

USACEHR TECHNICAL REPORT 0802

DERIVATION OF HUMAN LETHAL DOSES



Toxicology Excellence for Risk Assessment (TERA)

January 2006

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14. ABSTRACT Human lethal dose estimates are required, in conjunction with U.S. Army Military Exposure Guideline concentrations, to provide toxicity benchmarks for evaluation of candidate toxicity sensors for an Environmental Sentinel Biomonitor (ESB) system for drinking water protection. An approach was developed to estimate human lethal doses (lowest lethal dose - LD ₀₁) for 26 chemicals having varying amounts and qualities of toxicological data. Readily available toxicokinetic information was used to adjust the human lethal doses for uptake via drinking water consumed over the course of a day. Research recommendations are provided to improve LD ₀₁ estimation approaches.					
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Derivation of Human Lethal Doses

Prepared for:

GEO-CENTERS

Prepared by:

**Toxicology Excellence
for Risk Assessment (TERA)**

January 19, 2006

Source	Oral Lethal Dose/Concentration *	Basis
Sax's (Lewis R.J.)	0.5-1.1 mg CN ⁻ /kg (0.57 mg/kg for HCN; 2.86 mg/kg for KCN)	Human LD _{Lo} (Pesticide Chemicals Official Compendium, pg. 596, 1966; Deichmann and Gerarde, 1969 - Toxicology of Drugs and Chemicals, p. 191, 1969). Deichmann and Gerarde (1969) reported sodium and potassium cyanide ranges of 200 to 250 mg (equivalent to 1.1-1.9 mg/kg for a 70-kg person) as the lethal oral adult dose, but gave no reference.
Patty's Industrial Hygiene	2 mg CN ⁻ /kg (5 mg/kg for KCN)	Rat - LD ₅₀ (Lorke, 1983 - Arch. Toxicol. 54, 275, 1983). Lorke (1983) reported a range of 5-9 mg/kg for KCN, depending on the number of animals (1-5) used in the study; use of 3-5 rats resulted in a value of 5 mg/kg, while 6-9 mg/kg was obtained using 1-2 animals.
Sheehy and Way (1968)	3.3-3.4 mg CN ⁻ /kg (3.7 mg/kg for HCN; 8.5 mg/kg for KCN) 0.5-1.0 mg CN ⁻ /kg (1-2 mg/kg as NaCN) 3.4 mg CN ⁻ /kg (8.5 mg/kg as KCN)	Mouse - LD ₅₀ (Annales Pharmaceutiques Francaises 19, 740, 1961; J. Pharmacol. Exp. Ther. 161, 163, 1968). Fatal dose in man (Hartung, 1982). Hartung (1982) cited another source for the value. Mouse - LD ₅₀ . This is a primary source for this value.
Fluoroacetate (sodium fluoroacetate) [62-74-8]		
Handbook of Poisoning: Prevention, Diagnosis & Treatment	0.7 to 1.4 mg/kg (for a 70 kg person (50-100 mg fluoroacetate) 0.22 mg fluoroacetate/kg (as fluoroacetic acid) N/A	Estimated human fatal dose Rat - LD ₅₀ No LD ₅₀ for mouse
Disposition of Toxic Drugs and Chemicals in Man	1.5-7.7 mg fluoroacetate/kg (140-700 mg for sodium fluoroacetate) N/A	Mean lethal dose for an adult No LD ₅₀ for rat or mouse
Handbook of Emergency Toxicology	N/A	No LD ₅₀ for rat or mouse No LD _{Lo} , MLD, or lethal dose for humans; no LD ₅₀ for rat or mouse

Source	Oral Lethal Dose/Concentration*	Basis
NIOSH	0.55 mg fluoroacetate/kg (50 mg sodium fluoroacetate)	Lethal dose for humans (Deichmann and Gerarde, 1969). Deichmann and Gerarde (1969) reported 50 mg sodium fluoroacetate as the probable lethal oral dose for an adult, but gave no reference. For a 70-kg person, this dose is equivalent to 0.7 mg/kg).
ATLA - Alternatives to Laboratory Animals	1.3 mg fluoroacetate/kg (1.7 mg/kg sodium fluoroacetate)	Rat - LD ₅₀ (Lehman, 1951). This reference is not available for review.
Clinical Toxicology of Commercial Products	0.08 mg fluoroacetate (0.1 mg/kg sodium fluoroacetate)	Mouse - LD ₅₀ (Yakkyoku, 1977). This reference is in a foreign language and was not reviewed.
HSDB	N/A	No LD ₅₀ , MLD, or lethal dose for humans; no LD ₅₀ for rat or mouse
DuBois (1942)	4.6 mg fluoroacetate/kg (6 mg/kg sodium fluoroacetate)	Mean lethal dose in human adults (Gajdusek and Luther, 1950; Harrison et al., 1952a and b). Harrison et al. stated that the mean lethal dose of 5 mg/kg value was estimated on the basis of animal studies. However, these authors reported a fatal case following ingestion of 6 mg/kg sodium fluoroacetate. Therefore, the 2-10 mg/kg sodium fluoroacetate as reported earlier is replaced with 6 mg/kg.
	N/A	No LD ₅₀ for rat or mouse
	0.39 mg fluoroacetate/kg (0.5 mg/kg sodium fluoroacetate)	Mouse - LD ₅₀ (Lewis, R.J. Sax's Dangerous Properties of Industrial Materials, 9th ed. Volumes 1-3. New York, NY: Van Nostrand Reinhold, 1996, p. 2966); J. Am. Pharmaceutical Association 37, 307, 1948 (as cited in Sax's)
	2.5-5.0 mg/kg	Rat - LD ₅₀ . The author reported values of 2.5 mg/kg for white rats and 5.0 mg/kg for Norway rats. However, it appears the source of the values was Chenowith and Gilman (1946).
	0.5 mg/kg	Mouse - LD ₅₀ . The author reported a value of 0.5 mg/kg for meadow mice. However, it appears the source of the value was Chenowith and Gilman (1946).

Source	Oral Lethal Dose/Concentration*	Basis
<p>Medical Toxicology: Diagnosis and treatment of human poisoning</p>	<p>2-10 mg/kg (mean 5 mg/kg)</p>	<p>Estimates of mean lethal dose for humans (Gajdusek and Luther, 1950). The authors reported the estimated LD₅₀ value for man as 5 mg/kg, but gave no reference. The form of fluoroacetate was not specified; therefore, value is excluded from analysis – this is unlikely to affect the results.</p>
<p>RTECS</p>	<p>N/A</p>	<p>Rat – LD₅₀. A value of 5 mg/kg was reported, citing Gajdusek and Luther (1950) as the source. Gajdusek and Luther (1950) also cited Chenoweth and Gilman (1946) for the LD₅₀ value. However, Chenoweth and Gilman (1946) reported a value of 4 mg/kg for methyl fluoroacetate. LD_{Lo} in humans (Deichmann and Gerarde – Toxicology of Drugs and Chemicals, 1969, p. 542) (as cited in Sax's). Deichmann and Gerarde (1969) reported 50 mg sodium fluoroacetate as the probable lethal oral dose for an adult, but gave no reference. For a 70-kg person, this dose is 0.7 mg/kg.</p>
<p>ATSDR</p>	<p>0.6 mg fluoroacetate/kg (50 mg for sodium fluoroacetate)</p>	<p>Rat – LD₅₀ (Ward, 1946 - American Journal of Public Health and the Nation's Health, 1946, Vol. 36, p. 1427) (as cited in Sax's). The value reported by Ward (1946) was 1.0 mg/kg for rat (black species) and 3-4 mg/kg for Norway rat. Therefore, the RTECS value of 0.1 mg/kg has been replaced with 1.0 mg/kg.</p>
<p>Clinical Management of Poisoning and Drug Overdose</p>	<p>0.08 mg fluoroacetate/kg (0.1 mg/kg sodium fluoroacetate)</p>	<p>Mouse – LD₅₀ (Yakkyouku, 1977, Vol. 28, p. 182) (as cited in Sax's). This reference is not available for review. No LD_{Lo}, MLD, or lethal dose for humans; no LD₅₀ for rat or mouse</p>
<p>The Pharmacological Basis of Therapeutics – Goodman and Gilman's</p>	<p>3.9 mg fluoroacetate/kg (5 mg/kg sodium fluoroacetate)</p>	<p>Estimated lethal dose for humans (Proctor and Hughes, 1978). Proctor and Hughes cited Harrison et al. (1952a, b) as the source of the value; see below.</p>
<p></p>	<p>N/A</p>	<p>No LD₅₀ for rat or mouse</p>
<p></p>	<p>N/A</p>	<p>No LD_{Lo}, MLD, or lethal dose for humans; no LD₅₀ for rat or mouse</p>