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AN ESTIMATE OF THE HUMAN INHALATION L(Ct)50 FOR GB [U]

BY

R.J. SHEPHARD

CHEMICAL DEFENCE EXPERIMENTAL ESTABLISHMENT

Porton, Wilts.

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SUMMARY

1. Methods of estimating the inhalation L(Ct)50 are outlined.

2. Reasons are suggested for basing calculations on the ratio ChE50: LD50; this gives an estimate of the average L(Ct)50 that is probably valid to within ± 33% for brief exposures, with wider limits for longer exposures.

3. The L(Ct)50 varies with the metabolic state of those attacked. Under resting conditions, the average figure is probably at least 135 mg.min/m^3; with activity the average may be less than 50 mg.min/m^3.

4. These figures represent the best possible estimate based on data available from both U.S. and the U.K.

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1. HISTORICAL. The human inhalation L(Ct)50 has usually been calculated from an assumed ventilation (10 l/min in the resting state) and an LD50 (µg GB/kg) obtained by one of several methods of extrapolation. Complete retention of inhaled GB has usually been assumed.

(a) The U.K. approach. Ainsworth, Davies and McKee (1) gave single-breath inhalations of GB ($\frac{1}{2}$ - 3 µg/kg) to 36 subjects. The dose of GB was plotted against the logarithm of the percentage of uninhibited red cell enzyme, and by considerable extrapolation of the graph, the dose for 90% inhibition was estimated at 11 - 29 µg/kg, with a most probable value of 16 µg/kg. The assumptions of the method were

(i) that the dose of GB causing 90% inhibition of red cell cholinesterase was the LD50, and

(ii) that the dose of GB was linearly related to the logarithm of the percentage of enzyme remaining after administration of GB. The last assumption was checked by giving GB to rabbits (inhalation and i.v.) and guinea pigs (s.c.) over a wider dose range. No gross departure from this relationship was apparent, but the number of observations was not adequate to study the fine details of the curve.

Assuming a ventilation of 10 l/min, with 100% retention of GB, the resting L(Ct)50 was placed in the range 77 - 203 mg.min/m^3, with a most probable value of 112 mg.min/m^3. It is now known that assumption (i) is not universally true. Many species of animals remain active when the red cell cholinesterase is 90% inhibited, and recent U.S. experiments suggest the same is true of man. If a figure of 95% inhibition is taken, the estimated L(Ct)50 would be 224 mg.min/m^3.

(b) The U.S. approach Silver (2) considered that during short exposures to GB vapour, the inhalation LD50 for a number of laboratory animals approached the intravenous LD50 of about 15 µg/kg. It was assumed that the same would be true of man, and again accepting a respiratory minute volume of 10 l/min, with 100% retention of agent, the L(Ct)50 would be 105 mg.min/m^3 for a 70 kg man.

2. PRESENT POSITION. The basic method of estimation has altered little, but much more information is now available on the response of man to moderate doses of GB by inhalation, on the respiratory minute volume during exposure and simulated exposure to "nerve gas", and on the retention of inhaled vapours.

(a) Extrapolation to LD50. The estimation of the LD50 remains the weakest link in the chain of evidence. To the original two methods of extrapolation has been added a third, based on the ratio of the ChE50 to the LD50; this seems the procedure of choice, for the reasons discussed below.

(i) Cholinesterase inhibition at LD50. Whether log-probit (3) or semi-logarithmic plot of the data is used, the extrapolation is critically dependent on the slope, which in man can only be determined over a very small part of the dose range of interest; further, there is no certain evidence that 90% is the desired inhibition. From the data of Callaway, Davies and Rutland (4), in many species the LD50 dose corresponds to >95% inhibition of whole blood and red cell cholinesterase:

Species	LD50 (µg/kg, s.c.)	Corresponding cholinesterase inhibition	
		Whole blood	Red cell
Rabbit	35	97	> 99.9
Monkey	25	97	
Guinea Pig	38	98	> 99.9
Rat	109	91	
Pigeon	52	88	

(ii) Inter-species comparison of LD50: There is a wide range of species variation in inhalation toxicity of GB, and the supposition that inhalation toxicity approaches intravenous toxicity (2) is not fully borne out by experimental data. The inhalation toxicity apparently increases with a decrease in the duration of exposure (5 - 8); however, even with short exposures (9 - 10), the intravenous LD50 is exceeded by a factor of 1.7 - 2.0

Species	Inhalation LD50 µg/kg	Intravenous LD50 µg/kg
Rat (4)	165 - 209	80
Guinea Pig (4)	45 - 73	32
Guinea Pig (9)	42 - 79	32 - 36
Rabbit (4)	25 - 52	19
Monkey (4)	46 - 48	-
Monkey (9)	15 - 38	18 - 23
Sheep (4)	58 - 76	15 - 20
Dog (9)	28 - 52	18 - 28

(iii) Ratio of ChE50 to LD50. The ChE50: LD50 ratio has been thought rather constant in different species. U.K. data (4) show a range of 3.2 - 6.3, with a mean value of about 4.0:

Species	ChE50 : LD50 ratio	
	Whole blood	Red cell
Rabbit	1: 6.0	1 : 6.3
Monkey	1: 6.3	
Guinea Pig	1: 3.3	1 : 3.4
Rat	1: 3.2	
Pigeon	1: 4.0	

U.S. experiments show a mean value 3.9 (11). The use of the ChE50 : LD50 ratio as a basis of extrapolation seems preferable to methods (i) and (ii). The quantities involved (ChE50 and LD50 in animals, ChE50 in man) can all be measured accurately, and no assumptions are made about the shape of the cholinesterase inhibition curve in the range 90 - 95% inhibition, which is difficult to check experimentally. The influence of route of administration on the ChE50/LD50 ratio is less than might be anticipated, changes in LD50 being matched at least in part of changes in ChE50. Thus, the following ratios have been reported for the rabbit:

Route of administration	LD50 (µg/kg)	Whole blood ChE at LD50	ChE 50 : LD50 ratio
Subcutaneous (4)	35	97	1 : 6.0
Intravenous (9, 3)	19	94	1 : 5.4
Inhalation (9, 1)	25 - 52	97 - 100	1 : 5.2 to 1 : 10.8

In the case of the inhalation experiments, the ratio increased as the duration of exposure was lengthened. With large doses of GB, the cholinesterase inhibition at the LD50 also varies with exposure time. Thus some figures of Cullumbine, Callaway, Ainsworth and Lynch (12) show that in the sheep the LD50 with 2 min exposure is 76 µg/kg, with 90% cholinesterase inhibition, and with 10 sec exposure the LD50 is 58 µg/kg, with 95.9% inhibition of whole blood cholinesterase. This difference is sufficient to preclude effective use of prediction method (i). On the other hand, the ChE50 dose seems relatively independent of the duration of exposure (13, 14).

(b) <u>The inhalation red cell ChE50 in man.</u> Whether based on very brief exposures (single-breath technique, 2 sec or less) or 15 min chamber exposures, the ChE50 can be placed fairly certainly between 4.0 and 5.0 µg/kg:

Method of inhalation	Method of extrapolation	Number of subjects	Estimated red cell ChE50 (µg/kg)
Single breath (1)	Semi-log plot	36	4.7
" " (14)	Linear regression	73	5.0*
" "	log/probit plot(3)	29 paired obs.	4.0*
		131 obs.	4.4*
Chamber			
15 min seated	log/probit plot(3)	92	5.0
15 min marching		44	

In the chamber exposures, the inhaled dose has been back-calculated (14) from the Ct and the ventilation measured in parallel experiments, using 96% retention for the resting experiments (15) and 90% (10, 16) for the exercising men.

*In these calculations, 67% recovery of nominal dose assumed (14).

(c) <u>The inhalation LD50.</u> If man can be assumed to behave more like a monkey than some of the small species, the ChE50 : LD50 ratio of 1 : 4.0 may be rather low. A better estimate might be 1 : 5 for short exposures ($\leq \frac{1}{2}$ min) and 1 : 11 for longer exposures ($\geq$ 2 min). On this basis, the inhalation LD50 would be:

Duration	LD50	Total dose for 70 kg man
$\leq \frac{1}{2}$ min	20 - 25 µg/kg	1400 - 1750 µg
$\geq$ 2 min	44 - 55	3080 - 3950

The influence of duration of exposure on the LD50 remains somewhat uncertain. It is clear from the figures in section (b), above, that at doses likely to produce < 50% inhibition of circulating cholinesterase, the effectiveness of a given inhaled dose is similar during both "single-breath" and 15 min chamber exposures. However, with larger doses, the probability of extravascular spread will rise with increase of concentration of the agent in the blood stream, and for this reason the toxicity of a given large dose may be greater when it is inhaled rapidly.
The total dose corresponding to the LD50 will rise with body weight; however, this will be offset to some extent by corresponding differences of respiratory minute volume, and over a small range of body weights differences in L(Ct)50 from this factor can probably be neglected.

(d) Percentage retention of inhaled GB. Direct measurement has shown 96% retention of GB during nasal breathing (15). Calculation suggests 88 - 90% for oral breathing (16); U.S. figures are a little lower (83 - 88%, ref. 9).
Thus we may assume nasal breathing (96% retention) at rest, and a combination of oral and nasal breathing in exercise (say 90% retention).

(e) Respiratory minute volume. With exposures <15 sec, the breath may be held. With longer exposures ventilation will gradually come to equal the metabolic requirement of the activity undertaken. Typical figures for the period $\frac{1}{2}$ - 20 min are:

Activity	Range of minute volume l/min	Average l/min
Resting, seated	10 - 14	12
" standing	12 - 20	16
Marching 2.5 m.p.h.	18 - 60	29
Running (max. effort)	60 -100	80

(f) The inhalation L(Ct)50. Combining the information in (c), (d) and (e), the estimated L(Ct)50 for a 70 kg man may be tabulated as follows:

Activity	Exposure $\frac{1}{2}$ min		Exposure 2 min	
	Range mg.min/m^3	Average	Range	Average
Resting, seated	104 - 182	135	230 - 410	301
" standing	73 - 152	102	161 - 343	230
Marching 2.5 m.p.h.	26 - 108	60	57 - 244	135
Running (max. effort)	16 - 32	22	34 - 73	49

3. CONCLUSIONS

Although it is possible for planning purposes to tabulate the anticipated L(Ct)50 at various levels of metabolism, as above, there remain important uncertainties in the estimate. The ratio ChE50 : LD50 shows a twofold variation between species, and it is by no means certain which species man resembles. It is also quite probable that whereas the ratio found for brief inhalation exposures corresponds with the intravenous ratio, the ratio applicable to longer inhalation exposures is greater than the intravenous ratio. The average figures quoted above could thus still be in error by about a third in the case of brief exposures, and by a larger margin for longer exposures.

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