Comments on the "Proposed Modifications to Identified Acute Toxicity-Based Soil Cleanup Target Levels (SCTLs)"

[Prepared by Hazardous Substance & Waste Management Research, Inc., on behalf of the Florida Electric Power Coordinating Group]

Chris Saranko

Kristen Jordan

J. Keith Tolson

Stephen M. Roberts

Center for Environmental & Human Toxicology

University of Florida

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Introduction

In December, 1999, Hazardous Substance & Waste Management Research (HSWMR) prepared and distributed to the Methodology Focus Group of the Contaminated Soils Forum a document entitled *Proposed Modifications to Identified Acute Toxicity-Based Soil Cleanup Target Levels (SCTLs)*. This document discusses the derivation of SCTLs based on acute toxicity in Chapter 62-777, F.A.C., and proposes alternative acute toxicity-based SCTLs for six chemicals — barium, copper, cyanide, fluoride, nickel, and vanadium. At the request of the Florida Department of Environmental Protection (FDEP), we have reviewed the proposed alternative SCTLs and their bases, and in the process re-examined the literature regarding acute toxicity of these chemicals. The purpose of this document is to provide comments on the rationale for the proposed alternative SCTLs and to articulate our concerns with some of the assumptions and values. A brief background regarding the need for acute toxicity-based SCTLs is provided, followed by discussion of general issues associated with the proposed alternative SCTLs. This document also presents a specific, chemical-by-chemical discussion of acute toxicity-based SCTLs, including the basis for the current and proposed alternative values, as well as the implications of various choices that can be made regarding toxic endpoints, use of safety factors, etc. In some instances, recommendations for specific SCTLs are made here. For other chemicals, however, alternatives are outlined, with choices to be guided by policy decisions regarding the degree of protectiveness desired. It is hoped that this information will be of value to the Methodology Focus Group, the larger Contaminated Soil Forum, and to FDEP in considering whether the current acute toxicity-based SCTLs should be modified.

Background

The acute toxicity SCTLs were originally proposed and adopted in the context of the development of SCTLs for Chapter 62-785, F.A.C. Typically, risk-based criteria for contaminants in soils are based on prevention of chronic health effects, and values protective of children include an assumption of an average of 200 mg/day incidental soil

ingestion. Based on childhood soil ingestion data in the scientific literature, it was evident that children may, on occasion, ingest soil in amounts far greater than 200 mg/day. In this situation, the possibility existed that SCTLs based on chronic health effects might not provide adequate protection for some chemicals. The USEPA acknowledged this shortcoming for two of their soil screening levels (SSLs), cyanide and phenol, in the *Soil Screening Guidance: Technical Background Document* (USEPA, 1996).

Subsequent to the development of the *Soil Screening Guidance* by the USEPA, Calabrese and coworkers evaluated the potential for acute toxicity from a pica episode involving soil with contaminant concentrations equivalent to the SSLs (Calabrese et al., 1997). Calabrese and coworkers estimated doses of several contaminants expected to result from a one-time soil pica episode of 5 to 50 g of soil. Their analysis indicated that some of the USEPA residential SSLs corresponded to doses of chemicals associated with acute toxicity and even death in case reports of poisoning episodes in humans. Prompted by this information, FDEP adopted acute toxicity SCTLs for eight chemicals where acute toxicity might be a problem — barium, cadmium, copper, cyanide, fluoride, nickel, phenol, and vanadium. A soil ingestion value of 10 g per event was selected by FDEP for use in the calculation of the acute toxicity SCTLs. This value is within the range of values reported by Calabrese and other researchers studying soil ingestion by children. Based on the results of soil ingestion studies, Stanek and Calabrese (1995) developed a model to predict soil ingestion patterns in children. The results of this model indicated that "the majority (62%) of children will ingest >1g soil on 1-2 days/year, while 42% and 33% of children were estimated to ingest > 5 and > 10 g soil on 1-2 days/year, respectively." These researchers concluded that substantial soil ingestion can be expected in a significant proportion of children on a periodic basis. <u>It is emphasized that the ingestion value of 10 g of soil on a single occasion used to develop the acute toxicity SCTLs is not intended to represent extreme and exceptional behavior. Rather, based on empirical observations of soil ingestion in children, it reflects a soil ingestion event that likely occurs in a high percentage of normal children at play, albeit infrequently</u>. Much higher soil ingestion events have been observed in children, including quantities in the range of 20 to 60 g (Calabrese et al., 1997).

For many of the chemicals in question, the most sensitive effects (i.e., the adverse effects occurring at the lowest dose) were gastrointestinal (e.g., nausea, vomiting, diarrhea). In developing acute toxicity SCTLs for these chemicals, FDEP made the policy decision that some risk of developing gastrointestinal effects was acceptable as long as these effects were not severe enough to require medical attention. That is, ingestion of 10 g soil containing a contaminant at the acute toxicity SCTL might produce gastrointestinal effects, but the risk of severe gastrointestinal effects or other effects requiring medical attention was to be minimized. As a practical matter, distinguishing between doses associated with mild versus severe gastrointestinal effects is difficult for these chemicals because of the limited health effects data available. Nonetheless, this policy decision was taken into consideration when developing acute toxicity SCTLs based on this endpoint.

Brief summaries of relevant toxicological information and a discussion of the basis for the current acute toxicity SCTLs were provided in the document "Technical Report: Development of Soil Cleanup Target Levels (SCTLs) for Chapter 62-777, F.A.C." In each case, an attempt was made to identify the lower end of the dose range producing relevant health effects in humans, and this dose was reduced by some factor in order to obtain an acceptable upper limit dose from soil. Typically, this "safety factor" is based on a number of component uncertainty and modifying factors. For example, an uncertainty factor of up to 10X is typically employed so that the resulting value is protective for sensitive individuals. Another factor of up to 10X might be employed if the starting point is a dose that produces an adverse effect (as opposed to a "no-effect" dose). Another uncertainty factor of up to 10X might be incorporated when extrapolating from animal data (not relevant here since all of the toxicity data were derived in humans), and an additional modifying factor might be included if the quality of the data set is poor. Candidly, the rationale for the choice of the safety factors used in developing the acute toxicity SCTLs was not clearly articulated for many of the chemicals in the technical background document. This has led to some confusion regarding the basis for these values. In some instances, application of less than a full set of uncertainty factors resulted from willingness of FDEP to accept some risk of minor gastrointestinal effects; in others,

it was necessary to avoid the development of a safe acute dose limit below the chronic reference dose. [Note: These issues are also germane to the discussion of proposed alternative SCTLs for specific chemicals, below.]

The adoption of the acute toxicity SCTLs in Chapter 62-777, F.A.C. are properly viewed as an interim health-protection measure. It was acknowledged in the supporting technical document that the time constraints associated with the development of these numbers may not have permitted review of all of the relevant toxicological literature, citing in particular older literature not accessible through current computerized databases. Also, during adoption of Chapter 62-777, F.A.C., some parties expressed concern that they had not been given adequate opportunity to review and evaluate these numbers. FDEP agreed to re-visit after rule adoption the acute toxicity SCTLs, and the Contaminated Soil Forum became the logical vehicle to seek additional input. The modifications to the acute SCTLs and our comments here are a part of that re-appraisal process.

General Issues

HSWMR (1999) proposes modifications to six of the eight acute toxicity SCTLs. These are for barium, copper, cyanide, fluoride, nickel, and vanadium. All of the revisions in the acute toxicity SCTLs proposed by HSWMR result in a higher SCTL than the current values contained in Chapter 62-777, F.A.C., and are based on modifications to one or more of three basic factors: 1) the point of departure doses used to develop the acute toxicity values, 2) the safety factors applied to those doses; and 3) the compound-specific oral bioavailability. Issues relating to doses and safety factors are discussed in specific terms for each of the acute toxicity chemicals in the next section. However, in general terms, it is important to recognize that in some cases the usual method of identifying a no-effect level and applying a series of uncertainty factors does not apply. Specifically, for all of the chemicals but cyanide and nickel, the most sensitive effect is gastrointestinal symptoms, and these symptoms, if minor, are regarded as acceptable by

FDEP. The fundamental concept is one of a sentinel effect — a minor effect (in this case, gastrointestinal complaints) serves to warn that if greater exposure occurs, more serious health consequences may result. As such, the dose upon which the acceptable level in soil is based is derived from an effect level, rather than a no-effect level. Some application of an uncertainty factor (or "safety factor") may still be warranted, so that this effect level is applicable to sensitive individuals. However, the more typical, full set of uncertainty factors is not applied since the goal is not to prevent the effect in all individuals, but rather to limit the health consequences to that effect. We do not dispute this concept, but caution that the analysis must also consider the most sensitive effect to be avoided as well. For chemicals producing a sentinel effect, there is another more serious effect that occurs at a higher dose. In order to protect against this more serious toxicity, the dose producing this effect must be divided by a full set of uncertainty factors to produce a no-effect level applicable to the general population. If the more serious toxicity occurs at a dose not much greater than that producing the sentinel effect, the sentinel dose may not afford a sufficient margin of safety. This is suggested when the safe dose for a more serious toxicity (derived using all appropriate uncertainty factors) is less than the dose for the sentinel effect. As discussed in the subsequent section, there is evidence that this situation exists for many of the chemicals for which alternative SCTLs have been proposed.

The third basic area of difference between the SCTLs in Chapter 62-777, F.A.C. and the alternative values proposed by HSWMR is in the assumptions regarding bioavailability. Currently, the approach used by FDEP in developing the acute toxicity SCTLs (and indeed all of the SCTLs) is to assume a relative bioavailability of 1. This does not mean that the bioavailability is assumed to be complete. It indicates that the bioavailability of the chemical from soil is assumed to be equal to the bioavailability under the conditions in which the toxicity information was obtained. In the case of the acute toxicity SCTLs, which are based on human intoxication data, the assumption is therefore that absorption from soil is the same as the absorption that occurred during the poisoning event. HSWMR proposes the use of different relative bioavailability values for all but one (cyanide) of the acute toxicity SCTLs discussed in the their document. In support of their bioavailability assumptions, HSWMR cites a guidance document from the

State of Michigan Department of Environmental Quality (MDEQ) that recommends the use of a default soil bioavailability value of 50% for inorganics and non-volatile and semi-volatile organic chemicals. For some chemicals, other information is used to support a chemical-specific relative bioavailability value.

We disagree strongly with these bioavailability assumptions for the following reasons:

1. There is no empirical basis for the assumed bioavailability values. Data regarding the bioavailability of these chemicals from soils is limited or nonexistent. As a result, assumptions regarding their bioavailability are highly speculative. The cited MDEQ guidance document contains no discussion of the basis for their default bioavailability values. Our discussions with Linda Larson of MDEQ indicate that these default bioavailability factors were not based on scientific data, but rather were adopted as a policy decision on the part of regulators at MDEQ. For some chemicals, HSWMR used bioavailability from food in support of assumptions regarding bioavailability from soils. We could find no empirical data that indicate the relationship between bioavailability from food and soil for these chemicals, nor are any studies regarding this cited in the HSWMR report. We agree that bioavailability is likely to be an important factor in determining toxicity from soil ingestion, but point out that data to support any specific bioavailability assumption are absent.

2. Bioavailability is likely to be variable from site to site. Inorganic compounds can exist in multiple forms with different properties that can affect bioavailability (e.g., water solubility). Also, interactions with soils can influence bioavailability, and these in turn can vary with soil composition, pH, length of time of interaction, etc. Accordingly, it is reasonable to suspect that bioavailability of inorganics from soils can vary substantially from site to site. Consistent with this, data for the few inorganics whose soil bioavailability has been assessed to any appreciable degree (e.g., lead and arsenic) reveal marked differences among soils from different sites,

and in the case of lead, even among different soils from the same site (Casteel et al., 1998). We acknowledge that the methods to assess bioavailability for these chemicals on a site-specific basis do not yet exist, and suggest that this should be a priority topic for future discussion and research.

3. The toxic endpoint upon which many of the alternative SCTLs are based is probably independent of bioavailability. Most of the alternative SCTLs proposed by HSWMR are based on gastrointestinal effects. While gastrointestinal symptoms can sometimes arise from systemic effects (e.g., drugs which stimulate the chemoreceptor trigger zone in the central nervous system), local effects in the gastrointestinal tract are the most likely explanation for the nausea, vomiting, and diarrhea produced by these chemicals. Absorption of the chemical is not required to produce this effect, and therefore bioavailability is not a relevant issue. Dissolution from the soil matrix, rather than absorption, is probably the more pertinent factor influencing irritant effects, and insoluble forms are inherently less likely to produce gastrointestinal toxicity than soluble forms. Unfortunately, there is little information on dissolution of contaminants from soil within the gut. While bioavailability may be dependent in part on dissolution from soil, it is not necessarily a reliable indicator of dissolution. In some cases, extensive absorption of chemicals with limited aqueous solubility has been observed, and for others, absorption of the chemical in solution is limited. As a consequence, bioavailability data, even if available, may not provide reliable insight as to irritant potential. Further, as with bioavailability, the dissolution of contaminant in gut from soil is likely to be dependent upon both chemical- and soil-specific variables, and therefore to vary from site to site.

In our opinion, each of these points argues that bioavailability, although certainly important, is a site-specific factor that should be addressed on a site-specific basis. Incorporation of a specific bioavailability estimate in a broadly applicable SCTL would require a good deal of data on the plausible range of bioavailabilities from soil that may exist among sites. This information simply doesn't exist for any of the acute toxicity SCTL chemicals.

A related issue deals with the form of the chemical. In some cases, the chemical can exist in more than one form, with substantial differences in toxic potential. Differences in bioavailability can contribute to these differences, but there can be other factors that influence the toxicity of different forms. Since default SCTLs are intended to be applicable and protective, regardless the form of the chemical, the choice in developing SCTLs (including acute toxicity-based SCTLs) has consistently been to use data from the most toxic form. It is recognized that this will overestimate risk in situations where a less toxic form is present. The solution to this problem, we believe, is the development of tools capable of distinguishing between forms of chemicals present with different toxic potential on a site-specific basis.

Discussion of Specific Chemicals

Barium

Numerous poisonings with soluble forms of barium have been reported in the medical literature. Some have resulted from accidental ingestion, suicide attempts, or mistaken use of a soluble form of barium for medical procedures. Perhaps the most significant reported incidence of accidental poisonings with barium occurred when 144 persons ingested barium carbonate that was mistakenly substituted for potato starch in the preparation of sausage (Lewi and Bar-Khayim, 1964, Ogen et al., 1967). Among the individuals poisoned, 19 were hospitalized and one died. Vomiting, abdominal pain and spasms, diarrhea, weakness, hypokalemia (decreased blood potassium levels), cardiac arrhythmias, paresthesias (abnormal sensation such as tingling), and muscle paralysis are typical signs and symptoms of barium poisoning (Ellenhorn, 1997). For barium carbonate, the lowest reported acute lethal dose is 57 mg/kg, and the lowest reported toxic dose is 29 mg/kg (Ellenhorn, 1997). Effects at this lowest toxic dose include flaccid paralysis, weakness, and paresthesia. Barium chloride appears to be somewhat more toxic. The lowest lethal dose is reported to be 11.4 mg/kg (Ellenhorn, 1997). McNally

(1925) reports that under certain conditions, 2 g (barium) may be fatal, and serious toxicity could result from doses exceeding 0.2 g. The latter value, which corresponds to about 3 mg/kg in a 70 kg adult, is similar to the threshold toxic dose of soluble barium compounds of 200-500 mg (i.e., 3-7mg/kg), reported by Reeves and the World Health Organization (WHO) (Reeves, 1986, WHO, 1991). Unfortunately, the symptoms that constitute this threshold for the toxic effects are unclear and there is no clear distinction in the literature between doses producing gastrointestinal symptoms and those capable of more serious systemic effects like paresthesia, muscle paralysis, and cardiac arrhythmia. Clinical symptoms from acute ingestion of lesser toxic doses usually subside by 24 hours and the patient is ambulatory within 48 hours.

Chemical Form	Dose	Endpoint	Citation
Barium carbonate	57.0 mg/kg	Death	Ellenhorn, 1997
Barium chloride	11.4 mg/kg	Death	Ellenhorn, 1997
Barium carbonate	29.0 mg/kg	Flaccid paralysis and muscle weakness	Ellenhorn, 1997
Barium polysulphite	226 mg/kg	Flaccid paralysis and muscle weakness	Ellenhorn, 1997
Barium (soluble)	3-7 mg/kg	Threshold for toxic effects. (symptomology not included)	Reeves, 1986 WHO, 1991

The current acute toxicity SCTL for barium is based on the chronic oral RfD of 0.07 mg/kg-day developed by the USEPA. This value was selected because the application of traditional safety factors (10X for sensitive individuals and 10X for use of a LOAEL instead of a NOAEL, 100X total) to the lower end of the toxic effects range (3 mg/kg) results in a value less than the chronic oral RfD. Rather than use an acute dose lower than the chronic oral RfD for development of the acute toxicity SCTL, the RfD was selected as a lower limit for a safe dose based on acute toxicity. As noted in the Chapter 62-777 F.A.C Technical Report, the oral RfD is approximately 40-fold lower than the

lower end of the reported threshold toxic dose for soluble barium (3-7 mg/kg). The use of the oral RfD as an acute toxicity dose results in an acute toxicity SCTL of 110 ppm.

The HSWMR proposed revision to the acute toxicity SCTL for barium is also based on a dose of 3 mg/kg as a point of departure. To this dose, HSWMR applied a 10X safety factor for sensitive individuals to yield an acute toxicity dose of 0.3 mg/kg. HSWMR also included a bioavailability factor of 0.5, citing the MDEQ default bioavailability factor for inorganics. The acute toxicity SCTL corresponding to this set of assumptions is 900 ppm. No uncertainty factor for LOAEL to NOAEL extrapolation was included, implying that doses up to and including the lower end of the effects range would be regarded as acceptable.

As discussed under General Issues, we do not recommend the use of a bioavailability factor in development of default SCTLs unless sound data exist to support it. This does not appear to be the case for barium. The application of a single 10X uncertainty factor to a point of departure dose of 3 mg/kg appears reasonable, if the toxic endpoint is minor and the appearance of that effect in at least some individuals is regarded as acceptable. Without the bioavailability factor, this would result in an acute SCTL for barium of 450 ppm.

There are two potential concerns with use of an acute dose of 0.3 mg/kg for development of an acute toxicity-based SCTL. The first is that this dose is only about 40-fold lower than the lower end of the reported lethal dose range for soluble barium in humans. The second concern is that there is some question as to whether the 3 mg/kg threshold dose applies strictly to gastrointestinal distress. The literature is rather ambiguous on this point, and the 3 mg/kg barium threshold could be argued to be applicable to other effects as well (i.e., sensory and motor neurologic effects; cardiac arrhythmias) that might not be considered acceptable. If this is the case, an additional uncertainty factor might be required to insure that these effects did not occur in individuals exposed at the acute toxicity SCTL. Application of an additional, full factor of 10 leads to a dose less than the chronic oral RfD which, as discussed above, is not

practical. The use of the chronic oral RfD as the safe dose for acute toxicity, based on protection from effects other than gastrointestinal distress, represents the situation with the current acute toxicity SCTL. Whether or not to use this value (110 ppm) or a higher value (e.g., 450 ppm) depends, in our opinion, on two factors: 1) an acceptable margin of exposure relative to the human lethal dose; and 2) interpretation of the toxicity data with respect to the threshold dose for neurological and cardiac effects. Given the uncertainty associated with these two factors, we recommend that the acute toxicity SCTL of 110 ppm for barium be retained. As a practical measure, this value could be noted in the SCTL tables as being applicable specifically to soluble forms of barium [Note: Many barium salts are soluble in acidic medium, and solubility for barium would have to be defined in the context of the acidic environment of the stomach.]

Copper

Several studies have reported that ingestion of drinking water or beverages with elevated copper concentrations results in gastrointestinal effects including nausea, vomiting, diarrhea, and abdominal pain (Knobeloch et al., 1994; Sidhu et al., 1995; ATSDR, 1990). In fact, copper sulfate was used historically in medicine to induce vomiting (Goodman and Gilman, 1941). The acute gastrointestinal effects of copper in drinking water were investigated in a well-controlled prospective study (Pizarro et al., 1999). Sixty healthy adult woman were randomly assigned drinking water containing 0, 1, 3, or 5 mg Cu/L for 1 week intervals. After the first week, the participants were reassigned into a different consumption group so that each individual received one week of water at each of the exposure levels. At 3 mg/L Cu in water, a significant increase in gastrointestinal symptoms (nausea, abdominal pain, and vomiting) was reported. Using the mean water consumption (1.64 L/d) and body weight (63.6 kg) reported in the study, this corresponds to a gastrointestinal effects dose of 0.077 mg/kg. This dose is in agreement with the dose causing gastrointestinal symptoms in several other case reports we cited previously. A summary of the literature is provided in the table below.

Receptor	N	Dose	Effect	Reference
Adults		0.04 mg/kg	Upper-end of RDA	NRC, 1989
Children		0.07 mg/kg	Chronic Reference Dose	NCEA - provisional
Children		0.08 mg/kg	Upper-end of RDA	NRC, 1989
Children (1-6)		0.09 mg/kg	GI symptoms	WHO 1996
Family	5	0.06 mg/kg	GI symptoms	Spitalney et al., 1984
Adults	20	0.07 mg/kg	GI symptoms	Nicholas, 1968
Adults	60	0.077 mg/kg	GI symptoms	Pizarro et al., 1999
Adults	10	0.09 mg/kg	GI symptoms	Wyllie et al., 1957

In assessing the toxicity of copper, it is important to distinguish between copper in solution and dietary forms of copper that are principally bound to proteins associated with the metabolic role of copper. The HSWMR report proposes an acute toxicity value corresponding to a no effect level of 0.5 mg/kg cited in an NRC monograph (Recommended Dietary Allowances 10th Ed, NRC, 1989). The NRC monograph reports that the 0.5 mg/kg was derived from a 1971 WHO/FAO expert committee conclusion that no deleterious effects are expected with dietary copper intakes of 0.5 mg/kg. However, this is in contrast to more recent guidance from the WHO/FAO (Trace Elements in Human Nutrition and Health, WHO, 1996). The newer guidance sets an upper limit of the safe range of copper intakes specifically for children ages 1 to 6 years old of 0.09 mg/kg.

There is a narrow dose range of copper between gastrointestinal effects and accepted nutritional intakes for the maintenance of good health. Children, in particular, seem to be sensitive to the gastrointestinal effects of copper (Knobeloch et al., 1994). Based on the proceeding discussion, gastrointestinal effects from the ionic form of copper are expected with doses in the range of 0.06-0.09 mg/kg. As we reported previously, 0.07 mg/kg soluble copper is likely a dose associated with moderate gastrointestinal symptoms in children. The addition of safety factors would move that acute toxicity dose below the NCEA chronic reference dose for copper and below the dietary guidelines for copper intakes. Therefore, the use of 0.07 mg/kg copper, without an additional safety factor, was selected as the acute toxicity value. The resulting SCTL is 110 ppm copper in soil.

The HSWMR proposed acute toxicity value for copper is based on an acute toxicity value of 0.5 mg/kg (proposed as a no effect level), a reduction factor of 1

(professional judgment), and a bioavailability of 35% (dietary value). The resulting SCTL (2140 ppm) is somewhat lower than the chronic residential SCTL of 2900 ppm. In our opinion, a dose of 0.5 mg/kg is too high to use as a threshold toxicity dose. As discussed above, several lines of evidence indicate that acute doses of copper as low as 0.07 mg/kg are capable of producing gastrointestinal distress. With regard to bioavailability of copper from soils, it is unclear what insight is provided by observations of its bioavailability from foods. The quotation from the ATSDR toxicant profile for copper provided in the HSWMR report seems to also question the value of this information — "copper in soil is often bound to organic molecules, therefore, the bioavailability of copper from soil cannot be assessed based on bioavailability information from drinking water or food studies." (pg. 9). More importantly, since the effect of copper on the gastrointestinal tract is probably local rather than systemic in nature, the bioavailability of copper is probably not a relevant issue.

Cyanide

Cyanide is a potent and rapid-acting toxicant that has been involved in numerous intentional and accidental poisonings. The ATSDR reviewed the medical literature and determined that the average fatal dose of cyanide is 1.52 mg/kg (ATSDR, 1997). The lowest human lethal dose reported in the medical literature is 0.56 mg/kg (Gettler and Baine, 1938). Comparisons of acute oral toxicity data (with lethality as the endpoint) indicate that the toxicity of potassium cyanide, sodium cyanide, and hydrogen cyanide are similar on a molar basis. Symptoms of cyanide poisoning are systemic in nature and include anxiety, confusion, vertigo, and giddiness. Severe cases can result in loss of consciousness followed by convulsions, involuntary defecation, and death from respiratory failure (Salkowski and Penney, 1994). While clinical experience with cyanide is extensive, an upper-bound no-effect level has not been identified in humans. Any dose of cyanide capable of producing symptoms is potentially life-threatening and medical attention will be required.

Clearly the best dose-toxicity information for acute cyanide exposure exists for death as an endpoint. There is no standard set of uncertainty factors to develop a safe dose based on a lethal dose, particularly one established in humans. Given the severity of the endpoint, a margin of exposure of at least 100 to 1,000 would seem warranted. However, extrapolating from the average human lethal dose (approx. 1.5 mg/kg) places the safe acute dose below the USEPA chronic reference dose (0.02 mg/kg-day) if a factor as small as 100 is used. There is little logic in placing the safe acute dose lower than the safe chronic dose used for risk calculations, and so the acute toxicity SCTL was set at a value equal to the USEPA chronic reference dose. Even though the chronic reference dose is based on animal data, the primary consideration in setting the acute toxicity SCTL for cyanide in Chapter 62-777, F.A.C., was establishing a sufficient margin of exposure relative to the human lethal dose. The acute toxicity SCTL corresponding to this dose is 30 mg/kg.

In their evaluation of the acute toxicity SCTL for cyanide, the only change proposed by HSWMR is an adjustment to the modifying factor used by the USEPA to develop the chronic oral RfD. HSWMR contends that the 5X modifying factor used by the USEPA to account for the "apparent tolerance to cyanide when it is ingested in food rather than administered by gavage or by drinking water" (USEPA, 1999), should be removed from consideration in the development of the acute toxicity-based SCTL. The rationale for the removal of this modifying factor is that the observation of apparent tolerance may "reasonably be extended to the soil matrix as well" (HSWMR, 1999). We were unable to find any data to support the hypothesis that cyanide present in soil would be better tolerated than cyanide in drinking water. The adjustment of the modifying factor proposed by HSWMR results in an acute toxicity dose of 0.11 mg/kg and a final acute toxicity SCTL of 160ppm.

In deriving an acute toxicity SCTL for cyanide, the exceptional toxicity and steep dose-response curve of this chemical must be taken into consideration. The acute toxicity value of 0.11 mg/kg proposed by HSWMR is only 14-fold lower than the average fatal

dose in humans (1.52 mg/kg) and less than 5-fold lower than the lowest reported lethal dose (0.5 mg/kg). In our opinion, these margins of safety are simply not adequate.

Fluoride

Because of the widespread use of fluoride compounds as insecticides and supplementation to municipal water supplies for the prevention of dental caries, numerous cases exist documenting human exposure to fluoride. Malfunctioning fluoridation equipment is often the cause of fluoride intoxications. In an elementary school, 34 children became ill from ingestion of over-fluorinated water (Hoffman et al., 1980). The intakes were estimated to range from 1.4 to 90 mg fluoride (based on a 20 kg body weight this would result in an upper-end dose of 4.5 mg/kg). In another case 22 adults became ill after ingesting water containing 1041 ppm fluoride (Vogt et al., 1982). Doses producing nausea alone were estimated at 1.2 mg/kg. More severe gastrointestinal symptoms were reported in those individuals who received doses of 2-3 mg/kg.

Fluoride supplements are often recommended for children who do not live in an area served by a fluorinated water supply. These tablets are often flavored to aid in compliance and represent an important cause of accidental poisonings in the home. Spoerke et al. (1980) reviewed 150 reported cases of accidental poisoning with fluoride and found that a dose below 5 mg (absolute dose, not mg/kg) produced no gastrointestinal symptoms, a dose of 5-9 mg produced gastrointestinal symptoms in 10% of individuals, 10-19 mg caused symptoms in 21% of cases, 20-29 mg resulted in symptoms in 50% of cases, and 100% of individuals who ingested 30-39 mg were symptomatic. Augenstein et al. (1991) reviewed the medical records of children referred to the Rocky Mountain Poison Control Center for accidental fluoride ingestion. Of the 87 children included in the study 70 had intake estimates sufficient to construct a dose response. Results of the Augenstein et al. study are presented in the following table.

Fluoride Dose (mg/kg)	Number of Cases	% Symptomatic
<1	36	8
1-2	6	17
2-3	15	27
3-4	10	50
4-8.4	3	100

Gastrointestinal symptoms predominated and included nausea, vomiting, diarrhea, abdominal pain, and lethargy. Gastrointestinal symptoms are likely the result of corrosive effects of fluoride. Of the patients becoming symptomatic, only 3 had symptoms that developed later than one hour after ingestion. More serious effects result from the effects of fluoride to disrupt calcium homeostasis (Augenstein et al., 1991). Symptoms of more serious toxicity include hypocalcemia, hyperkalemia, cardiac arrthymias, muscle spasms, and seizures.

Emergency medicine and toxicology texts often make recommendations about treatment options and dosages expected to produce serious adverse effects. Ellenhorn (1997) suggests seeking immediate medical treatment for doses of fluoride exceeding 5 mg/kg. This is the same fluoride dose for which the CDC recommends prompt medical treatment (Reeves, 1995). Estimates of the lethal dose of fluoride in adults vary widely in the literature ranging from approximately 32 to 64 mg/kg. However, a 3-year-old weighing 12.5 kg died after ingesting 200 mg fluoride (16 mg/kg). The lowest reported fatality from fluoride was in a boy of 27 months who died after ingestion of 50 mg of fluoride (*Fluoride,* 1979). Based on the mean body weight for his age (12 kg) the fatal dose was only 4 mg/kg. Two factors may have contributed to the severity of his reaction: The mother had been taking fluoride tablets during pregnancy and the child had received daily fluoride supplements (0.5 mg) for the 15 months prior to his death. The possibility that dietary or supplemental fluoride could lower the threshold for serious toxicity may be relevant for consideration of acute toxicity from ingesting fluoride-contaminated soil.

The additional studies detailed above agree closely with the studies reviewed in our initial report. The toxicity data for fluoride is summarized on the table below.

Receptor	N	Dose	Effect	Reference
Adults	22	2-3 mg/kg	GI symptoms	Vogt et al., 1982
Children	70	3-4 mg/kg	GI symptoms	Augenstein et al., 1991
Children	34	4.5 mg/kg	GI symptoms	Hoffman et al., 1980
Children		5 mg/kg	Seek medical attention	Ellenhorn, 1997
Children		5 mg/kg	Severe toxicity	Whitford 1992
Child (27 mo.)	1	4 mg/kg	Death	*Fluoride*, 1979
Child (3 yr)	1	16 mg/kg	Death	Eichler et al., 1982
Adults		32-64 mg/kg	Death	Hodge & Smith 1965

The acute toxicity value for fluoride proposed by HSWMR is based on an acute effects level of 3 mg/kg (lower end of gastrointestinal symptoms), a reduction factor of 1 (endpoint derived in the population of interest), and a bioavailability of 90% (dietary value). The resulting SCTL (5000 ppm) is slightly higher than the chronic residential SCTL of 4700 ppm. Based on the proceeding discussion, gastrointestinal effects from fluoride are expected with doses in the range of 2-5 mg/kg. As we reported previously, 5 mg/kg is a 'probable toxic dose' associated with prolonged symptoms requiring medical attention. Therefore, the use of 3 mg/kg fluoride as a point of departure associated with moderate gastrointestinal effects is not unreasonable. However, the proximity of the acute gastrointestinal symptoms to the lethal doses reported above, and the lack of any safety factors in the analysis, are a matter of concern. The HSWMR report argues that the chronic residential SCTL of 4700 ppm is protective of acute toxicity in children. But, if a child were to consume 10 g of soil, an event that Calabrese et al. (1997) have modeled might occur as often as once a year for 33% of the population, the resulting fluoride dose would be only 5-fold lower than the lethal dose reported by Eichler (1982; 16 mg/kg) and approach the lethal dose reported in the *Fluoride* editorial (1979; 4 mg/kg). Because of the severity of the endpoint (death) some additional margin of safety is warranted.

The current acute toxicity SCTL is based on a no-effect level for gastrointestinal symptoms of 5 mg (absolute dose; from the Spoerke et al. study) in 10 g of soil (acute fluoride SCTL = 500 ppm). An alternative approach would be to use an effect level of 5 mg/kg (threshold for severe toxicity requiring medical attention) along with a safety factor

of 10X for sensitive individuals. This would result in an acute toxicity SCTL for fluoride of 750 ppm. Gastrointestinal symptoms may occur in a few children ingesting a 10 g dose of soil at this concentration, but very large amounts of soil (80 g or more) would be required to produce fluoride doses associated with serious toxicity.

Nickel

In humans, there is little information regarding nickel toxicity following oral exposure. Occupational exposure to nickel is primarily through inhalation. Therefore, the respiratory effects are well characterized and documented. However, only two cases of toxicity following oral exposure to nickel were identified in the primary literature. In the first, a 2-year old child ingested nickel sulfate crystals (570 mg/kg) and died from cardiac arrest 8 afterwards (Daldrup, 1986). The second documented case involving nickel toxicity was reported by Sunderman and coworkers (1988). In this report, 32 individuals drank from a water fountain contaminated with nickel sulfate and nickel chloride. It was estimated that the ingested doses ranged between 0.5 to 2.5 g of nickel. Twenty workers promptly developed symptoms of gastrointestinal distress including nausea, vomiting and abdominal cramps. Systemic effects included episodes of giddiness, lassitude, headache and cough. The lower end of the dose associated with adverse side effects was 7 mg/kg (assuming a 70 kg body weight).

The current acute toxicity SCTL for nickel is based on a LOAEL of 7 mg/kg from the Sunderman study. Two 10X uncertainty factors (10X for sensitive individuals and 10X for extrapolation from a LOAEL to a NOAEL, total 100X) were applied to this dose to yield an acute toxicity dose of 0.07 mg/kg. Although some gastrointestinal symptoms were regarded as acceptable in developing the acute toxicity SCTL for nickel, the second factor of 10X was applied because the poisoning episode from which the 7 mg/kg dose was obtained involved hospitalization of 10 out of 20 of the poisoned individuals. A 0.07 mg/kg dose of nickel corresponds to an acute toxicity SCTL of 110 ppm.

The alternative acute toxicity SCTL for nickel proposed by HSWMR is based on the same point of departure dose of 7 mg/kg used to calculate the current SCTL. HSWMR suggests the application of a single 10X safety factor for sensitive individuals and a bioavailability factor of 0.05. This results in a final alternative SCTL of 21,000 ppm, which in practice would be limited by the chronic SCTL of 1500 ppm.

Key differences between the current and proposed alternative acute toxicity SCTL for nickel include interpretation regarding the need for a second 10X uncertainty factor and the use of a bioavailability factor. Disagreement with the use of the bioavailability factor is articulated in the General Issues section, above. In assessing the need for uncertainty factors, HSWMR has assumed that the individuals in the Sunderman et al. (1988) report that received the lowest doses were those that experienced the least effects. With this assumption, the lower end of the dose range represents the dose producing limited gastrointestinal effects (i.e., effects that resolved in a day or two and did not require hospitalization). However, the report by Sunderman et al. is not clear on which subjects received what doses. As a result, it is possible that differences in sensitivity to nickel gastrointestinal effects existed among the subjects such that individuals receiving the lower doses experienced some of the more severe effects. Under these circumstances, the 7 mg/kg dose would represent the lower end of the dose range observed to produce serious gastrointestinal effects. In this situation, a single 10X uncertainty factor may not afford sufficient protection.

In discussing the development of risk-based criteria for nickel in soils, it worth mentioning that gastrointestinal effects are not the most sensitive effects of nickel. Nickel ingestion has been shown to produce dermal hypersensitivity reactions in individuals with nickel sensitivity. Nickel sensitivity appears to exist in about 10% of women and 1% of men. Nickel exposure in these individuals via the inhalation, dermal, or oral route results in dermal responses characterized by eczema, erythema, and dermal eruptions. Several clinical studies document the exacerbation of eczema and dermal eruptions following ingestion of nickel (Burrows et al., 1981; Gawlrodger et al., 1986; Nielsen et al., 1990). For example, a single dose of nickel as low as 0.08 mg/kg resulted in dermatitis, eczema,

and measle-like eruptions on the limbs of women previously sensitized to nickel (Gawkrodger et al., 1986). Cronin et al. (1980) found that a single oral dose as low as 0.009 mg/kg elicited a dermal reaction. Protection against this effect would involve the development of an acute toxicity SCTL so small that its implementation may be impractical. As a matter of policy, both the USEPA and the FDEP have chosen not to consider this effect when developing risk-based criteria for nickel.

Vanadium

Vanadium toxicity in humans primarily occurs following respiratory exposure in occupational settings and data regarding toxicity following oral ingestion is lacking. However, vanadium has been examined for its therapeutic applications, including the treatment of syphilis, as a cholesterol-lowering agent (Dimond et al., 1963), and its ability to lower blood glucose in diabetic patients (Boden et al., 1996; Goldfine et al., 1995). Recently, vanadium supplements have been introduced to the consumer market for improving athletic endurance (Fawcett et al., 1997).

From clinical studies, information is available regarding adverse side effects following oral ingestion of vanadium compounds. In several cases it was reported that patients experienced some form of gastrointestinal distress following oral ingestion of vanadium. Dimond and coworkers (1963) administered vanadium (ammonium vanadyl tartrate) to six patients for a period of six weeks. The subjects received 25, 50, 75 or 100 mg of the compound per day (0.36, 0.71, 1.1, and 1.4 mg/kg/day, assuming a 70 kg body weight). It is stated in the manuscript that all patients experienced gastrointestinal difficulties manifested by diarrhea and cramps. Two patients reported greater fatigue and lethargy. In addition, the oral dosage for each patient was limited by cramping and diarrhea. Also, on a daily dosage of 50 mg or more, a purple, green-tint developed on the tongue.

Chemical form	N	Dose	Effect	Reference
ammonium vanadyl tartrate	6	25 to 100 mg/day 6 wks	Diarrhea, cramps	Dimond et al., 1963
vanadyl sulfate	8	100 mg/day 4 wks	Diarrhea, cramps, flatulence - resolved within 1 wk of final tx (n=8)	Boden et al., 1996, Halberstam et al., 1996
sodim meta-vanadate	5	125 mg/day 2 wks	Diarrhea (n=4), vomiting (n=1)	Goldfine et al., 1995
vanadyl sulfate	31	35 mg/day 12 wks	2 subjects withdrawn from study because of side-effects	Fawcett et al., 1996.

The current acute toxicity SCTL for vanadium (15 ppm) is based on a 50-fold reduction from the lowest dose reported to produce gastrointestinal symptoms in the study by Dimond et al. (1963). HSWMR has proposed a revision of the acute toxicity SCTL for vanadium to 430 ppm, derived using 1.43 mg/kg as the point of departure dose. This dose is obtained from a clinical study in which vanadyl sulfate (100 mg per day for 4 weeks) was administered orally to non-insulin dependent diabetic patients (Boden et al., 1996). Out of eight patients, four complained of diarrhea and cramps during the first week of the study. Two other patients experienced a combination of nausea, diarrhea, cramps and flatulence. Therefore, 1.43 mg/kg was defined here as a LOAEL, and a safety factor of 10X was applied to account for sensitive individuals. A bioavailability factor of 50% (per Michigan guidelines) was also included in the calculation.

In our opinion, a dose of 1.43 mg/kg (corresponding to an absolute dose of 100 mg vanadyl sulfate for a 70 kg adult) is probably too high to use as a LOAEL. Subjects given 50 mg (0.71 mg/kg) of ammonium vanadyl tartrate uniformly experienced gastrointestinal effects (cramps and diarrhea) and some developed a discolored tongue in the study of Dimond et al. (1963). A reduction to a 25 mg dose was needed to reduce symptoms to tolerable levels. In the study by Fawcett et al. (1996), two subjects receiving a 35 mg dose of vanadyl sulfate had to withdraw from the study due to health complaints. These studies suggest that the threshold dose for gastrointestinal toxicity is probably close to 25

mg of these vanadium compounds. Using the molecular composition of vanadyl sulfate, where vanadium comprises 31% of the total molecular weight, this would correspond to a dose of 7.8 mg. Assuming a 70 kg body weight for adults in these studies, this corresponds to a dose of 0.11 mg/kg. [Note: This dose, when expressed per unit body weight, can be applied to children as well as adults.] As discussed in the General Issues section above, we do not recommend incorporating a bioavailability factor. An acute toxicity SCTL for vanadium based on the apparent threshold dose for gastrointestinal toxicity in humans would be 165 ppm. If a 10X uncertainty factor is incorporated for sensitive individuals, this corresponds to an acute toxicity SCTL of 17 ppm.

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