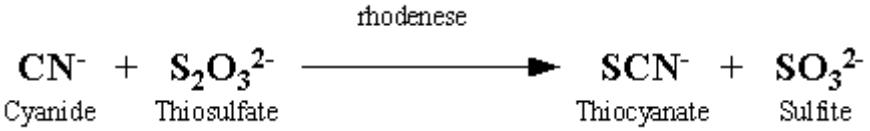
b. Acute cyanide poisoning

Health Endpoints: Adverse health effects associated with human exposure events of cyanides, particularly HCN, are well documented (Ballantyne and Marrs, 1987). Effects reported include: "anxiety and excitement; rapid breathing; faintness; weakness; headache (pulsating); constricting sensations in the chest; facial flushing; dyspnoea; drowsiness; confusion; convulsions; incontinence of urine and feces; coma; respiratory irregularities." and death (Ballantyne and Marrs, 1987). Neurotoxicity has also been observed in cyanide exposed humans. Acute human cyanide poisoning has been observed via ingestion, inhalation and dermal exposures.

Mechanism of Action: Cyanide acts primarily by inhibiting the cytochrome c oxidase enzyme in the mitochondria. When this enzyme is inhibited, oxygen can no longer be utilized by the cells, resulting in *histotoxic hypoxia*, similar to that seen with hydrogen sulfide poisoning (Klassen, 1986). Simply stated by Gossel and Bricker (1984), cyanide has the same physiological effect as a complete lack of oxygen. Synergistic effects may occur if cyanide exposure is accompanied by exposure to other substances known to inhibit cytochrome oxidase, such as sulfide and azide (U.S. EPA, 1988).

Absorption: Cyanides are rapidly absorbed in the human lung. It has been reported that somewhat less than 100% of the inhaled HCN is retained in the lung (Landahl and Herrmann, 1950). Suicide by ingestion of cyanide salts provides evidence that cyanides are absorbed in the gastrointestinal tract, with estimates as high as 82% (Gettler & Baine, 1938). Acute cyanide poisoning in humans exposed to cyanide solutions dermally have been reported (Potter, 1950).

Detoxification: Cyanides are rapidly metabolized upon human exposure. An important detoxification pathway converts the cyanide to thiocyanate, catalyzed by the mitochondrial enzyme rhodenese. (Klassen, 1986)



As described by the U.S. EPA (1978), this enzymatic reaction occurs *in vivo* since sulfurtransferase (rhodenese) is widely distributed in the tissues. This reaction is very rapid, but is incapable of handling massive doses of cyanide primarily due to substrate limitation of the sulfur donors.

The degree to which an exposure will result in toxicity depends in large part on the relationship between the absorption rate and the rate of detoxification. Gossel and Bricker (1984) note that when this built-in detoxification system becomes saturated, death may result unless some specific antidotal measures are taken.

c. Acute Cyanide Poisoning - Dose-Response Information

Although there is a considerable body of information on the toxicity of cyanides to animals and humans, there is surprisingly little documentation of the sublethal doses (single events) to which humans have been exposed. The most commonly cited dose-response information in humans comes from Gettler and Baine (1938). Based on analysis of tissues of four suicide victims, the average absorbed oral lethal dose was 1.7 mg/kg (as HCN). The lowest reported absorbed lethal dose in the literature, 0.5 mg/kg, also comes from the Gettler and Baine study.

There are very few well-documented cases which report administered or absorbed doses which were non-lethal or which produced no effects in humans. Ballantyne and Marrs (1987) cite a report by Barcroft (1931) which indicates a "man survived, apparently without symptoms, a 1.5 min exposure to" an air concentration of HCN in the range of 550-677 mg/m^3. Ballantyne and Marrs (1987) also cite a report by Bonsall (1984) in which a human male survived a 3 minute exposure to an estimated 500 ppm HCN in air (roughly 550 mg/m^3 HCN). The exposed individual survived, but only after intensive medical treatment over a 72 hour period. This suggests the exposure would have been lethal without medical intervention.

Moore and Gates (1946), as cited by Ballantyne and Marrs (1987), estimated the median absorbed lethal HCN inhalation dose for humans to be 1.1 mg/kg by assuming humans are as susceptible to HCN as dogs, cats, monkeys, rabbits, guinea pigs, rats and mice. Intravenous LD_{50}'s were reported for the animal species previously mentioned, with values ranging from 0.66 mg/kg to 1.43 mg/kg.

The American Conference of Governmental Industrial Hygienists' (ACGIH) Documentation of the Threshold Limit Values and Biological Exposure Indices, Fifth Edition reported that 0.05 mg/l (50 mg/m^3) of HCN in air was "tolerated for 0.5 - 1.0 hour without immediate or late effects." ACGIH cited Flury and Zernik (1931a) as the source of that information. The U.S. EPA Region I office has provided the Department with notes translated from the original German article (Flury and Zernik, 1931b) which indicate that this exposure is, in fact, associated with adverse health effects, and thus should not be considered as a NOAEL. The National Institute for Occupational Safety and Health considers this concentration to be the Immediately Dangerous to Life or Health (IDLH) level, not a NOAEL (NIOSH, 1985).

Given the uncertainty in the data from Moore and Gates, Flury and Zernik, and Barcroft, the lowest reported absorbed lethal dose (0.54 mg/kg) reported by Gettler and Baine is here

identified as the lowest observed adverse effect level (LOAEL) in humans for a single exposure event. No reliable, well documented no-observed adverse effect level (NOAEL) in humans for a single exposure event has been identified in the literature.

The U.S. EPA has not published an allowable one-time dose for hydrogen cyanide. The U.S. EPA has published an oral Reference Dose (RfD), which is a daily dose to which sensitive humans could be exposed on a chronic basis with no adverse effects. The Reference Dose value is 0.02 mg/kg/day (U.S. EPA, 1989d).

This Reference Dose was derived by extrapolating results from chronic dietary exposures of HCN in rats. The hydrogen cyanide fumigated food was made available to the rats in a feeding jar (Howard and Hanzel, 1955). Presumably the daily dose estimated by the researchers was delivered in small amounts over the course of the day rather than in a single dose.

One conclusion which may be reached from this is that the *chronic* oral Reference Dose may not be adequately protective for *acute* exposures, due to the rapid detoxification of cyanide. While this may seem counter-intuitive, the dietary study which is the basis of the RfD is not analogous to the acute exposure scenario about which we are concerned. This phenomenon is clearly demonstrated in a study (Hayes, 1967) where rats tolerated doses 25 times the acute dose LD50 when the cyanide was mixed with their regular food. Hayes noted that this result "*undoubtedly indicates the ability of the body, and especially the liver, to detoxify these materials provided there is time in which to accomplish the task.*"

A Modifying Factor (MF) equal to 5 was applied in the development of the Reference Dose "*to account for the apparent tolerance to cyanide when it is ingested with food rather than when it is administered by gavage or drinking water*". Telephone conversations with members of the U.S. EPA Cyanide ADI Verification workgroup (James Murphy, Christopher DeRosa and Michael Dourson) and Edward O'Hanian of the U.S. EPA Office of Drinking Water revealed that there was much controversy over the choice of this modifying factor and its applicability to cyanide.

The Reference Dose (then an Allowable Daily Intake, or ADI) was originally developed for The *Drinking Water Criteria Document for Cyanide* (U.S. EPA, 1988) which notes that "*It is inappropriate to use a net absorption coefficient to account for presumed differences in the absorption of CN- in food vs. water*". The modifying factor of 5 was used in recognition of the measure of uncertainty which is generally associated with the use of a dietary study to estimate a drinking water criterion. Edward O'Hanian indicated that the value of 5 originated in work conducted for the metal cadmium, and was not meant to be specific to cyanides. The uncertainty of the ADI Verification workgroup is expressed in the written hope (U.S. EPA, 1985a) that the Agency fund a study to test for the possible differences in absorption of cyanide between food and water.

2. REGULATORY STANDARDS, GUIDELINES AND ADVISORIES FOR HUMAN CYANIDE EXPOSURES

The following standards, guidelines and advisories, reported by the Agency for Toxic Substances and Disease Registry (ATSDR, 1989) and the National Institute for Occupational Safety and Health (NIOSH, 1987) can provide some perspective for this situation involving cyanide in soil.

a. Food Related Exposures
Interim acceptable daily intake for 70 kg adult in food set by the World Health Organization is 3.5 mg/person/day (0.05 mg/kg bodyweight/day).

Tolerances for hydrogen cyanide in foods when used as a postharvest fumigant set by U.S. EPA range from 25 ppm in dried beans, peas and nuts to 250 ppm in spices. In this case 1 ppm = 1 mg HCN/1kg food.

b. Drinking Water Related Exposures
Drinking water standard for cyanides set by the World Health Organization (1977) is 0.05 mg/liter.

Drinking water health advisory for a 10 kg Child for HCN, NaCN and KCN (1-day, 10-day and longer term exposures) set by the U.S. EPA is 0.2 mg/liter (U.S. EPA Drinking Water Regulations and Health Advisories, 1989).

Drinking water health advisory for a 70 kg Adult for HCN, NaCN, and KCN set by the U.S. EPA is 0.8 mg/liter (longerterm exposure) and 0.2 mg/liter (lifetime exposure) (U.S. EPA Drinking Water Regulations and Health Advisories, 1989).

Drinking water concentration not to be exceeded as stated by the U.S. Public Health Service (1962) is 0.2 mg/liter.

c. Workplace Related Exposure
(from: NIOSH, 1985, second printing)
Permissible Exposure Limit (PEL) in air for HCN published by OSHA is 10 ppm (11 mg/m^3).

Ten-minute ceiling limit in air for HCN published by the National Institute for Occupational Safety and Health (NIOSH) is 4.7 ppm (5 mg/m^3).

Ceiling Threshold Limit Value (TLV) for HCN in air published by the American Conference of Governmental Industrial Hygienists (ACGIH) is 10 ppm (10 mg/m^3).

The Immediately Dangerous to Life or Health (IDLH) Level for HCN published by NIOSH is 50 ppm (55 mg/m^3). This level is defined for the purpose of respirator selection. It represents a maximum concentration from which, in the event of a respirator failure, one could escape within 30 minutes without experiencing any "escape-impairing or irreversible health effects."

B. ESTIMATION OF ALLOWABLE ONE-TIME ABSORBED DOSE (AOTAD) FOR AVAILABLE CYANIDE
The allowable one-time absorbed dose for a sensitive human is estimated as summarized in Section I.B. Essentially, two uncertainty factors were applied to the lowest reported absorbed lethal dose of cyanide [which we have designated as the lowest observed adverse effect level (LOAEL)] to estimate a dose which would not be associated with any adverse health effects. Use of such a "safe" dose is consistent with current regulatory practice, which focuses on no-effect levels rather levels at which adverse effects would be expected.

Uncertainty factors are commonly used in regulatory health risk assessment and in the development of public health standards and guidelines for air, water, soil and food. These uncertainty factors are used in a systematic fashion to adjust existing data to account for

uncertainty in the ability of the data to describe the "safe" dose for a sensitive human. In this case, the population of concern consists of those individuals who are most sensitive to cyanide compared to the typical individual. By applying these uncertainty factors, the regulatory agency makes it less likely that toxicity to sensitive individuals is underestimated. The two uncertainty factors used in this analysis are described below.

1. UF1

The first Uncertainty Factor (UF1) is used to account for individuals more sensitive to cyanide than the individuals for whom lethal doses are available. The traditional value of 10 was used in this analysis. In other words, it is estimated that the most sensitive human may be ten times more sensitive to cyanide than the suicide victims reported by Gettler and Baine (1938). A discussion of this uncertainty factor and documentation for the traditional value of 10 is presented by Dourson and Stara (1983).

There is also information specific to cyanide which supports the need for this uncertainty factor and the value of 10 which was employed. No lethal dose information was located for children: an obvious, important sub-population which is of great concern. In addition, the U.S. EPA (1981) reports that there are certain medical problems which may make some individuals more susceptible to cyanide poisoning. Individuals with metabolic defects in the rhodanese system (the system which mediates transformation of cyanide to thiocyanate) would be very sensitive. Vitamin B_{12} deficiencies or defective vitamin B12 metabolism may also make individuals more susceptible to cyanides. As noted previously, exposure to sulfides or azides may result in synergistic effects (U.S. EPA, 1988) which could render an individual more susceptible to cyanides. The low number of cyanide cases for whom information has been reported in the literature is not considered to be sufficient to accept a lower value for this uncertainty factor.

2. UF2

The second Uncertainty Factor (UF2) is used to estimate the "safe" dose (no adverse effect level, or NOAEL) from a documented lowest observed adverse effect level (LOAEL). When there is a clearly documented NOAEL, this uncertainty factor is unnecessary.

As was discussed previously, no clearly documented NOAEL is available for acute exposures. In this document, the UF2 is used to estimate a one-time absorbed dose of *available* cyanide which would result in no adverse health effects by applying it to the lowest reported absorbed lethal dose for cyanide. A numerical value ranging from one to ten is traditionally assigned to this factor. We assign a value of **5** to this uncertainty factor. The limited information which is available indicates that the human ***N***o ***O***bserved ***A***dverse ***E***ffect ***L***evel (NOAEL) is likely to be roughly 5 times lower than the lowest reported absorbed lethal dose. The supporting information for this numerical value of 5 is presented in Appendix A.

3. CALCULATION OF ALLOWABLE ONE-TIME ABSORBED DOSE (AOTAD)

The "allowable one-time absorbed dose of cyanide" (AOTAD) which is protective against all adverse effects for the sensitive human is calculated as follows:

AOTAD = LOAEL/UF1 * UF_2

Where:

AOTAD = Allowable one-time dose
LOAEL = **0.54 mg/kg**, Lowest observable adverse effect level (Gettler and Baine, 1938)
UF1 = **10**, Uncertainty Factor to account for the variability in the sensitivity to HCN in humans
UF2 = **5**, Uncertainty Factor to extrapolate from the LOAEL to the NOAEL.

THUS:

AOTAD = 0.54 mg/kg / (10 * 5)

AOTAD = 0.0108 mg/kg, or 0.01 mg/kg

An allowable one-time absorbed dose of *available* cyanide equal to 0.01 mg/kg is used in the next section of this analysis to derive a benchmark soil concentration which represents a no-effect level for a reasonable worst-case child exposure scenario.

C. DERIVATION OF BENCHMARK SOIL CONCENTRATION FOR *available* CYANIDE

The benchmark soil concentration of *available* cyanide is derived as summarized in Section I.B. A reasonable worst-case exposure scenario for an acute exposure event is identified as a child who ingests 1 gram of soil in a single event. Using this exposure scenario, it is possible to estimate the *available* cyanide soil concentration which would yield the allowable one-time absorbed dose (0.01 mg/kg). This *available* cyanide soil concentration is the benchmark concentration which will be used to evaluate the need for immediate action at a disposal site.

Exposures from dermal contact with soil and inhalation of soil-derived particulates are not quantified here because these exposures, *for a short duration event*, are much smaller than the soil ingestion exposure. Such exposures are potentially of concern in the evaluation of chronic exposure scenarios.

Using the MA DEP's *Guidance for Disposal Site Risk Characterization and Related Phase II Activities - In Support of the Massachusetts Contingency Plan*, (1989), the AOTAD and exposure assumptions can be substituted into a generalized dose equation for soil ingestion. This equation is then solved for the remaining unknown quantity in the equation: the benchmark soil concentration.

The following sections describe further the exposure scenario, the exposure assumptions and the calculations for the derivation of the benchmark soil concentration.

1. EXPOSURE SCENARIO

Exposure assumptions consistent with a *maximally exposed receptor* have been selected for the unrestricted access scenario which is the basis for the derivation of the benchmark soil concentration. Such assumptions are considered appropriate due to the potentially lethal effects of the contaminant of concern and the accessibility to the contaminated soil assumed in the scenario.

Under this scenario, a 2 year old child has access to the surficial soil under investigation. Examples of such accessible soils would include playgrounds, park lands and residential yards. During the course of play activities, the child comes into contact with the contaminated soil and ingests a quantity. The ingested soil weighs 1 gram.

2. EXPOSURE ASSUMPTIONS

Soil ingestion is the sole significant route of exposure for a short duration event (a few minutes) involving cyanide in soil. The magnitude of dermal contact and inhalation of dust exposures are at least an order of magnitude lower than the soil ingestion exposure.

The receptor of concern is a 2-year old child who has access to contaminated surface soil. The child exhibits "normal" pica behavior, or the normal ingestion of nonfood objects which is common in children.

The soil ingestion event involves the ingestion of 1 gram of soil. This value is an approximation of what a child who experiences normal tendencies to ingest nonfood items may ingest on a day when the child ingests an amount greater than their "average" amount. As a child would ingest an amount greater than average on roughly 50% of the days exposed, a protective approach for the maximally exposed individual would estimate some upper level of soil intake.

The 2-year old child weighs 10 kg. This value is an approximation of the lower 5th percentile for the body weight of female children (U.S. EPA, 1989). The choice of this body weight is consistent with the U.S. EPA evaluations of childhood exposures and is considered to be protective considering the range of weights in the population.

An absorption efficiency of 100% from ingested soil is used in this analysis. This value is based upon information indicating that the percentage of an applied dose of *available* cyanide which is absorbed depends **directly** on the time allowed for absorption to take place and **inversely** on the quantity ingested (Gettler and Baine, 1938). A report for the U.S. EPA by Oak Ridge National Labs (U.S. EPA, 1978) notes that *the percentage of a given dose absorbed is a factor of dose size and absorption rate: death may intervene before absorption is complete*. While stomach contents and the release rate of the cyanide ion may affect the ***rate*** of absorption the ***percent*** may still approach 100% unless death occurs.

A Bioavailability Adjustment Factor (MA DEP, 1989) or Relative Absorption Factor (U.S. EPA, 1989e) is not required in this analysis. The AOTAD is based upon an absorbed oral dose of *available* cyanide and this scenario is concerned with the identical route of exposure for *available* cyanide.

3. ESTIMATION OF THE BENCHMARK CONCENTRATION

The general equations given in the DEP Guidance Document (1989) are used to estimate an unknown receptor dose given a known concentration of a compound and a set of exposure assumptions. In this exercise, the reverse is true: the allowable one-time absorbed dose (AOTAD) is known, and the benchmark *available* cyanide soil concentration is unknown. The general equations may thus be solved for the unknown soil concentration ([HCN]).

By setting the allowable one-time absorbed dose (AOTAD) equal to the "one-time dose" (OTD) associated with the reasonable worst-case exposure event, and substituting the exposure assumptions into the general equation, we can solve for [HCN] which is the benchmark soil concentration. The one-time soil ingestion exposure should not result in a dose to the receptor greater than the allowable one-time absorbed dose.

THUS:

$$\mathbf{AOTAD = OTD_{soi}}$$

Where:

AOTAD = **0.01 mg/kg** = Allowable one-time absorbed dose
OTD_{soi} = One-time absorbed dose associated with the worst case exposure event

The generalized equation for calculating one-time soil ingestion dose is:

$$\mathbf{OTD_{soi} = ([AV\text{-}CN] * I * BAF * F * D1 * D2 * C) / (BW * AP)}$$

Where:

OTDsoi = The one time dose for the ingestion of soil based upon the exposure scenario (mg/kg)
[AV-CN] = The soil concentration of *available* cyanide (mg/kg)
BAF = **1** = Bioavailability Adjustment Factor, set equal to the percent absorption
I = **1 gram** = Soil intake in grams
F = **na*** = Frequency (events/time)
D1 = **na*** = Average duration of each event (time/event)
D2 = **na*** = Duration of exposure period (time)
C = **1 kg/10^3 g** = Units conversion factor
BW = **10 kg** = Bodyweight of hypothetical child (kg)
AP = **na*** = Averaging period (time)

na* - *not applicable*: Since the calculated dose is for a single event, duration, frequency and averaging period are irrelevant.

Substituting appropriate values,

$$\mathbf{0.01\ mg/kg = (\ [AV\text{-}CN](1\ gram)(1)(1\ kg/10^3\ g))\ /\ (10\ kg)}$$

and solving for [AV-CN],

$$\mathbf{[AV\text{-}CN] = ((0.01\ mg/kg)(10\ kg))/\ ((1\ gram)(1)(1\ kg/103\ g))}$$

and,

$$\mathbf{[AV\text{-}CN] = 100\ mg/kg.}$$

The benchmark soil concentration of AV-CN is 100 mg/kg.

III. DISCUSSION OF UNCERTAINTY

There are a number of areas in which there may be considerable uncertainty which affect the outcome of this assessment. These areas are discussed below.

A. DEVELOPMENT OF AN ALLOWABLE ONE-TIME DOSE

1. Since no well documented human no-observed effect level (NOAEL) for *available* cyanide was available, a human NOAEL was estimated from the lowest reported absorbed lethal dose. An uncertainty factor of 5 was utilized in this process. "Apparent" human NOAELs (from those studies which suggest that no adverse effects were observed) were used to support this value. Appendix A describes how this uncertainty factor was derived.

2. The allowable one-time dose was derived for a sensitive human, utilizing an uncertainty factor of 10. A value of 10 has traditionally been used, but other values are used when there is specific information available about the sensitivity of the human population to a particular substance. The traditional value appears to be appropriate, although 10 is not always a "cautious" value for this uncertainty factor (Dourson and Stara, 1983).

3. It has been argued that the lowest reported lethal dose defines the lower end of the range of human susceptibility. However, as indicated previously, information concerning toxicity to children is lacking and certain medical conditions may make certain individuals more susceptible.

B. DERIVATION OF BENCHMARK SOIL CONCENTRATION

1. The identification of 1 gram of soil as a single *one-time* ingestion event for a maximally exposed individual is based on literature estimates for average soil intakes by children with an "intermediate tendency" (to ingest soil (U.S. EPA, 1989) and on an informal survey of parents.

The trace metal studies to date (Binder, 1986; Clausing, 1987; Calabrese, 1989) have reported average daily soil intake estimates over periods of up to two weeks. The upper-range estimate of 0.8 grams (U.S. EPA, 1989) is an estimate of average soil intake during a period of high exposure, which is not the same as a one-time realistic worst-case soil ingestion estimate. A soil ingestion rate of 1 gram per day is also presented (U.S. EPA, 1989) for a child

with an intermediate tendency to ingest soil. Additional technical information could reduce the large amount of uncertainty in this value.

2. available cyanide was assumed to be 100% absorbed in the gastrointestinal tract after ingestion in a soil matrix based upon evidence that cyanide absorption depends upon both time and the applied dose. In the one study which attempted to estimate *absorbed* doses, percent absorption ranged as high as 82%. A higher percent absorption could be attained as absorption would continue until the death of the victim.

Although the U.S.EPA (IRIS, 1989) assumed HCN was 5 times more available in drinking water than in food (suggesting that absorption from food is substantially less than 100%), no documentation was found to support that assumption and no information was found concerning absorption efficiency after ingestion of contaminated soil. Scientists of the U.S. EPA Environmental Criteria and Assessment Office (U.S. EPA, 1985a) have noted this lack of data in a call for more research on this topic.

3. There has been considerable discussion concerning the theoretical receptor who is being protected. The general philosophy for evaluating the need for immediate action to protect public health is to consider a reasonable worst-case exposure scenario.

This document defines that scenario as the maximum likely one-time exposure which the maximally exposed individual could experience. This document considers the maximally exposed individual to be a child who might ingest contaminated soil at least once. It is assumed this child could ingest 1 gram of soil in one event of short duration. The exposure point concentration of *available* cyanide is assumed to be the maximum reported concentration of *available* cyanide reported in accessible soil at a given disposal site.

There is considerable uncertainty about the prevalence of pica in the general population, and even more uncertainty about the rate of soil ingestion among children. It is also uncertain whether the maximum one-time soil intake would actually differ between "normal" pica and "habitual" pica children. "Normal" pica should not be confused with "habitual" or "severe" pica which is considered a pathological condition, and is not considered in the exposure assumptions.

The prevalence of "normal" pica behavior is reported (Barltrop, 1966; Milligan, 1962) in the range of 15-20% for children aged 1 to 6 years, with the younger children experiencing a higher incidence, perhaps up to 60% in some populations (U.S. EPA, 1989). A distinction is made in these studies between simple mouthing of objects (reported in approximately 80% of the children aged 1 - 2 years) and the ingestion of nonfood material.

4. There is also uncertainty surrounding the analytical methods which might be used to measure *available* cyanide in soil.

U.S. EPA Methods 9010 and 9012, Total and Amenable Cyanide (U.S. EPA, 1986), are used to determine the concentration of inorganic cyanide in an *aqueous waste* or *leachate*. These methods detect inorganic cyanides that are present either as simple soluble salts or in complexed forms. They are used to determine values for both total cyanide and cyanide amenable to chlorination. Each of these methods for analyzing *aqueous waste and leachate* has been used to quantify cyanides in *soil* at Ch. 21E disposal sites. Sulfides interfere with these procedures, making it necessary to pretreat samples containing hydrogen sulfide, metal

sulfides or other compounds that might produce sulfides. Since these methods are for aqueous *waste and leachate*, a standardized method for sampling soil, sample preservation, and sample pretreatment for these methods is necessary.

Methods 412F, Cyanides Amenable to Chlorination after Distillation, and 412G, Cyanides Amenable to Chlorination without Distillation (Short-Cut Method) from *Standard Methods For the Examination of Water and Wastewater, Sixteenth Edition* (hereafter called *Standard Methods* (1985)) have also been used to measure *available* cyanide in soil. Sulfides also interfere with these methods and effluents of coal gasification wastes require stabilization with hydrated lime prior to distillation (*Standard Methods* (1985)).

Method 412H, Weak and Dissociable Cyanide from *Standard Methods* (1985) has also been used to measure *available* cyanide in soil for health risk assessment purposes, although this method can not account for any bound cyanides which may become *available* under either the physiological conditions of the human digestive system or varied environmental conditions.

Historically, "amenable cyanide" analyses of soil samples have been problematic. The results have been difficult to reproduce, and results have often been negative numbers (reported as no amenable cyanides detected). Dr. John Delaney of DEP's Lawrence Experiment Station has indicated that the alkaline treatment of a sample prior to chlorination may actually destabilize some complexed cyanides, making them measurable upon subsequent acidification. These same complexed cyanides would not have been detected in the Total Cyanide analysis, which does not involve alkaline treatment prior to acidification. Thus the U.S. EPA "Total" Cyanide analysis does not necessarily measure *all* the cyanide which may be present in the sample, but some fraction of that total.

If the process Dr. Delaney refers to does actually occur, amenable cyanide concentrations would be underestimated by the "amenable cyanide" analysis.

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APPENDIX A

LOAEL TO NOAEL EXTRAPOLATION

As discussed in Section I. B., a human no adverse effect level for a short-term or instantaneous oral exposure to *available* cyanide was estimated by applying an uncertainty factor of 5 to the lowest observed adverse effect level (LOAEL) in humans. In this case the LOAEL is the lowest reported absorbed lethal dose in humans, 0.54 mg/kg (Gettler and Baine, 1938). The following discussion supports the selection of 5 as the uncertainty factor for this extrapolation.

There were no well-documented human no observed adverse effect levels (NOAEL) in the literature. There are, however, a few reported incidents for which exposure concentrations and duration of exposure have been estimated which are useful in estimating the relationship between the human LOAEL and the human NOAEL. Three studies cited previously, Barcroft (1931), Flury and Zernik (1931), and Bonsall (1984) provide some limited information about the magnitude of a human NOAEL. Table A-1 summarizes those three cyanide exposure incidents.

TABLE A-1 - SUMMARY OF NON FATAL HCN EXPOSURES *

Author	HCN Air Conc.	Exposure Duration (minutes)	Observed Effects
Barcroft (1931)	550-677 mg/m^3	1.5	apparently without symptoms
Flury & Zernik (1931)	0.05 mg/liter	30-60	tolerated without immediate or late effects
Bonsall (1984)	500 ppm (550 mg/m^3)	3	survived only because of intense medical intervention

*** These results are <u>estimated</u> exposures.**

It is possible to estimate absorbed intakes and doses for these three incidents. The absorbed intakes are estimated by the following expression:

$$\mathbf{AI = [HCN] * VR * D * AE * C}$$

Where:

AI = Absorbed intake of HCN (mg)
[HCN] = Concentration of HCN in air (mg/m^3)
VR = **1 m^3/hr** = Ventilation rate (m^3/hr)
D = Duration of exposure (min)
AE = **70%** = Inhalation absorption efficiency (ATSDR, 1989)
C = **1 hr/60 min** = Units conversion factor

Once absorbed intakes are calculated, absorbed doses and absorbed dose rates are obtained by dividing the intakes by the adult bodyweight and the product of adult bodyweight and duration of exposure respectively. The resulting intakes, doses, and dose rates are presented in Table A-2.

TABLE A-2
SUMMARY OF INTAKES, DOSES AND DOSE RATES - NON-FATAL EXPOSURE INCIDENTS*

Author	Total Absorbed Intake (mg)	Total Absorbed Dose (mg/kg)	Total Absorbed Dose Rate (mg/kg/min)
Barcroft (1931)	9.6 - 11.9	0.1 - 0.2	0.1 - 0.1
Flury & Zernik (1931)	17.5 - 35	0.25 - 0.5	0.004 - 0.02
Bonsall (1984)	19.3	0.3**	0.1

* These values are obtained from estimated exposures.
** Fatality prevented by immediate medical intervention.

In Table A-2, the dose from the Barcroft study, 0.1-0.2 mg/kg, appears to roughly estimate an instantaneous non-lethal, no-effect level. However, since the concentrations and duration of exposure are estimated, this dose cannot be considered a veritable NOAEL.

The Flury & Zernik report states that the 0.25 mg/kg exposure over a period of 30-60 minutes was tolerated without immediate or late effects. This total dose was received over a period of time rather than instantaneously. This dose , therefore, should not be considered an instantaneous non-lethal dose. The dose received in ten minutes by the person in that study (0.08-0.2 mg/kg) is probably a better estimate of an instantaneous no effect level.

The dose estimated for the incident reported by Bonsall should be considered an approximate instantaneous lethal dose. The person exposed was unconscious for approximately 48 hours and experienced convulsions despite immediate and prolonged medical intervention.

A rough estimate of an instantaneous human NOAEL can be made from the doses above. The NOAEL would have to be lower than 0.3 mg/kg (a potentially lethal dose) and in the range of the instantaneous doses from Barcroft and Flury & Zernik (0.1-0.2 mg/kg). If a cautious approach is taken, the NOAEL can be approximated by 0.1 mg/kg. An uncertainty factor which describes the relationship between the LOAEL (0.54 mg/kg) and the estimated NOAEL (0.1 mg/kg) would then be roughly 0.54/0.1 or 5. An uncertainty factor of 5 appears to be cautious and appropriate.