

The assessment of the lethal properties of chemicals is usually associated with the acute toxicity phase of the safety evaluation process. Both the dosages and the exposure conditions that lead to the lethal response must be established in properly performed toxicological assessments. If humans are likely to come in contact with a particular chemical (voluntarily or involuntarily, accidentally or by design), one must know where the lethal range exists, if these individuals are to be protected. The safe handling of potentially lethal chemicals depends on adequate knowledge of lethal dosages and exposure conditions. The design of treatment procedures or specific antidotes to be used in the case of chemical intoxications depends on adequate knowledge of the lethal process. Questions raised regarding the precision one needs when performing the "LD50 test" are legitimate questions. On the other hand, questions dealing with the necessity of lethality assessment must be rational and in keeping with the responsibility of protecting society.

Large amounts of LD50 data have been accumulated; their utility has been questioned by a number of toxicologists. Toxicologists have deplored the misuse of the LD50 value as a kind of "biological constant". Variability is the rule in biology. This is also true when the biological response is death. LD50 values exhibit both interspecies and intraspecies variation. Furthermore, factors such as age, nutritional state and environmental conditions are known to effect lethal potency. Thus, the LD50 value, regardless of its precision, can never be regarded as a constant.

Toxicologists also realize that a precisely determined (in a statistical sense) LD50 value (with its 95% fiducial limits) is still only an estimate of the situation that may prevail in the population of species under test. In view of the well known interspecies variation, is great precision really necessary? Toxicologists are questioning the need for precision in the determination of LD50 values.

Toxicologists can obtain significant information on lethal potency and the process leading to lethality without the calculation of a precise LD50 value (one with very small 95% fiducial limits). It is important that the animals given lethal or near-lethal dosages be observed closely to gain knowledge of the functional and pathological alterations manifested by the animals. Questions regarding lethal potency can be resolved by the use of less precise statistical estimates than the ones traditionally employed to calculate LD50 values. Methods that require fewer numbers of animals can certainly be used to estimate an LD50 value or to yield a reasonable estimate of the dosages that border the lethal range. It is doubtful that much meaningful knowledge is lost by the application of such techniques in the safety evaluation process. On the other hand, a more complete examination of the animals employed to estimate lethal potency is to be encouraged. More can be done to obtain more meaningful biological data from animals used in lethality studies.

Questions have been raised about the utility of determining LD50 values in a number of different animal species. It must be remembered that one of the goals of the safety evaluation process is to provide data where one can extrapolate the findings observed in laboratory animals to the potentially adverse effects that might be observed in humans, domestic and wild animals, or animals in captivity exposed to the same chemicals. If the lethal dosage of the chemical is found to be similar in several species, extrapolation of toxicity to humans is more secure. If similar toxicological effects are observed in several animal species, it is probable that a common mechanism of action is involved in these species and probably will occur in humans as well. Thus, extrapolation to humans should be more reliable. However, if the lethal dosage is found to vary considerably in a number of different species, extrapolation to humans becomes tenuous. Such an observation indicates that the toxicity is species-related and that further investigations are needed to determine which species resembles the human. Thus, the determination of lethal potency in several species can have a marked influence on the confidence