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ESTIMATES OF THE TOXICITY OF HYDROCYANIC ACID VAPORS IN MAN

by

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Biomedical Laboratory

AUGUST ~~February~~ 1976

DEPARTMENT OF THE ARMY
Headquarters, Edgewood Arsenal
Aberdeen Proving Ground, Maryland 21010

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When the data on which the internationally accepted LCt50 of inhaled hydrocyanic acid (AC, HCN) vapors in man were reviewed and the figures published widely in scientific journals were examined, it was decided that more valid estimates of the toxicity of HCN in man should be developed. LCt's for 1% 16%, 30%, 50%, 84%, and 99% of an exposed population for exposure times of from 0.5 to 30 minutes were derived. Because of the paucity of data on controlled experiments with man, it was necessary to use animal data. Among the assumptions made were that man falls into the species that are relatively resistant to HCN; that man is at least as resistant as the goat; and that man is at least four times as resistant as the mouse. The values derived are given.

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PREFACE

The work described in this report was authorized under Project/Task 1W762718AD2101, Toxicology of Chemical Agents. This report is a review of existing data.

In conducting the research described in this report, the investigator adhered to the "Guide for the Care and Use of Laboratory Animals" as promulgated by the Committee on Revision of the Guide for Laboratory Animals Facilities and Care of the Institute of Laboratory Animal Resources, National Research Council.

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CONTENTS

ESTIMATES OF THE TOXICITY OF HYDROCYANIC ACID VAPORS IN MAN

I. INTRODUCTION.

A reexamination of the estimated LCt's for inhaled hydrocyanic acid (AC, HCN) vapors revealed that the internationally accepted figure of 5000 mg min/cu m[1] and the figures published in scientific journals were invalid for reasons explained in this report. A new estimate has been proposed.

II. BACKGROUND.

A. Previously Accepted Estimates of the Toxicity of HCN in Man.

1. Military Estimates.

a. Department of the Army Technical Manual 3-215, Military Chemistry and Chemical Agents. December 1963. p 19.[2]

The following is cited from this reference: "Median lethal dosage varies widely with concentration because of the rather high rate at which AC is detoxified by the body. For example, at 200 mg/m^3 concentration, the lethal dosage is approximately 2000 mg min/m^3, whereas at 150 mg/m^3 the lethal dosage is approximately 4,500 mg min/m^3."

These estimates appear to be based on mouse data without consideration of species difference in toxicity (see table 1).

b. Summary Technical Report of Division 9, NDRC, Vol 1, Chemical Warfare Agents and Related Chemical Problems, Washington, 1946, p 12.[1]

As mentioned above, the estimates of 2000 mg min/cu m (200 mg/cu m for 10 minutes) and 4500 mg min/cu m (150 mg/cu m for 30 minutes) appear to be based on mouse data without consideration that the mouse is known to be more sensitive than man to HCN. (See table 1.)

Moore and Gates[1] estimated the LCt50 for HCN in man in the following manner:

The intravenous LD50's for HCN in mg/kg are 1.34, 0.81, 1.30, 0.66, 1.43, 0.81, and 0.99 for dog, cat, monkey, rabbit, guinea pig, rat, and mouse, respectively. Assuming man to be like other mammals, an intravenous LD50 of 1.1 mg/kg was estimated for man. The minute volumes of different species are stimulated to different degrees by HCN; 7-fold in the dog, 2- to 3-fold in the rabbit, and 1.5-fold in the guinea pig.

Table 1. LCt50's for HCN in Animals and Man

Animal species	LCt50 (mg min/cu m) for various exposure times													
	0.5 min	ref	1 min	ref	2 min	ref	3 min	ref	10 min	ref	30 min	ref	60 min	ref
Dog	800	1	700	1			1,000	1						
	800	3	616	3										
Mouse	450	4	750	4	1,348	3			2,300	1	5,425	1		
	566	3	911	3	1,268	1	1,100	1	736	3	4,890	5		
					1,258	5								
Rat	800	1	1,550	1	2,200	1	1,800	1						
	769	3	932	3	2,190	6								
Rabbit	904	3	850	1										
			980	3					3,200	1				
Sheep	1,441	3												
Cat	1,474	3	850	1	1,226	3								
Monkey	1,616	3	1,700	1										
Pig	1,740	3												
Guinea pig	2,500	1	2,100	1										
	2,112	3												
Goat	1,300	1			2,200	1								
	2,354	3			2,170	7								
Man														
15 l/min	7,200	1	7,590	1			7,830	1	8,600	1	10,800	1	[illegible],400	1
25 l/min	4,357	1	4,400	1			4,500	1	5,040	1	6,300	1	8,400	1
			5,000	1*					2,000	2**	4,500	2**		

*Mouse values seem to be used – mouse is a sensitive species.

**Internationally accepted value.

The intravenous injection of cyanide stimulates respiration in man to various degrees depending upon dose and speed of administration. [However, Barcroft[8] could detect no effects on respiration when a concentration of about 550 mg/cu m was inspired.]

The detoxication rate for HCN injected intravenously in man is about 0.017 mg/kg/min. This value is not markedly different for animals.

The LCt50 was calculated from the following formula:

$$VaC - Dt = K$$

where

V = total volume of air breathed in liters/kg
a = fraction of inhaled gas absorbed (70% measured in dogs)
C = concentration in mg/liter
D = rate of detoxication in mg/kg/min
t = exposure time in minutes
K = lethal dose in mg/kg

For a 70-kg man breathing 25 liters for 1 minute, the calculation would be:

$$0.36 \text{ liters/kg} \times 0.7 \times C - 0.017 \text{ mg/kg/min} \times 1 \text{ min} = 1.1 \text{ mg/kg}$$
$$C = 4.4 \text{ mg/liter, or } 4400 \text{ mg/cu m}$$

The LCt50 for 1 minute would be 4400 mg min/cu m. Values for other exposure times and breathing rates calculated by this method are shown in table 2. An earlier calculation of this type by British investigators led to the internationally agreed estimate of 5000 mg min/cu m for the LCt50 for HCN in man.

Table 2. LCt50 Estimates for HCN in Man Calculated by the Moore-Gates Formula

Exposure time	LCt50's			
	25 liters/min*		15 liters/min*	
	Concentration	Ct	Concentration	Ct
min	mg/cu m	mg min/cu m	mg/cu m	mg min/cu m
0.5	8,800	4,400	14,400	7,200
1	4,400	4,400	7,590	7,590
3	1,500	4,500	2,610	7,830
10	504	5,040	860	8,600
30	210	6,300	360	10,800
60	140	8,400	240	14,400

*Breathing rate.

The LCt50's calculated for man are much higher than those for even the most resistant animal species. The calculations include two major assumptions: the intravenous LD50 of 1.1 mg/kg and the pulmonary absorption of 70%.

2. Origin of Widely Published Open Literature Estimates.

The most widely published values for the toxicity of HCN vapors in man are reported to have originated with K. B. Lehmann prior to 1912. A report by Kobert[9] is the first journal publication reference to the work of Lehmann. Kobert's paper and the numerous subsequent citations of the work consistently presented toxicity values for man without developing the experimental basis for the values. As shown below, prior to 1919, Lehmann studied the toxicity of HCN in rabbits only and declined from making quantitative statements concerning the toxicity of HCN for man.[10]

The following abstracts are given for historical purposes and to show the common origin of toxicity values which are accepted for HCN in man.

a. Kobert, Rudolph (Kompendium der Praktischen Toxikologie zum Gebrauche für Ärzte, Studierende und Medizinalbeamte. Ferdinand Enke, Publisher, Stuttgart, 1912).[9]

This compendium presents a table which was credited to K. B. Lehmann. There was no indication of whether the toxicity estimates for man were based on human or animal experiments, or whether there was any basis for the values.

The following citations were made by Kobert:

"Concentrations (parts per thousand* by volume) . . . of HCN which:

Produce rapid death for man and animals	0.3
Are dangerous to life after 1/2-1 hr	0.12-0.15
May be tolerated for 1/2-1 hr without severe illness	0.05-0.06
Cause only minimal symptoms after several hours exposure	0.02-0.04

*Multiply by 1000 to convert to parts per million."

b. Henderson, Yandell, and Howard W. Haggard (Noxious Gases and the Principles of Respiration Influencing Their Action. The Chemical Catalog Co., Inc., 1927 N. Y., N. Y., pp 110-112).[11]

In 1927, Henderson and Haggard reported the work of Kobert[9] as follows:

"Physiological Response to Various Concentrations of Hydrocyanic Acid Gas*

	Parts of Hydrogen Cyanide Per Million Parts of Air
Several symptoms after several hours exposure	20 to 40
Maximum amount that can be inhaled for 1 hour without serious disturbance	50 to 60
Dangerous in 30 minutes to 1 hour	120 to 150
Rapidly fatal	3,000

*Kobert, R., Kompend. der Prak. Toxikol., Stuttgart, 1912."

Note that the rapidly fatal value of 3000 ppm, as given by Henderson and Haggard,[11] does not agree with that given by Kobert.[9]

c. Flury, F., and F. Zernik (Schädliche Gase, Springer, 1931).[12]

Flury and Zernik stated that the degree of toxicity of inhaled HCN for man is probably the same as for the monkey, the dog, or the cat. The following table was presented.

"Toxicity of Inhaled HCN According to Lehmann-Hess

	mg/l	Parts of Vapor in 1 million (cm^3/m^3) about:
Immediately fatal	0.3	270
Fatal after 1/2-1 hr, or later	0.12-0.15	110-135
Dangerous to life after 1/2-1 hr (Hess)	0.12-0.15	110-135
Tolerated for 1/2-1 hr without immediate or late effects	0.05-0.06	45-54
Slight symptoms after several hours (Hess)	0.02-0.04	18-36
Tolerated 6 hrs without symptoms	0.02 (-0.04)	18 (-36)

*1 mg/kg inhaled HCN is absolutely fatal to man according to Lehmann."

d. Dudley, H. C., T. R. Sweeney and J. W. Miller (Toxicology of Acrylonitrile (Vinyl Cyanide). J. Ind. Hyg. Toxicol. *24*, 255-258 (1942)).[13]

Dudley *et al.*[13] stated the following: "... Data on the acute toxicity of hydrocyanic acid as published by Lehmann and Hess and quoted from Flury and Zernik are summarized ..."

"Toxicity of HCN for Humans (Flury and Zernik, 1931)

Concentration		Symptoms
mg/liter	p.p.m.	
0.3	270	Immediately fatal
0.12-0.15	110-135	Fatal after 1/2-1 hour or later or dangerous to life
0.05-0.06	45-54	Tolerated for 1/2-1 hour without immediate or late effects
0.02-0.04	18-36	Some effects after exposure for several hours."

e. Fassett, D. W. Cyanides and Nitriles. Chapter XLIV in Industrial Hygiene and Toxicology. Patty, F. A., ed. 2d Edition. Volume II. Interscience Publishers, New York City. 1963.[14]

A table similar to that appearing in Dudley *et al.*[13] was presented in Patty's book[14] as shown below:

"Physiological Response to Various Concentrations of Hydrogen Cyanide in Air – Man*

Response	Concentration	
	mg/liter	p.p.m.
Immediately fatal	0.3	270
Fatal after 10 min	0.2	181
Fatal after 30 min	0.15	135
Fatal after 1/2 to 1 hr or later, or dangerous to life	0.12-0.15	110-135
Tolerated for 1/2 to 1 hr without immediate or late effects	0.05-0.06	45-54
Slight symptoms after several hours	0.02-0.04	18-36

*H. C. Dudley, T. P. Sweeney and J. W. Miller, J. Ind. Hyg. Toxicol., *24*, 255 (1942)

F. Flury and P. Zernik, Schädliche Gase, Springer, Berlin, 1931."

f. Lehmann, K. B., Short Textbook on Mechanical and Industrial Hygiene - S. Hirzel, Leipzig, 1919.[10]

All of the above references on the toxicity of HCN in humans apparently originated with K. B. Lehmann prior to 1912 when first quoted by Kobert.[9] None of these references give the experimental basis for the human values. The publication is not cited by any of those who quote Lehmann. Our attempts to locate such an article have been fruitless. However, the above referenced textbook indicated that the original research was performed only on rabbits. This publication states the following:

"I have studied the effect of HCN vapors quantitatively with my students Hagschal and Ahlmann. Doses of 0.06 mg are tolerated well even after 5 hrs; 0.14 mg was tolerated by a rabbit with some increased respiration even for 2 hrs; others died even at 0.13 mg in 1 hr, and at 0.15 mg in 1/2 hr. At 0.2 mg even after 4 min, sudden collapse occurs; we saw an actual pulmonary hemorrhage in a rabbit poisoned with HCN vapor (until now published only in the dissertations of my students). As yet we have not conducted experiments on cats and dogs. I can make no quantitative statements about men. - See Schankies Dissertation, Konigsberg, 1918."

The doses, given by Lehmann as mg, appear to correspond with the parts per thousand (mg/liter) which were credited to Lehmann by Kobert.[9]

B. Toxicity Data on Deliberately Exposed Men.

In 1927, Grubbs[15] reported that several volunteers breathed gas from 1/2- and 3/4-ounce sodium cyanide per 1000 cu ft for 2 minutes and for 1-1/2 minutes, respectively, without feeling any effect, but that this has at other times caused dizziness. One-half ounce of sodium cyanide in 1000 cu ft yields a concentration of about 501 mg/cu m of sodium cyanide, the equivalent of about 276 mg/cu m of cyanide ion. Three-quarters ounce of sodium cyanide in 1000 cu ft yields a concentration of 750 mg/cu m of sodium cyanide, equivalent to 401 mg/cu m of cyanide ion. The respective Ct's would be about 522 (2 minutes) and 602 (1-1/2 minutes) for cyanide ion; and 1002 (2 minutes) and 1125 mg min/cu m (1-1/2 minutes) for sodium cyanide.

Katz and Longfellow[16] cited the human exposures of Grubbs.[15] In addition, they stated that in experiments during the war, men had been exposed to concentrations of 500 ppm (550 mg/cu m) for about 1 minute without injury.

Koritschoner (cited by Reid Hunt in Heffter's Handbook of Experimental Pharmacology[17]) exposed tuberculous patients to concentrations up to 20 mg/cu m for 120 minutes twice daily. These patients rapidly developed a tolerance to HCN.

In 1931, Barcroft[8] studied the toxicity of inhaled HCN in man. The following is cited from his paper.

"The question of where man stands in relation to the animal is most important. Clearly it is very difficult to obtain exact information on this subject, for when fatalities are concerned the concentrations which produce them are not known.

"The experiment about to be described shows, however, that man is not very susceptible. It took place in the airtight chamber already described, the human subject was about 45 years of age and weighed about 70 kg.

"One human being and one dog (about 12 kg)[1] were exposed simultaneously, without protection, to atmosphere containing a nominal concentration of 1/1600 hydrocyanic acid[*] the actual concentration being probably between that and 1/2000.[*] The dog was placed in one corner of the chamber, the man in the corner diagonally opposite to him, so that they faced one another. The utmost care was taken lest if the dog succumbed first it should not be because its respiration was stimulated by a greater degree of muscular activity, therefore each movement made by the dog was followed by an imitative movement on the part of the man, so that the degree of activity of two might be as nearly as possible the same. This procedure was followed up to the point at which the dog became unconscious. After that no effort was made by the man to imitate the muscular spasms which form so conspicuous a feature of the later stages of cyanide poisoning. The experiment ran the course as shown in the following notes which were taken by the man as the experiment proceeded.

"Time from Zero	Dog	Man
50 sec.	Became unsteady	–
1 min. 15 sec.	On floor unconscious	–
1 min. 30 sec.	Crying sounds and tetanic convulsions sufficiently established to render it probable that animal was in extremis	–
1 min. 31 sec.	–	Came out of chamber and put on respirator having felt no symptoms. No apparent dyspnea.
1 min. 33 sec.	Respiration apparently* ceased, animal believed to be dead, was pulled out by lead.	Re-entered chamber in respirator for purpose of pulling out dog. Having done this he remained outside.
5 min.	–	Momentary feeling of nausea.
10 min.	–	Attention difficult to concentrate in close conversation.

*Although the corpse was set aside for burial about 6:30 p.m., the dog did in point of fact recover, and was found walking about next morning. It showed no further symptoms.

[1] The weight of this dog is not recorded and the above figure is guessed from memory of its general appearance. It is intended only to give an idea of the sort of sized dog used."

[*] 1/1600 = 625 ppm, 688 mg/cu m, Ct, 1032 mg min/cu m.
1/2000 = 500 ppm, 550 mg/cu m, Ct, 825 mg min/cu m.

[Cyanide is rapidly detoxified.[1,18] However, there are some accounts that Barcroft suffered certain persistent effects of this exposure for about a year.[19,20] It was stated that Professor Barcroft suffered nausea and definite mental symptoms a few minutes after his withdrawal from the gas atmosphere but that at least some of these symptoms persisted for about a year.[19,20]] Continuing with the quote from Barcroft[8] – "A report by S. H. Katz and E. S. Longfellow from the American Bureau of Mines issued in July 1923 states: 'Men employed in fumigation with HCN have been tested while at rest in 250 parts per million of air for 2 minutes[*] and 350 parts per million for 1-1/2 minutes[**] but felt no dizziness, although possibly on exertion they might have done so.' In experiments during the war men have been exposed to 500 parts per million for about a minute without injury. Hydrocyanic acid gas was formerly considered one of the deadliest gases in minute concentrations, but later experience, especially in the war, has shown that man is more resistant than some other forms of life. – (Lehmann, Tabelle der Kleinsten Mengen, welche allenfalls ertragen werden, in book by Kobert, Kompendium der Praktischen Toxikologie zum Gebrauche für Ärzte, Studierende und Medizinalbeamte. Stuttgart, p. 45) whereas recently Kohn-Abrest (Notice toxicologique sur les gas. Annales des Falsifications, 8:215-39, 1915) determined that 1000 parts per million are impossible to breathe for many minutes."

C. Toxicity Data on Animals.

A summary of toxicity values for HCN in animals is shown in table 1. The original data from some of the reports were analyzed by the Bliss statistical method to obtain dose-response regression lines and frequency distributions for mortality fractions of 1%, 16%, 30%, 50%, 84%, and 99%. These values are shown in tables 3 and 4.

The toxicity data shown in table 5 were read from figures published by Barcroft.[8] Although the data are somewhat inconsistent, they indicate that the LCt50's increase with exposure time to a greater degree than that indicated by calculations for man (table 2) which were based on intravenous LD50 and internal detoxication rate.

These data (tables 1 through 4) also indicate that LCt50's in animals for 0.5-, 1-, 2-, and 3-minute exposure times are consistently lower than those calculated for man by the Moore-Gates method.

III. CURRENT RECOMMENDED AND APPROVED ESTIMATES OF THE TOXICITY OF HCN VAPORS IN MAN.†

A. Derivation of the Estimates.

The animal data contained in this report indicate that goats, sheep, pigs, monkeys, and guinea pigs are relatively insensitive to the lethal effects of HCN, whereas dogs, mice, rats, and rabbits are relatively sensitive. Barcroft[8] reported that when two dogs and two monkeys were exposed together, the monkeys were only beginning to show signs of unsteadiness when the dogs died. He also reported that when a man and a dog were exposed together, the dog almost died, but the man had minimal effects.

[*]275 mg/cu m, Ct, 550 mg min/cu m.

[**]385 mg/cu m, Ct, 582 mg min/cu m.

† Recommended and approved in minutes of 31 March 1971 Research Laboratories Human Estimates Committee, subject: Research Laboratories Human Estimates for HCN, dated 31 March 1971.

Table 3. LCt50's of HCN in Several Animal Species – Statistical Analysis of Data in OSRD 1432[3]

Species	Exposure time	LCt50 – mg min/cu m					
		1%	16%	30%	50%	84%	99%
	min						
Mouse	0.5	215 (83-554)	373 (277-614)	405 (312-644)	566 (455-703)	856 (628-1167)	1493 (712-3133)
	1	612 (392-955)	769 (620-953)	833 (725-958)	911 (844-984)	1081 (914-1279)	1358 (914-2017)
	2	738 (262-2061)	1042 (605-1794)	1178 (819-1690)	1348 (1198-1517)	1746 (1534-1985)	2466 (1381-4400)
Rat	0.5	668 (567-785)	724 (708-739)	745 (691-802)	769 (694-851)	817 (726-917)	885 (814-962)
	1	–	–	–	932 (1028-845)	–	–
Rabbit	0.5	855	882	891	904	922	950
	1	967 (909-1029)	975 (915-1038)	977 (917-1041)	980 (920-1044)	986 (925-1050)	994 (933-1056)
Dog	0.5	743 (522-1056)	775 (541-1109)	787 (549-1127)	800 (558-1146)	826 (577-1182)	862 (605-1225)
	1	122 (21-699)	309 (224-424)	428 (217-842)	616 (253-1499)	1230 (579-2613)	3104 (921-10,454)
Cat	0.5	761 (591-979)	1111 (683-1808)	1270 (764-2113)	1474 (911-2387)	1956 (1643-2339)	2857 (1364-5987)
	2	429 (145-1264)	782 (640-958)	968 (582-1612)	1226 (664-2266)	1922 (1192-3102)	3507 (1494-6250)
Pig	0.5	1667 (1364-2038)	1708 (1393-2095)	1723 (1404-2115)	1740 (1418-2135)	1772 (1445-2173)	1815 (1485-2218)
Sheep	0.5	745 (527-1055)	1037 (559-2114)	1242 (585-2641)	1441 (637-3259)	1910 (816-4467)	2786 (1341-5786)
Goat	0.5	1369 (731-2567)	1867 (1559-2236)	2083 (1528-2841)	2354 (1680-3297)	2967 (2703-3259)	4046 (2007-8157)
Guinea pig	0.5	614 (143-2643)	1246 (695-2232)	1599 (1117-2288)	2112 (1481-3118)	3581 (1354-9468)	7262 (1105-47,738)
Monkey	0.5	1441	1539	1575	1616	1697	1813

Table 4. LCt50's of HCN in Mouse, Rat, and Goat – Statistical Analysis of Data from EATR 136, EATR 360, TRLR 22, and TRLR 23

Species	Exposure time	Ref	No. of animals	LCt50 (mg min/cu m)					
				1%	16%	30%	50%	84%	99%
	min								
Mouse	2	5	260	285 (173-470)	448 (356-564)	526 (458-604)	629 (594-666)	882 (726-1072)	1388 (872-2209)
	10	21	300	124 (82-187)	172 (141-210)	193 (170-219)	220 (209-232)	282 (248-321)	392 (279-552)
	30	5	178	45 (25-80)	94 (70-126)	122 (100-150)	163 (144-185)	283 (231-347)	593 (368-956)
Rat	2	6	100	753 (617-919)	933 (844-1032)	1006 (938-1080)	1095 (1042-1151)	1285 (1180-1400)	1593 (1327-1912)
Goat	2	7	14	921 (748-1132)	1011 (983-1041)	1046 (958-1142)	1085 (981-1200)	1164 (1139-1190)	1279 (1033-1584)

Table 5. Toxicity of HCN in Various Animal Species (Data from Barcroft)[8]

Animal species	Concentration	Exposure time	Ct	Mortality fraction
	mg/cu m	min	mg min/cu m	
Goat	120	60	7,200	0/4
	150	60	9,000	0/4
	180	60	10,800	0/4
	240	15	3,600	0/4
	240	30	7,200	3/4
	240	60	14,400	4/8
	300	30	9,000	4/4
	360	15	5,400	1/4
	360	20	7,200	3/4
	360	24	8,640	4/4
	480	5	2,400	0/4
	480	10	4,800	3/4
	480	20	9,600	3/4
	600	6	3,600	1/4
	630	10	6,300	4/4
	860	3	2,580	1/3
	920	3	2,760	1/1
	1,200	3	3,600	5/5
Monkey	120	60	7,200	0/8
	180	30	5,400	1/3
	200	60	12,000	3/3
	240	30	7,200	1/3
	360	20	7,200	0/2
	480	3	1,440	0/3
	600	2	1,200	1/2
	600	6	3,600	0/2
	600	10	6,000	1/2
	600	30	18,000	1/1
	720	5	3,600	2/2
	860	3	2,580	1/2
	1,200	3	3,600	1/4
Dogs	70	60	4,200	0/4
	100	30	3,000	2/4
	120	15	1,800	1/2
	120	10	1,200	0/2
	240	15	3,600	2/2
	240	10	2,400	2/3
	240	5	1,200	0/3
	400	3	1,200	2/2
	600	1	600	2/2
	800	1	800	1/1
	1,200	1	1,200	2/4

Table 5. (Contd)

Animal species	Concentration	Exposure time	Ct	Mortality fraction
	mg/cu m	min	mg min/cu m	
Rabbit	120	60	7,200	0/2
	180	60	10,800	2/4
	240	30	7,200	0/4
	240	15	3,600	2/6
	300	10	3,000	1/2
	300	7	2,100	0/1
	300	5	1,500	0/3
	350	10	3,500	2/6
	350	7	2,450	0/1
	350	4	1,400	0/1
	350	2	700	0/1
	380	3	1,140	1/2
	480	8	3,840	1/2
	480	5	2,400	5/8
	480	2	960	2/3
	480	10	4,800	4/4
	600	3	1,800	3/4
	600	10	6,000	4/4
	660	2	1,320	2/2
	860	1	860	1/1
	1,200	3	3,600	4/4
	1,200	1	1,200	2/2
Cats	120	60	7,200	0/3
	120	30	3,600	0/3
	180	60	10,800	2/5
	180	3	540	0/1
	200	15	3,000	2/2
	200	10	2,000	1/2
	240	30	7,200	3/3
	240	15	3,600	3/3
	240	10	2,400	3/3
	350	10	3,500	4/4
	380	3	1,140	0/2
	420	3	1,260	0/2
	600	10	6,000	3/3
	600	3	1,800	4/5
	690	1	690	1/2
	730	3	2,190	2/2
	840	1	840	2/2
	1,200	3	3,600	3/3
	1,200	1	1,200	3/4

Table 5. (Contd)

Animal species	Concentration	Exposure time	Ct	Mortality fraction
	mg/cu m	min	mg min/cu m	
Rats	40	60	2,400	1/6
	120	60	7,200	3/6
	120	45	5,400	5/6
	120	30	3,600	2/6
	180	60	10,800	1/6
	240	30	7,200	4/4
	240	15	3,600	1/4
	400	3	1,200	1/6
	600	10	6,000	6/6
	600	3	1,800	3/6
	600	1	600	1/6
	1,200	3	3,600	6/6
	1,200	2	2,400	2/6
Mice	60	60	3,600	3/6
	110	60	6,600	2/6
	150	60	9,000	4/6
	170	60	10,200	4/6
	180	24	4,320	1/1
	200	16	3,200	1/1
	220	30	6,600	1/1
	240	13	3,120	1/1
	270	20	5,400	1/1
	290	11	3,190	1/1
	460	5	2,300	1/1
	570	3	1,710	1/1
Fowl	110	105	11,550	1/3
	170	49	8,330	1/1
	250	9	2,250	1/1
	300	14	4,200	1/1
	340	6	2,040	1/1
	420	5	2,100	1/1
	540	3	1,620	1/1
Guinea pig*	390	60	23,400	–
	420	31	13,020	–
	480	12	5,760	–
	600	4.5	2,700	–
	720	2.5	1,800	–
	960	2	1,920	–

* Read from graph – no points. Unable to determine mortality fraction.

Although there have been few controlled experiments with man, those reported indicate that man belongs among the resistant species. However, it is doubtful that man is so much more resistant than the monkey as could be assumed if the LCt50's obtained by the Moore-Gates calculation were compared with those for the monkey.

There is another doubt concerning the validity of the Moore-Gates formula. The LCt50's for HCN in animals increase with exposure time, or perhaps with decrease in concentration of agent. The same phenomenon occurs with other inhaled substances. In the case of sarin, the increase in LCt50 is greater than that attributable to the systemic detoxication of the agent. Perhaps this represents a detoxication on the surfaces of the lungs at low concentrations. The experimental LCt50's for HCN in animals increase with exposure time at a greater rate than the LCt50's calculated for man by the Moore-Gates formula.

Since there is reason to question the previous LCt50 values for HCN, new human estimates have been derived based on the following assumption:

1. Man has a susceptibility to HCN similar to that of the resistant goat or monkey.

2. Only in the mouse are LCt50 values available at various exposure times from 0.5 to 30 minutes. These values allow estimation of the LCt50 as related to exposure time. The values for mice were multiplied by 4 to obtain LCt50 estimates for man at each time interval. These derived LCt50's are comparable to available corresponding values for the goat, thus placing man near the goat in sensitivity to HCN.

3. The LCt50 for HCN in man increases with exposure time in a manner similar to that determined experimentally in animals.

4. The dose-response distribution found at a given exposure would apply over the exposure range of 0.5 to 30 minutes.

5. Since all experimental values are for inactive animals, resting breathing rates must be used. The resting rate for man is assumed to be 10 liters per minute.

6. The frequency of death for man (1%, 16%, 30%, 50%, 84%, and 99%) is similar to that for the resistant goat.

The LCt50 values for man, shown in table 6, were derived by using the frequency of deaths in a population of goats as a model to derive corresponding percentages of deaths in a population of men whose LCt50's were those established as explained in assumption 2, above.

B. <u>Limitations of the Estimate</u>.

1. The concentrations of HCN in controlled human exposures have not exceeded 550 to 625 mg/cu m, or Ct's of 825 to 1032 mg min/cu m.

2. The estimated LCt50's for humans have been derived primarily from animal experimental data.

Table 6. Estimates of the Toxicity of Hydrocyanic Acid Vapors in Man

Exposure time	LCt						Average mouse LCt50
	1%	16%	30%	50%	84%	99%	
min	mg min/cu m						mg min/cu m
	Goat						
	1,369	1,867	2,083	2,354	2,967	4,046	
	Man (estimates)						
0.5	1,177	1,606	1,791	2,032*	2,552	3,480	508
1	1,930	2,632	2,937	3,404*	4,183	5,705	851
3	2,546	3,473	3,874	4,400*	5,519	7,526	1,100
10	3,888	5,302	5,916	6,072*	8,426	11,491	1,518
30	11,992	16,355	18,247	20,632*	25,991	35,443	5,158

*Man LCt50 = mouse LCt50 X 4 at various exposure times.

This places man in the sensitivity range of the goat (and monkey). The mouse values were used since these are available at all exposure times (0.5 to 30 minutes).

The frequency distributions for percentage of deaths (other than 50%) are based on those determined experimentally in goats and calculated by the statistical method of Bliss.

3. It is assumed that the LCt50 for man will increase with exposure time in a manner similar to that noted in the mouse.

4. There is no available information on man on which to develop dose-response regression lines for lethality. The use of the information on goats to develop a frequency distribution is based only on the postulation that man and goat are among the relatively resistant species.

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