SOCIETY OF TOXICOLOGY OF CANADA

APPENDIX 1

POSITION PAPER ON THE LD50 *

Historical Background

In the early part of the 20th Century, many medicinal agents in use were available as impure mixtures or extracts of biologically derived materials ("biologicals") rather than as pure chemical forms. It was often difficult to prepare uniform products by such processes, since the amount of "active" ingredient varied considerably from product to product. For several of these agents, the active *therapeutic potency* of the mixture could be correlated with the *lethal potency* of the mixture or extract. If one could calculate with precision the lethal potency of the material, one could indirectly assess the therapeutic potency of the same material. Effective therapeutic "dosages" for biologicals were often expressed in "units of activity" rather than in units of weight. Thus, quantitative methods were devised to assess lethal potency with precision, as a means of establishing standardization of biologically derived medicinal agents.

For statistical reasons, the median lethal dosage (LD50, the dosage estimated to kill 50% of the universal population of the species under test) was found to be the most accurate means of quantifying lethal potency. Furthermore, the mathematical precision of the statistically estimated LD50 was found to be directly related to the number of animals that were subjected to each test dose and the number of dosage levels (yielding values between 10% and 90% mortality) utilized to derive the lethality dose-response data. Thus, the LD50 was introduced in pharmacology and toxicology because of an important need in the estimation of potency of certain classes of medicinal agents.

A more general application of the LD50 determination followed. The quantification of lethality became widespread. The LD50 became one of the first quantifiable experimental tools available to the toxicologist. With such a tool, toxicologists could classify and compare chemicals according to their quantitative lethal potencies. Extrapolations to the potential dangers to humans due to acute exposures to relatively large amounts of chemicals were made on the basis of LD50 data derived in animals. These determinations were carried out in a variety of species and by different routes of administration.

Present Situation

One cannot discuss the utility of the so-called "LD50 test" in isolation. The assessment of life-threatening qualities of chemicals is an absolutely essential component of the safety evaluation process employed for the toxicological evaluation of diverse chemical substances, such as medicinal agents, cosmetics, food additives, pesticides, chemicals encountered in the household or the occupational setting, chemicals encountered in recreation or hobbycrafts, and chemicals dispersed in the environment. The toxicologist determines the potentially adverse effects that such substances might cause when various living species are exposed to chemicals under a variety of conditions. The species of greatest interest is of course the human being, but it is important to realize that many other mammalian and non-mammalian species can be the biological target of concern.

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