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Deriving Allowable Daily Intakes for Systemic Toxicants Lacking Chronic Toxicity Data

D. W. LAYTON,* B. J. MALLON,* D. H. ROSENBLATT,† AND M. J. SMALL†

*Environmental Sciences Division, Lawrence Livermore National Laboratory, Livermore, California 94550; and †U.S. Army Medical Bioengineering Research and Development Laboratory, Frederick, Maryland 21701

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The lack of human toxicological data for most chemical compounds makes it difficult to quickly assess health risks associated with exposure to contaminants at hazardous waste sites. It would therefore be advantageous to have a technique for estimating acceptable daily intakes (ADIs) of potentially toxic substances based on more widely available animal toxicity data. This article focuses on the use of LD_{50} data to derive provisional ADIs, and it suggests multiplying oral LD_{50} values (expressed in mg/kg of body wt) by a factor in the range of 5×10^{-6} to 1×10^{-5} day^{-1} to convert them to such ADIs. It is emphasized that these interim ADI values are no substitute for toxicity testing, but that such testing would most likely result in higher ADI estimates.

INTRODUCTION

Assessments of human health risks that result from exposure to contaminants at hazardous waste sites are rarely based on human toxicological or epidemiological data because such data are lacking for most chemical compounds. Instead, dose–response data for mammalian species are evaluated and used to estimate effects on man. The acceptable daily intake (ADI) of a noncarcinogenic substance for an exposed human population has normally been based on a no-observed-effect level (termed NOEL) obtained from one or more chronic toxicity studies on laboratory animals. An ADI is computed by dividing the animal dose rate by a safety factor that incorporates uncertainties associated with animal-to-human dose equivalence, type of toxic response, nature of the study, and other factors.

Unfortunately, chronic toxicity tests are unavailable for most substances because of the time (1 to 2 years) and expense of completing the tests. In contrast, measures of acute toxicity, such as the median lethal dose to a sample population of laboratory animals, i.e., an LD_{50}, are easier to obtain and more widely available. Acute toxicity studies are usually undertaken prior to chronic studies to identify possible dosing regimes or as an end in themselves.

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The lack of available ADIs or chronic toxicity data from which an ADI can be derived is a problem for health officials faced with decisions as to "safe" or "acceptable" levels of unregulated substances in contaminated environmental media. In a hazardous waste site assessment situation, such officials do not have time or the financial resources to have chronic toxicity tests performed, even if they have the authority to commission such tests. Therefore, methods should be developed to estimate interim ADIs for substances for which only acute toxicity data are available.

This paper focuses specifically on the use of oral LD_{50}s to provide *provisional* estimates of the acceptable intakes of noncarcinogenic chemicals. These estimates are meant to be conservative; that is, if the ADI could be computed from a NOEL determined in a chronic toxicity study, it would nearly always be higher than the value estimated from the LD_{50}. We begin this article with a discussion of the uncertainties associated with acute and chronic toxicity tests. We then evaluate the ratios of chronic, no-effect dose rates in laboratory animals to the oral LD_{50}s for the same substances. A similar analysis of dose rates derived from existing ADIs for pesticides and threshold limit values (TLVs) for chemicals in the workplace is also performed. The analyses are based on the assumption that the ratios are distributed lognormally. Finally, we examine the ramifications of applying the ratio-estimation techniques for calculating dose rates that have a high probability of being below toxic levels. The statistical approach is described in the Appendix.

CHRONIC NOELs AND LD_{50}s: BACKGROUND

Chronic NOELs are usually based on 2-year feeding studies with rats, mice, dogs, or other small mammals. Measures of toxicity include changes in body and organ weights as well as food and water consumption. Biochemical indicators (e.g., inhibition of cholinesterase) and pathological abnormalities are also used to determine toxicity (Heywood, 1983; Weil and McCollister, 1963). The highest dose level at which toxic effects and indicators are absent (or where the difference in measures of toxicity between test and control animals is insignificant) identifies that dose level as a maximum NOEL (or simply NOEL). The LD_{50}, in contrast, is an estimate of the lethal dose to 50% of a sample population of laboratory animals following a single oral dose (see Finney, 1985). The LD_{50} is not measured directly; it is calculated from a statistical analysis of the fractions of animals dying after receiving different doses of a toxicant.

Neither the LD_{50} nor the chronic NOEL should be considered as biological constants—both are subject to variations caused by inter- and intraspecies differences, as well as differences in test protocols and conditions. Zbinden and Flury-Roversi (1981) have shown that the LD_{50} is subject to variation according to the age, weight, sex, and health of the test animals. In addition, diet, housing conditions, and ambient temperature can influence test results. Variations occur within and among species due to genetic differences. Other influences on LD_{50} values include differences among laboratory practices and facilities, measurement technologies, and experimental protocols. Weil and Wright (1967) conducted an interlaboratory study of the LD_{50}s for 10 compounds. The 8 participating laboratories used three experimental procedures to determine the LD_{50}s of the chemicals. Procedure I was a specific experimental protocol for determining oral LD_{50}s with a common strain of rats; Procedure II fol-

lowed the same protocol as Procedure I except that each laboratory used its own strain of rats; and Procedure III was simply to have each laboratory use the procedures it normally follows as well as its own rat strain. Under Procedure I the ratios of the highest to lowest LD_{50} for the ten chemicals ranged from 1.30 to 4.98, and for Procedure II the corresponding range was 1.81 to 4.54. For Procedure III, which permitted the greatest variation in test factors, the ratios were from 1.83 to 5.48. Griffith (1964) performed a similar comparison between 6 laboratories and four chemicals. Each laboratory used its own experimental protocols. The ratios of the extreme LD_{50} values ranged from 2.0 to 2.8. Zbinden and Flury-Roversi (1981) cite an unpublished study sponsored by the Commission of the European Communities in which 65 laboratories were allowed to use their own experimental protocols to determine the LD_{50}s for five chemicals. The ratios of the maximum to minimum LD_{50} values reported for each chemical ranged from 3.66 to 11.89. These ratios are somewhat misleading because they do not provide information on the actual variation in the LD_{50} values. However, if we assume that the natural logarithms of the LD_{50} values are normally distributed (see Appendix for a discussion of lognormal distribution) and that the maximum and minimum LD_{50}s define the 97.5 and 2.5 percentile limits of the distribution, then the geometric standard deviation (GSD) for each distribution can be estimated from the following equality:

$$\frac{GM \times GSD^{1.96}}{GM \times GSD^{-1.96}} = \frac{LD_{50}\,(max)}{LD_{50}\,(min)}, \tag{1}$$

where GM is the geometric mean of the LD_{50} values. Thus, the estimated GSD values range from 1.4 (i.e., from Eq. (1) $GSD = 3.66^{1/3.92}$) to 1.9 (i.e., $11.89^{1/3.92}$) for the five chemicals considered. The GSD estimates for the reviews by Weil and Wright (1967) and Griffith (1964) are less than 2 as well. In other words, most of the existing studies indicate that the actual variation in LD_{50} values for a given species is surprisingly low, given the various sources of uncertainty associated with lethal toxicities.

COMPARISONS OF ACUTE, SUBCHRONIC, AND CHRONIC TOXICITY

The time and expense of completing chronic toxicity studies has prompted toxicologists to compare subchronic (defined here as studies lasting 30 to 200 days) and long-term (>200 days) toxicity tests to determine whether dose–effect relations (e.g., a NOEL or minimum-effect level) for short-term tests can be used to estimate similar endpoints for chronic tests. Early studies on the relationship between the short- and long-term tests were completed by Weil and McCollister (1963) and Weil *et al.* (1969). In the first study, the authors analyzed the ratios of maximum NOELs (expressed as percentage of diet) for short-term tests (i.e., 30- to 90-day duration) to the maximum NOELs for 2-year studies for 33 substances. They found that 95% of the ratios were less than 6.0 (or conversely, 95% of the inverse ratios were greater than 0.17). In the second study, Weil *et al.* calculated the ratios of 90-day minimum-effect levels to 2-year minimum-effect levels for 20 other substances. Based on the statistical data they reported, we estimated the GM of the inverse of the ratios to be 0.6 with a GSD of 2. Later, McNamara (1976) divided 2-year NOELs by the 90-day NOELs for 74 substances, and the GM of the ratios was 0.7 with a GSD of 2.3. More recently, Rulis and Hattan (1985) analyzed the ratios of the highest NOEL derived from long-

term (i.e., >200 days) toxicity studies to the NOEL from short-term (i.e., <200 days) studies for 20 food additives. The GM of those ratios was 0.5 with a GSD of 3. The long- to short-term ratios corresponding to the 5th cumulative percentile for these four studies are 0.17, 0.19, 0.18, and 0.08, respectively. A lower-bound estimate of the chronic NOEL for a substance can therefore be calculated by dividing its subchronic NOEL by a factor ranging from 5 to 10.

Unfortunately, even subchronic tests are not available on most substances, and so investigators have also examined the relationship between LD_{50} values and chronic NOELs. McNamara (1976), for example, computed the ratios of 2-year NOELs (in mg kg^{-1} day^{-1}) for rats to the rat oral LD_{50} (in mg/kg) doses for 36 substances, including 14 substances reported by Weil and McCollister (1963). The GM of the lognormal distribution was 0.02 day^{-1} with a GSD of 5.4. Venman and Flaga (1985) prepared another set of toxicity data on 17 chemical substances (including 7 of the substances from McNamara) that consisted of chronic NOELs from 2-year studies with rats and oral rat LD_{50}s. The GM of the ratios they presented was 0.007 day^{-1} and the GSD was 9.7. To obtain an expanded set of ratios for analysis, we pooled the ratios for the organic substances reported in the three papers. If a chemical had two or more ratios, we adopted the NOEL/LD_{50} ratio reported in the latest paper. The resulting 41 compounds and associated ratios are presented in Table 1. The GM of those ratios is 0.015 day^{-1} and the GSD is 8.2 (see Fig. 1 for a log–probability plot of the ratios).

Although the previous studies have relied on rat toxicity data to study the relationship between chronic NOELs and LD_{50}s, the rat is not the best model for all toxic responses in humans nor is it always the most sensitive species to any given toxic response. To examine how interspecies variability in LD_{50} values would affect the ratios, we prepared a set of 26 substances (including some of the compounds in Table 1) for which there was both a 2-year oral rat NOEL in the open literature and two or more oral LD_{50} values in the *Registry of Toxic Effects of Chemical Substances* (RTECS) (Lewis and Sweet, 1984) for a small mammal (see Table 2). We then calculated the ratios for each substance, and the GM of the resulting 85 ratios (see Fig. 2) was 0.018 day^{-1} with a GSD of 5.8. The GM and GSD values for the ratios calculated from only the rat LD_{50}s in Table 2 were similar—0.016 and 6.2, respectively. The GM of the lowest ratios for each of the substances was 0.011 and the GSD was 5.6.

LOWER-BOUND ESTIMATES OF ADIs FROM LD_{50}s

The acceptable daily intake is usually expressed as

$$\mathrm{ADI} = \frac{\mathrm{NOEL}}{\mathrm{SF}}, \tag{2}$$

where ADI, acceptable daily intake, mg (kg body wt)$^{-1}$ day^{-1}; NOEL, highest no-observed-effect level, mg (kg body wt)$^{-1}$ day^{-1}; and SF, safety factor (>1) for extrapolating animal toxicity data to man, unitless. We used the following equation to derive a lower-bound estimate of the acceptable daily intake of a toxic chemical based on oral LD_{50} data:

$$\mathrm{ADI} = \frac{R(p) \times \mathrm{LD}_{50}\,(\mathrm{oral})}{\mathrm{SF}}, \tag{3}$$

where $R(p)$ is a NOEL/LD_{50} ratio (in units of day^{-1}) corresponding to a cumulative

TABLE 1

RATIOS OF RAT NOELS TO RAT LD_{50}S FROM VALUES PRESENTED IN VENMAN AND FLAGA (1985), MCNAMARA (1976), AND WEIL AND MCCOLLISTER (1963)[a]

CASID[b]	Chemical	NOEL ($mg\ kg^{-1}\ day^{-1}$)	LD_{50} ($mg\ kg^{-1}$)	Ratio NOEL/LD_{50}
50-29-3	DDT	15	113	0.13
57-55-6	Propylene glycol	3675	27000	0.14
62-56-6	Thiourea	188	400	0.47
63-25-2	Carbaryl	7	510	0.014
64-72-2	Chlortetracycline · HCl	750	3000	0.25
72-43-5	Methoxychlor	120	5500	0.022
72-54-8	DDD	90	3600	0.025
76-06-1	Acrylamide	3	170	0.018
80-33-1	Ovex	1.9	2000	0.001
80-62-6	Methyl methacrylate	8.4	8410	0.001
86-50-0	Methylazinphos	2.5	13	0.19
86-88-4	α-Naphthylthiourea	7.5	100	0.075
87-86-5	Pentachlorophenol	3	142	0.021
90-43-7	1-Phenylphenol	100	2700	0.037
92-52-4	Biphenyl	50	3280	0.015
94-20-2	Chlorpropamid	125	2000	0.062
101-21-3	Chlorpropham	1500	6251	0.24
117-81-7	Bis(2-ethylhexyl) phthalate	97.5	31000	0.0031
119-36-8	Methyl salicylate	50	887	0.056
123-91-1	*p*-Dioxane	14	5170	0.0027
126-92-1	Tergitol 08	290	5760	0.050
127-20-9	Sodium 2,2-dichloropropionate	9.75	7744	0.0013
128-37-0	BHT	400	1700	0.24
136-78-7	Sesone	15	11070	0.0014
148-79-8	Thiabendazole	50	3100	0.016
297-78-9	Telodrin	0.38	8	0.048
299-84-3	Ronnel	5	1740	0.0029
299-85-4	Zytron	0.75	270	0.0028
299-86-5	Crufomate	2.25	750	0.003
314-40-9	Bromacil	12.5	5200	0.0024
520-45-6	Dehydroacetic acid	75	1000	0.075
555-89-5	Bis(4-chlorophenoxy)methane	22.5	5800	0.0039
709-98-8	Propanil	20	1384	0.014
1746-01-6	2,3,6,8-TCDD	0.000001	0.022	0.000045
2227-13-6	Tetrasul	0.5	3500	0.00014
3570-61-4	2,4,5-TES	15	805	0.019
5064-31-3	Trisodium nitrilotriacetate	22	2000	0.011
5902-52-3	Dowco 109	2.25	820	0.0027
8001-54-5	Benzalkonium chloride	94	400	0.24
9003-13-8	Butoxypolypropylene glycol	480	9100	0.053
7681-93-8	Pimaricin	25	2730	0.0092

[a] Only one NOEL is included for each organic compound.
[b] Chemical Abstracts identification number.

percentile (p) on a lognormal distribution chosen to reduce to an acceptable degree the probability that the calculated dose rate is above a toxic level (see Appendix for an explanation of how $R(p)$ is computed). For the purpose of this paper, we selected

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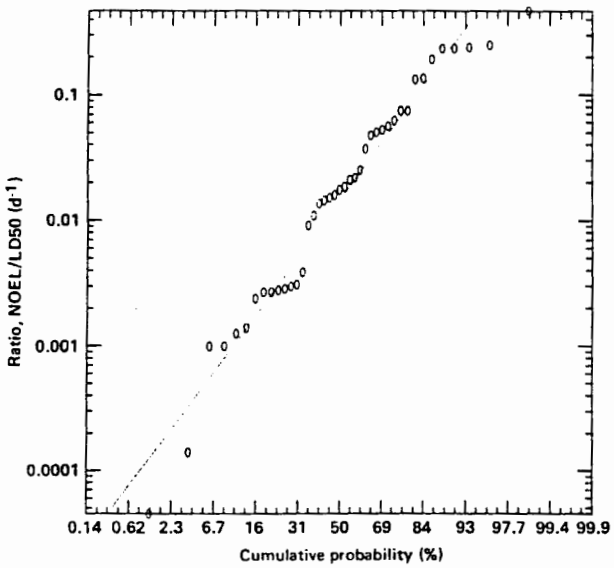

FIG. 1. Log-probability plot of the ratios of chronic NOELs (oral, rat) to oral LD_{50} values for 41 substances. The geometric mean is 0.015 with a geometric standard deviation of 8.2. Ratios are from Table 1.

the $R(p)$ value corresponding to the 5th cumulative percentile. The $R(5)$ value for the lognormal distribution of pooled ratios calculated using only rat LD_{50} values (Table 1) equals 4.7×10^{-4} day^{-1} (i.e., $0.015 \times 8.2^{-1.645}$), and for the distribution of ratios calculated from the LD_{50} values for small mammals (Table 2), $R(5)$ equals 1.0×10^{-3} day^{-1} (i.e., $0.018 \times 5.8^{-1.645}$). $R(5)$ for the lowest ratios of each of the substances in Table 2 is 6.5×10^{-4} (i.e., $0.011 \times 5.6^{-1.645}$). A conversion factor, defined as $R(5)$/SF, can then be used to calculate an ADI directly from an LD_{50}. Generally, a safety factor of 100 is used to convert a chronic NOEL for rats or small mammals to an ADI (Dourson and Stara, 1983), and from the ratios calculated above, conversion factors would range from about 5×10^{-6} to 1×10^{-5}. The conversion factors are higher than the 10^{-6} value presented by Venman and Flaga (1985) in their paper dealing with the use of acute toxicity data to estimate chronic NOELs. The discrepancy is due in part to the smaller data set they used to calculate NOEL/LD_{50} ratios and to a disproportionate number of small ratios (22% of their 17 ratios were less than 0.001).

COMPARISON OF ADIs AND ORAL LD_{50}s FOR PESTICIDES

The World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations established a joint expert panel in 1966 to establish ADIs for pesticides (Vettorazzi, 1975). Since that time, the WHO/FAO have established ADIs on over 100 pesticides. The expert panel followed the same procedure discussed earlier—the toxicology of a pesticide is evaluated, an animal NOEL is identified, and a safety factor is selected to extrapolate the safe intake level for the animal to a safe intake level for humans. The normal safety factor is 100, but factors can range from 10 to "several hundredfold" (Vettorazzi, 1975).

TABLE 2

RATIOS OF 2-YEAR NOELS FOR RATS TO LD_{50}S FOR SMALL ANIMALS

CASID[a]	Chemical	NOEL (mg kg^{-1} day^{-1})	LD_{50} (mg kg^{-1})	Species	Ratio NOEL/LD_{50}
50-29-3	DDT	15*	200	Monkey	0.075
50-29-3	DDT	15	250	Rabbit	0.06
50-29-3	DDT	15	150	Guinea pig	0.1
50-29-3	DDT	15	87	Rat	0.17
50-29-3	DDT	15	135	Mouse	0.11
62-33-9	Calcium disodium edetate	375**	12000	Dog	0.031
62-33-9	Calcium disodium edetate	375	7000	Rabbit	0.054
62-44-2	Phenacetin	47	1500	Rat	0.031
62-44-2	Phenacetin	47	1220	Mouse	0.038
62-44-2	Phenacetin	47	2500	Rabbit	0.019
62-44-2	Phenacetin	47	2650	Guinea pig	0.018
63-25-2	Carbaryl	7*	275	Mouse	0.025
63-25-2	Carbaryl	7	250	Rat	0.028
63-25-2	Carbaryl	7	150	Cat	0.047
63-25-2	Carbaryl	7	710	Rabbit	0.0098
63-25-2	Carbaryl	7	280	Guinea pig	0.025
80-05-7	Bisphenol A	8**	2500	Mouse	0.0032
80-05-7	Bisphenol A	8	3250	Rat	0.0025
80-05-7	Bisphenol A	8	2230	Rabbit	0.0036
80-33-1	Ovex	1.9*	2000	Rat	0.00095
80-33-1	Ovex	1.9	4280	Mouse	0.00044
80-33-1	Ovex	1.9	5660	Rabbit	0.00034
80-33-1	Ovex	1.9	640	Guinea pig	0.0030
86-50-0	Methylazinphos	2.5*	11	Rat	0.23
86-50-0	Methylazinphos	2.5	15	Mouse	0.17
86-50-0	Methylazinphos	2.5	80	Guinea pig	0.031
87-86-5	Pentachlorophenol	3*	50	Rat	0.06
87-86-5	Pentachlorophenol	3	168	Hamster	0.018
90-43-7	1-Phenylphenol	100*	2000	Rat	0.05
90-43-7	1-Phenylphenol	100	900	Mouse	0.11
92-52-4	Biphenyl	50*	3280	Rat	0.015
92-52-4	Biphenyl	50	2400	Rabbit	0.021
94-20-2	Chlorpropamid	125*	1550	Mouse	0.081
94-20-2	Chlorpropamid	125	2390	Rat	0.052
117-81-7	Bis(2-ethylhexyl) phthalate	97.5*	31000	Rat	0.0031
117-81-7	Bis(2-ethylhexyl) phthalate	97.5	30000	Mouse	0.0032
117-81-7	Bis(2-ethylhexyl) phthalate	97.5	34000	Rabbit	0.0029
117-81-7	Bis(2-ethylhexyl) phthalate	97.5	26000	Guinea pig	0.0038
119-36-8	Methyl salicylate	50*	887	Rat	0.056
119-36-8	Methyl salicylate	50	2100	Dog	0.024
119-36-8	Methyl salicylate	50	1300	Rabbit	0.038
119-36-8	Methyl salicylate	50	1060	Guinea pig	0.047
123-91-1	*p*-Dioxane	14*	4200	Rat	0.0033
123-91-1	*p*-Dioxane	14	5700	Mouse	0.0025
123-91-1	*p*-Dioxane	14	2000	Cat	0.007
123-91-1	*p*-Dioxane	14	2000	Rabbit	0.007
123-91-1	*p*-Dioxane	14	3150	Guinea pig	0.0044
126-92-1	Tergitol 08	290*	4000	Rat	0.072
126-92-1	Tergitol 08	290	1550	Mouse	0.19
126-92-1	Tergitol 08	290	3580	Rabbit	0.081
126-92-1	Tergitol 08	290	1300	Guinea pig	0.22

CASID[a]	
127-20-8	Dalapo
127-20-8	Dalapo
127-20-8	Dalapo
133-90-4	Amibe
133-90-4	Amibe
297-78-9	Telodri
297-78-9	Telodr
297-78-9	Telodr
297-78-9	Telodr
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297-78-9	Telodr
299-84-3	Ronne
299-84-3	Ronne
299-84-3	Ronne
299-84-3	Ronne
533-74-4	Dazor
533-74-4	Dazor
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555-89-5	Bis(4-
555-89-5	Bis(4-
2227-13-6	Tetra
2227-13-6	Tetra
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2439-10-3	*n*-Do
2439-10-3	*n*-Do
7681-93-8	Pima
7681-93-8	Pima
7681-93-8	Pima
7773-06-0	Amm
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25155-30-0	Sodi
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TABLE 2—*Continued*

CASID[a]	Chemical	NOEL (mg kg^{-1} day^{-1})	LD_{50} (mg kg^{-1})	Species	Ratio NOEL/LD_{50}
127-20-8	Dalapon	22**	3860	Rat	0.0057
127-20-8	Dalapon	22	3400	Rabbit	0.0065
127-20-8	Dalapon	22	3400	Guinea pig	0.0065
133-90-4	Amiben	750**	3730	Mouse	0.20
133-90-4	Amiben	750	3500	Rat	0.21
297-78-9	Telodrin	0.38*	8.4	Mouse	0.045
297-78-9	Telodrin	0.38	4.8	Rat	0.079
297-78-9	Telodrin	0.38	1	Dog	0.38
297-78-9	Telodrin	0.38	5	Cat	0.076
297-78-9	Telodrin	0.38	4	Rabbit	0.095
297-78-9	Telodrin	0.38	2	Guinea pig	0.19
297-78-9	Telodrin	0.38	7.5	Hamster	0.05
299-84-3	Ronnel	5*	420	Rabbit	0.012
299-84-3	Ronnel	5	1400	Guinea pig	0.0036
299-84-3	Ronnel	5	2000	Mouse	0.0025
299-84-3	Ronnel	5	906	Rat	0.0055
533-74-4	Dazomet	8**	180	Mouse	0.044
533-74-4	Dazomet	8	640	Rat	0.012
533-74-4	Dazomet	8	160	Guinea pig	0.05
533-74-4	Dazomet	8	120	Rabbit	0.067
555-89-5	Bis(4-chlorophenoxy) methane	22.5*	5800	Rat	0.0039
555-89-5	Bis(4-chlorophenoxy) methane	22.5	5800	Mouse	0.0039
2227-13-6	Tetrasul	0.5*	5010	Mouse	0.00010
2227-13-6	Tetrasul	0.5	3960	Rat	0.00013
2227-13-6	Tetrasul	0.5	500	Guinea pig	0.0010
2439-10-3	*n*-Dodecylguanidine acetate	60**	566	Rat	0.0071
2439-10-3	*n*-Dodecylguanidine acetate	60	1200	Mouse	0.0033
7681-93-8	Pimaricin	25*	2730	Rat	0.0092
7681-93-8	Pimaricin	25	1500	Mouse	0.017
7681-93-8	Pimaricin	25	1420	Rabbit	0.018
7773-06-0	Ammonium sulfamate	38**	3100	Mouse	0.012
7773-06-0	Ammonium sulfamate	38	3900	Rat	0.0097
25155-30-0	Sodium dodecylbenzenesulfonate	150**	1260	Rat	0.12
25155-30-0	Sodium dodecylbenzenesulfonate	150	2000	Mouse	0.075

Note. The NOEL values marked with a single asterisk are from Table 1, and the ones marked with a double asterisk are derived from Frawley (1967). The oral LD_{50} values are from the RTECS.

[a] Chemical Abstracts identification number.

In order to study the relationship between the pesticide ADIs and their acute oral toxicity as defined by LD_{50}s, we prepared a data base composed of the ADIs derived by the WHO/FAO expert committee for 96 pesticides (see FAO, 1984) and associated LD_{50} values from the RTECS data base. For each pesticide, we calculated the ratio(s) of its ADI (in mg kg^{-1} day^{-1}) to all of the oral LD_{50}s reported for small mammals for that pesticide. Figure 3 is a log–probability plot of the calculated ratios. The GM of the distribution is 3.6×10^{-5} day^{-1} and the GSD is 6.8 (n = 308 and $R(5) = 1.5 \times 10^{-6}$). One reason that the GM is so low is that the toxic response measured for many of the organophosphorus pesticides addressed was cholinesterase inhibition—a more sensitive measure of toxicity than other chronic endpoints such as depressed

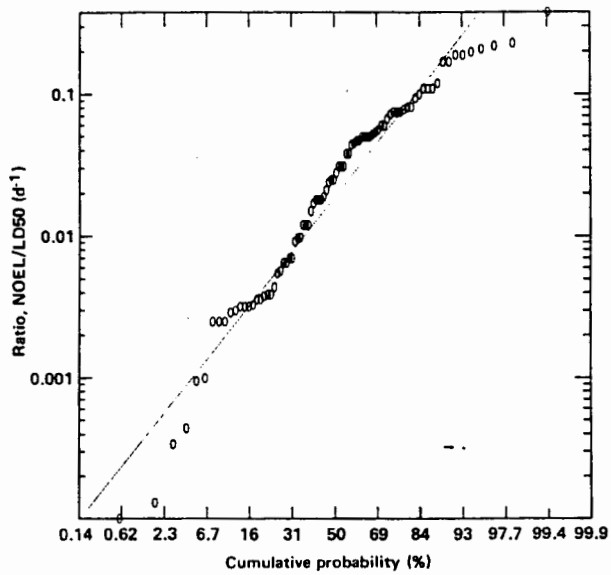

FIG. 2. Log–probability plot of the ratios of chronic NOELs (oral, rat) to oral LD_{50} values (small mammals) for 26 substances. The geometric mean is 0.018 with a geometric standard deviation of 5.8 (n = 85). Ratios are from Table 2.

body or organ weights. Consequently, ADI estimates based on toxicity studies using enzyme inhibition as a measure of toxicity would be lower than ADIs based on studies that address other toxic responses. To study this issue further, we obtained chronic

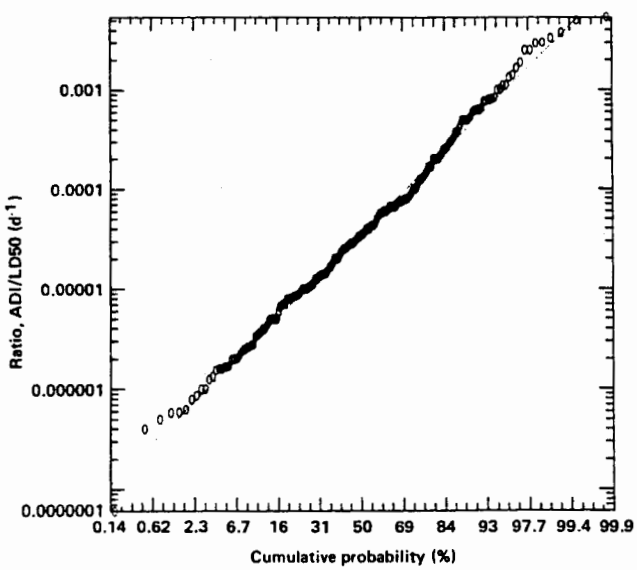

FIG. 3. Log–probability plot of the ratios of ADIs to oral LD_{50} values (small mammals) for 96 pesticides. The geometric mean is 3.6×10^{-5} with a geometric standard deviation of 6.8 (n = 308).

NOELs for nine organophosphorus pesticides (dimefox, malathion, formothion, phosalon, mevinphos, carbophenothion, chlorpyrifos, pirimiphos-methyl, and parathion) along with the lowest rat LD_{50} doses reported in Hayes (1982). The specific effect the chronic dose rates measured was cholinesterase inhibition. The GM of the NOEL/LD_{50} ratios was 3.5×10^{-3} day^{-1} with a GSD of 5.2. Interestingly enough, if we divide the GM of the ratios for the organophosphorus pesticides by the GM of the ratios calculated for the pesticide ADIs and oral LD_{50}s, we find that the ADI ratios are almost exactly 100 times lower—equivalent to the safety factor used in deriving the acceptable intakes.

COMPARISON OF TLV-DERIVED DOSE RATES AND ORAL LD_{50}s

The American Conference of Governmental Industrial Hygienists (ACGIH) has recommended air concentration threshold limit values (TLVs) for many substances used in industry (ACGIH, 1980). The TLVs can be converted to dose rates and then compared with LD_{50} values (see Handy and Schindler, 1976). Stokinger and Woodward (1958) proposed the use of TLVs as one means of calculating concentration limits of chemicals in water. If we assume complete absorption of a chemical by both inhalation and ingestion and an inhalation volume of 10 m^3 per 8-hr workday, the conversion of a TLV in mg/m^3, which is based on a 5-day workweek, to a continuous dose rate (DR) is calculated as

$$\mathrm{DR} = \mathrm{TLV}\left\{\frac{\mathrm{mg}}{\mathrm{m}^3}\right\} \times \frac{10^3\ \mathrm{m}}{\mathrm{day}} \times \frac{5\ \mathrm{days}}{1\ \mathrm{week}} \times \frac{1\ \mathrm{week}}{7\ \mathrm{days}} \times \frac{1}{70\ \mathrm{kg}}, \tag{4}$$

or

$$\mathrm{DR} = \mathrm{TLV} \times 0.1. \tag{5}$$

TLVs are designed to protect workers, and so it is inappropriate to assume that dose rates calculated from them would protect all members of the general public. Further, route-to-route extrapolation carries with it a number of uncertainties regarding the similarity of toxic effects between routes, including differential absorption between routes and detoxification or activation processes. With these caveats in mind, we calculated the ratios of the TLV-derived dose rates and the LD_{50}s (small mammals) for 250 substances. The GM of the ratios was 1.5×10^{-3} day^{-1} with a GSD of 7.4 (n = 583). The log–probability plot is shown in Fig. 4. In order to make the TLV-based dose rate applicable to the general population, we divided it by 10 to account for sensitive individuals (see Calabrese, 1985). The ratio corresponding to the 5th cumulative percentile of the distribution is 5.5×10^{-5} day^{-1} and so the adjusted ratio for the general population becomes 6×10^{-6} day^{-1}.

APPLICATIONS

Our analyses of the ratios of chronic NOELs to oral LD_{50} values indicate that lower-bound estimates of a chronic NOEL can be made by multiplying an oral LD_{50} (for small mammals) by a factor ranging from 5×10^{-4} to 1×10^{-3} day^{-1}. If a conservative, interim ADI is to be estimated, then conversion factors from approximately 5×10^{-6} to 1×10^{-5} day^{-1} could be adopted, based on a safety factor of 100. To test

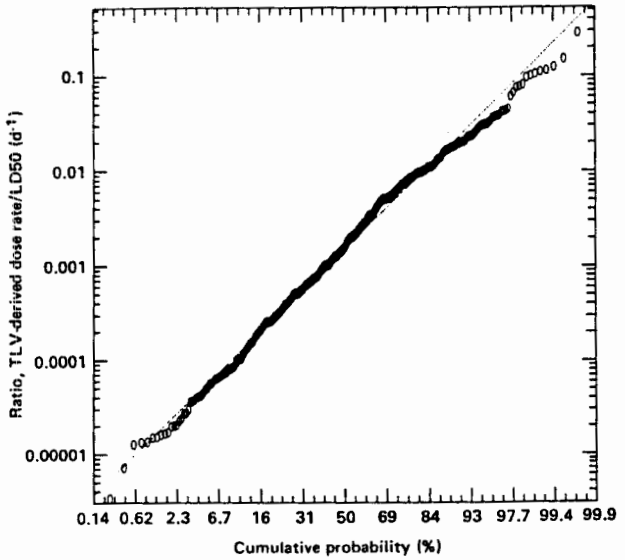

FIG. 4. Log-probability plot of the ratios of daily intakes (in mg (kg body wt)$^{-1}$), calculated from the TLVs for over 250 substances, to oral LD_{50} values for small mammals. The geometric mean is 1.5×10^{-3} with a geometric standard deviation of 7.4 (n = 583).

the performance of the extrapolation factors for making lower-bound estimates of ADIs, we derived ADIs from water-quality standards developed by the USEPA on 26 organic compounds (USEPA, 1980, 1985). Concentration limits in mg liter^{-1} were converted to an equivalent daily intake in mg kg^{-1} day^{-1} by adjusting for water intake, reference body weight, and fish intake. We also computed a lower-bound ADI (LB-ADI) for each compound by multiplying its oral rat LD_{50} by 1×10^{-5}. As a means of comparing the ADI values, we divided the LB-ADI by the derived ADI (Table 3). The results indicate that the LB-ADI routinely underestimates the derived ADIs; only 4 of the 26 ratios were greater than 1, with the largest being a factor of 8.5 higher. With a conversion factor of 5×10^{-6} day^{-1}, the largest ratio was only 4.25.

This methodology should only be applied to substances that are unlikely to be human carcinogens according to the weight of available toxicological evidence (see USEPA, 1984). However, it is conceivable that the approach could have been applied to substances that were eventually identified as possible human carcinogens through cancer bioassays completed on laboratory animals. What are the consequences of such unintended misapplications? To address this question, we calculated the probabilities of incurring cancer for lifetime intakes of eight chemicals at their estimated LB-ADI dose rates (Table 4). Cancer risks were calculated as the product of the LB-ADI we estimated for each substance and its carcinogenic potency to humans, as presented in Crouch and Wilson (1979). Potency values have units of kg day mg^{-1} and represent the probability of cancer per unit lifetime intake of a substance (in mg kg^{-1} day^{-1}). We used oral rat LD_{50}s to derive the LB-ADI estimates. The cancer probabilities of the LB-ADIs in Table 4 ranged from 9×10^{-6} for chloroform to 4×10^{-1} for 3,3′-dichlorobenzidine. Some of the calculated cancer risks presented in the table were higher than 10^{-4} to 10^{-7}, a range that might be used for establishing virtually safe dose rates of substances at contaminated sites. We note, however, that

TABLE 3

COMPARISON OF LOWER-BOUND ADI ESTIMATES AND ADI VALUES DERIVED FROM DRINKING-WATER LIMITS DEVELOPED BY THE USEPA (1980, 1985)

CASID	Substance	Oral LD_{50} (rat)[a] (mg kg^{-1})	LB-ADI[b] (mg kg^{-1} day^{-1})	Derived ADI (mg kg^{-1} day^{-1})	Source[c]	Ratio LB-ADI/ derived ADI
107-02-8	Acrolein	46	4.6×10^{-4}	0.0155	WQC	0.03
79-06-1	Acrylamide	170	1.7×10^{-3}	0.0002	SOC	8.5
108-60-1	Bis(2-chloroisopropyl) ether	240	2.4×10^{-3}	0.001	WQC	2.4
1563-66-2	Carbofuran	5.3	5.3×10^{-5}	0.005	SOC	0.01
510-15-6	Chlorobenzene	2,910	2.9×10^{-2}	0.125	SOC	0.2
84-74-2	Dibutyl phthlate	12,000	1.2×10^{-1}	1.25	WQC	0.1
95-50-1	*o*-Dichlorobenzene	500	5.0×10^{-3}	0.089	SOC	0.06
94-75-7	2,4-Dichlorophenoxyacetic acid	370	3.7×10^{-3}	0.01	SOC	0.4
117-81-7	Di-2-ethylhexyl phthalate	30,700	3.1×10^{-1}	0.612	WQC	0.5
84-66-2	Diethyl phthalate	9,000	9.0×10^{-2}	12.5	WQC	0.007
131-11-3	Dimethyl phthalate	6,900	6.9×10^{-2}	10	WQC	0.007
534-52-1	4,6-Dinitro-*o*-cresol	10	1.0×10^{-4}	0.00039	WQC	0.2
51-28-5	2,4-Dinitrophenol	35	3.5×10^{-4}	0.002	WQC	0.2
115-29-7	Endosulfan	18	1.8×10^{-4}	0.004	WQC	0.04
100-41-4	Ethylbenzene	3,500	3.5×10^{-2}	0.097	SOC	0.4
206-44-0	Fluoranthene	2,000	2.0×10^{-2}	0.0054	WQC	3.7
78-59-1	Isophorone	2,330	2.3×10^{-2}	0.15	WQC	0.2
72-43-5	Methoxychlor	5,000	5.0×10^{-2}	0.05	SOC	1
608-93-5	Pentachlorobenzene	1,080	1.1×10^{-2}	0.016	WQC	0.7
87-86-5	Pentachlorophenol	50	5.0×10^{-4}	0.03	SOC	0.02
100-42-5	Styrene	5,000	5.0×10^{-2}	0.2	SOC	0.2
95-94-3	1,2,4,5-Tetrachlorobenzene	1,500	1.5×10^{-2}	0.0052	WQC	2.9
108-88-3	Toluene	5,000	5.0×10^{-2}	0.29	SOC	0.2
71-56-6	1,1,1-Trichloroethane	10,300	1.0×10^{-1}	0.54	WQC	0.2
93-72-1	2,4,5-TP (Silvex)	650	6.5×10^{-3}	0.0075	SOC	0.9
1330-20-1	Xylene	5,000	5.0×10^{-2}	0.063	SOC	0.8

[a] The LD_{50} values are from the RTECS (Lewis and Sweet, 1984).
[b] Lower-bound ADIs are calculated as the product of the oral LD_{50} (mg kg^{-1}) and 1×10^{-5} day^{-1}.
[c] WQC, ADI derived from water-quality criteria developed by the USEPA (1980); SOC, ADI derived from concentration limits proposed by the USEPA (1985) for synthetic organic compounds.

the potencies in Table 4 can have large uncertainties (see Crouch and Wilson, 1979, for the derivations of the potencies). The potency value for 3,3′-dichlorobenzidine, for example, is an upper-bound estimate, and the real value could be significantly lower.

We also calculated the lifetime cancer risks of LB-ADIs for several organic compounds for which cancer potencies had been estimated by the Cancer Assessment Group (CAG) of the U.S. Environmental Protection Agency. The CAG used a linearized multistage model (see Crump and Crockett, 1985) with quantal dose–response data (i.e., tumor incidence at different dose levels) from animal bioassay studies to estimate an upper 95% confidence limit of the cancer potencies of a number of inorganic and organic substances. Many of the potencies developed by the CAG were summarized by Anderson (1983), and for our calculations we arbitrarily selected several of the CAG-assessed organic compounds that exhibited a wide range of potencies—from 4×10^5 kg day mg^{-1} for 2,3,7,8-tetrachlorodibenzodioxin to 0.01 kg day mg^{-1} for trichloroethylene. The LB-ADI values for the compounds (Table 5) were

TABLE 4

CANCER RISKS OF THE ACCEPTABLE DAILY INTAKES ESTIMATED FOR EIGHT SUBSTANCES

CASID	Substance	Oral LD_{50} (rat)[a] (mg kg^{-1})	LB-ADI[b] (mg kg^{-1} day^{-1})	Cancer potency[c] (kg day mg^{-1})	Probability of cancer[d]
75-01-4	Vinyl chloride	500	5×10^{-3}	0.02	1×10^{-4}
1162-68-8	Aflatoxin B_1	5	5×10^{-5}	200	1×10^{-2}
67-66-3	Chloroform	908	9.1×10^{-3}	<0.001	9×10^{-6}
71-43-2	Benzene	4894	4.9×10^{-2}	0.001	5×10^{-5}
92-87-5	Benzidine	309	3.1×10^{-3}	34	1×10^{-1}
107-13-1	Acrylonitrile	82	8.2×10^{-4}	<0.3	2×10^{-4}
106-93-4	Ethylene dibromide	108	1.1×10^{-3}	0.8	9×10^{-4}
91-94-1	3,3′-Dichlorobenzidine	7070	7.1×10^{-2}	≤5	4×10^{-1}

[a] The LD_{50} values are from the RTECS (Lewis and Sweet, 1984).
[b] Lower-bound ADIs are calculated as the product of the oral LD_{50} (mg kg^{-1}) and 1×10^{-5} day^{-1}.
[c] Cancer potencies are derived from human data (Crouch and Wilson, 1979).
[d] The lifetime probability of cancer is calculated as the product of the cancer potency and the estimated ADI.

calculated from oral rat LD_{50} values reported in the RTECS. Most of the lifetime cancer risks associated with the LB-ADIs were on the order of 10^{-3}.

CONCLUSIONS

The lack of long-term toxicity data for both humans and laboratory animals has made it difficult to establish ADIs for contaminants found in different environmental media or foods. In this paper we have reviewed existing methods and assumptions

TABLE 5

CANCER RISKS OF THE ACCEPTABLE DAILY INTAKES ESTIMATED FOR NINE SUBSTANCES

CASID	Substance	Oral LD_{50} (rat)[a] (mg kg^{-1})	LB-ADI[b] (mg kg^{-1} day^{-1})	Cancer potency[c] (kg day mg^{-1})	Probability of cancer[d]
56-23-5	Carbon tetrachloride	2800	2.8×10^{-2}	0.1	2.8×10^{-3}
67-66-3	Chloroform	908	9.1×10^{-3}	0.2	1.8×10^{-3}
57-74-9	Chlordane	283	2.8×10^{-3}	1.6	4.5×10^{-3}
75-35-4	1,1-Dichloroethylene	200	2×10^{-3}	1	2×10^{-3}
60-57-1	Dieldrin	40	4×10^{-4}	30	1.2×10^{-2}
1746-01-6	2,3,7,8-TCDD	0.0225	2.2×10^{-7}	4×10^{5}	9×10^{-2}
76-44-8	Heptachlor	40	4×10^{-4}	3	1.2×10^{-3}
127-18-4	Tetrachloroethylene	8850	8.8×10^{-2}	0.04	3.5×10^{-3}
79-01-6	Trichloroethylene	7193	7.2×10^{-2}	0.01	7.2×10^{-4}

[a] The LD_{50} values are from the RTECS (Lewis and Sweet, 1984).
[b] Lower-bound ADIs are calculated as the product of the LD_{50} (mg kg^{-1}) and 1×10^{-5} day^{-1}.
[c] Cancer potencies are derived from animal bioassay data (Anderson, 1983).
[d] The lifetime probability of cancer is calculated as the product of the cancer potency and the estimated ADI.

for establishing ADIs. We have also statistically analyzed the ratios of NOELs, ADIs, and daily intakes derived from TLVs to oral LD_{50} values for small mammals to define an application factor for use with an oral LD_{50} to estimate a daily intake that has a high probability (e.g., >95%) of being below a human toxic intake level. We suggest values from 5×10^{-6} to 1×10^{-5} day^{-1} for establishing interim ADIs from oral LD_{50} data (in mg kg^{-1}). The use of such factors is meant primarily for situations where there is a need to manage the health risk of exposures to contaminated soils, waters, crops, or other material at a particular site.

We recognize, though, that in some instances it might be desirable to use higher or lower conversion factors. The NOEL/LD_{50} ratios given in this paper can easily be reevaluated to establish different conversion factors. For example, $R(2.5)$ values could be used as the basis of alternative conversion factors rather than the $R(5)$ values that we chose. We also stress that this approach is not a method for making a "best estimate" of a substance's ADI; it does not indicate what noncarcinogenic effects are prevented; and finally, it is not meant to replace the toxicity testing of substances.

APPENDIX

The statistical analyses in this paper are based on the lognormal distribution. We also used log–probability plots to analyze graphically the distributional fits of data. In this Appendix we summarize the main features of this distribution and the associated probability plots.

To analyze the relationships between long-term and acute dose–response data, we developed sets of paired ratios of the chronic NOEL to oral LD_{50} for various chemicals. Each set of n ratios (denoted $R_1, R_2, \ldots, R_n$) is treated as a random sample drawn from a population of ratios that is assumed to be lognormally distributed (i.e., $\ln(R_i)$ is normally distributed). The geometric mean (GM) of the distribution is estimated by the following equation:

$$\mathrm{GM} = \exp\left(\frac{1}{n}\sum_{i=1}^{n} \ln R_i\right). \tag{A-1}$$

The variance of the population is estimated by the sample variance

$$s^2 = \frac{1}{n-1}\sum_{i=1}^{n} (\ln R_i - \ln \mathrm{GM}^2), \tag{A-2}$$

and the sample geometric standard deviation (GSD) is then calculated as GSD = $\exp(s)$. As an example, the five ratios 0.001, 0.004, 0.007, 0.0022, and 0.015 have a GM and GSD of 0.0039 and 2.83, respectively.

Once the GM and GSD have been estimated, the ratio (R) corresponding to any cumulative percentile (p) on the lognormal distribution can be calculated from

$$R(p) = \mathrm{GM} \times \mathrm{GSD}^{Z(p)}, \tag{A-3}$$

where $Z(p)$ represents the number of standard deviations from the mean to the specified cumulative percentile on a normal distribution. To calculate the value of $R(5)$ for the example data set above we need to know $Z(5)$. The Z values for different

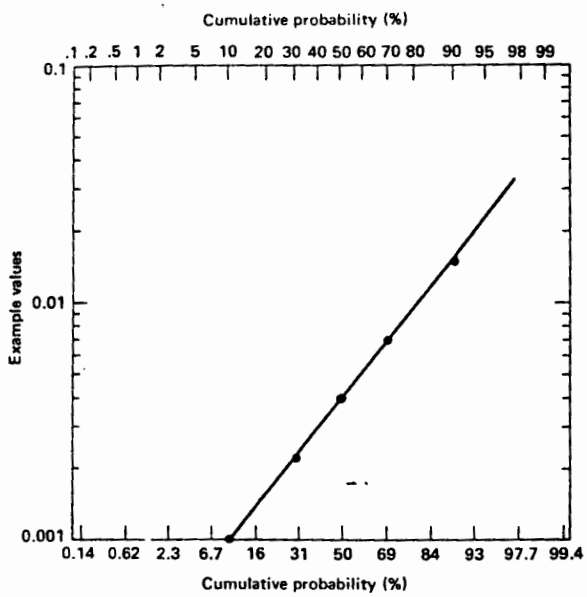

FIGURE 1A

percentiles on a standard normal distribution are tabulated in most statistical texts or handbooks. For $p = 5$, $Z(5)$ equals -1.645, and therefore from Eq. (A-3), $R(5)$ equals 7.0×10^{-4} (i.e., $0.0039 \times 2.83^{-1.645}$).

An alternative to using a table of the standard normal distribution function is to estimate $Z(p)$ from an empirical equation of the following form (Abramowitz and Stegun, 1964):

$$Z(p) = t - \left[\frac{(2.30753 + 0.27061t)}{(1 + 0.99229t + 0.04481t^2)}\right], \tag{A-4}$$

where

$$t = (\ln(1/q^2))^{1/2} \tag{A-5}$$

and

$$q = p/100 \qquad \text{if } p < 50 \tag{A-6}$$

$$q = (1 - p)/100 \qquad \text{if } p > 50. \tag{A-7}$$

For values of $p > 50$, $Z(p) = -Z(p)$.

One way of testing for the lognormality of a distribution of numbers is to analyze the data graphically through the use of a probability plot. With this procedure, the set of n numbers is rank-ordered from smallest to largest (i.e., $x_1, \leqslant x_2 \leqslant x_k \leqslant \cdots \leqslant x_n$) and a cumulative percentage is calculated for each number according to the formula $(k - 0.5)100/n$, where k refers to the rank of each number (see Hahn and Shapiro, 1967). For example, the cumulative percentages for the sample of numbers 0.001, 0.0022, 0.004, 0.007, and 0.015 would be 10, 30, 50, 70, and 90%. Each number is then plotted against its calculated cumulative percentile as shown in Fig. 1A. In the log–probability plot, the cumulative percentiles along the abscissa are arranged so that a straight line occurs if the data are distributed lognormally. Note that in this

particular probability plot, the cumulative percentiles are presented in two ways. On the bottom scale, the percentiles are spaced one-half standard deviation apart, and on the top scale, they are shown as they would appear on conventional log–probability paper. The geometric mean is at the 50th cumulative percentile and the geometric standard deviation can be calculated as the ratio of the 84th percentile value and the geometric mean (or, alternatively, the 50th divided by the 16th). The closer the data fall along a straight line, the closer is the fit to a lognormal distribution.

ACKNOWLEDGMENTS

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