DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

September 9, 2003

Kenneth Olden, Ph.D.
Director
National Institute of Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, North Carolina 27709

Dear Dr. Olden:

Thank you for the opportunity to consider the recommendations of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) for two alternative toxicological test methods.

The first test recommendation, *in vitro* methods for assessing acute systemic toxicity, addresses the potential use of *in vitro* tests in determining the starting dose of agents in acute systemic toxicity tests. The recommendation is based upon (a) the *Report of the International Workshop on In Vitro Methods for Assessing Acute Systemic Toxicity*, NIH Publication No. 01-4499, and (b) the *Guidance Document on Using In Vitro Data to Estimate In Vivo Starting Doses for Acute Toxicity*, NIH Publication No. 01-4500.

The second test recommendation, a revised Up-and-Down Procedure (UDP) for determining acute oral toxicity, addresses the use of the UDP as a replacement for the conventional LD50 test to determine the acute oral toxicity hazard of chemicals. That recommendation is based on the report, *The Revised Up-and Down Procedure: A Test Method for Determining the Acute Oral Toxicity of Chemicals; Results of an Independent Peer Review Evaluation Organized by ICCVAM and NICEATM*, NIH Publication No. 02-4501.

I am pleased to provide you with this response from the Food and Drug Administration (FDA) to the first test recommendations developed and transmitted to ICCVAM agencies pursuant to Section 3(e)(4) of the ICCVAM Authorization Act of 2000 (P. L. 106-545).

FDA views the test methods for which ICCVAM recommendations were developed to have been appropriately validated according to ICCVAM procedures and considers the methods technically acceptable. The guidance document, NIH Publication No. 01-4500, describes how to use *in vitro* methods to estimate starting doses for acute oral toxicity animal tests. FDA agrees that such *in vitro* methods could help predict acute oral toxicity in animals and humans and could reduce the number of animals used for this testing. FDA supports activities (e.g., research, development, validation) that could advance the use of such *in vitro* predictive methods and will communicate that to its research and regulatory units. FDA also concurs with the conclusions of the Peer Review Panel (NIH Publication No. 02-4501) on the utility of the UPD as a substitute for the traditional LD50 test and acknowledges the potential reduction in animal usage.

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In meeting its regulatory mandate to promote and protect public health, FDA generally seeks toxicity information in order to assess a complete toxicological profile and determine a no observed effect level rather than lethality. Thus, FDA does not issue guidance documents for industry that specifically solicit data from LD50 or lethality tests. This is exemplified by the enclosed *Federal Register* notice of October 11, 1988, 53 FR 39650. Although FDA does not request acute lethality data or LD50 data, it recognizes that these ICCVAM-recommended alternative methods may have regulatory utility for those agencies that have a need for such data. The use of such methods should be encouraged to minimize the numbers of animals used and the extent of lethality.

FDA is fully committed to ICCVAM and the ICCVAM process, as shown by the energetic participation of representatives from each of FDA's research and regulatory centers and offices. FDA's dedicated ICCVAM members include Dr. Leonard Schechtman of the National Center for Toxicological Research (NCTR), Chair of ICCVAM; Dr. William Allaben (NCTR), Dr. Atin Datta (Office of Regulatory Affairs), Dr. Suzanne Fitzpatrick (Office of the Commissioner), Dr. David Hattan (Center for Food Safety and Applied Nutrition), Dr. Abigail Jacobs (Center for Drug Evaluation and Research), Dr. Devaraya Jagannath (Center for Veterinary Medicine), Dr. Raju Kammula of the Center for Devices and Radiological Health (CDRH), Dr. Richard McFarland (Center for Biologics Evaluation and Research), Dr. Martha Moore (NCTR), and Dr. Melvin Stratmeyer (CDRH).

The role played by ICCVAM is a unique one. FDA looks forward to its continuing involvement in important and far-reaching ICCVAM activities.

Sincerely,

Mark B. McClellan, M.D., Ph.D.
Commissioner of Food and Drugs

Enclosure

53 FR 39650

2 of 2 DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

AGENCY: Food and Drug Administration.

[Docket No. 86P-0224]

53 FR 39650

October 11, 1988

LD 50 Test Policy
ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is issuing this general statement of policy concerning the use of the "classical" LD 50 test by the agency. That test is not an FDA-required procedure for determining safety, and its use is not part of agency testing policy. This general statement of policy is being issued in response to a citizen petition (86P-0224/CP) submitted on May 15, 1986, by the American Society for the Prevention of Cruelty to Animals and other animal welfare organizations requesting FDA to issue a regulation or regulations concerning the subjects addressed by this policy and by other agency pronouncements on the "classical" LD 50 test.

ADDRESS: Comments on this general statement of policy should be submitted to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.
FOR FURTHER INFORMATION CONTACT: Richard P. Bradbury, Center for Veterinary Medicine (HFV-4), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4557.

TEXT: SUPPLEMENTARY INFORMATION: As a part of FDA's responsibility for administration of the Federal Food, Drug, and Cosmetic Act (the act), the agency is required to evaluate safety data submitted in support of applications for research or marketing permits for products regulated by FDA, including new drugs, biological products, new animal drugs, food additives, color additives, and certain medical devices intended for human use. Because it is unreasonable that people be exposed to substances whose safety has not been established, initial safety studies, by necessity, are conducted on animals.

Safety testing has evolved over several decades. Some useful tests have been modified and retained; other safety tests have become recognized as being inappropriate or unnecessary. An example of the latter category is the "classical" LD 50 test. The "classical" LD 50 test requires large numbers of animals (usually rodents), ranging from 60 to more than 120 animals per test substance. Large numbers of animals are needed to attain a statistically precise median number with 95 percent confidence limits. Normally, the "classical" test uses six dose levels with five animals per sex per dose level. Following the receipt of a dose, all animals are observed over a period of 14 days for signs of toxicity and other effects.

The "classical" LD 50 test became generally accepted during the 1930's for standardization of toxic plant and biological extracts and other chemicals. Subsequently, FDA incorporated it into its acute toxicology testing requirement for new compounds. When the "classical" LD 50 test became generally recognized as unnecessarily precise, the agency ceased to require such data. In 1985, the agency revoked its only regulatory requirement for that test (See the Federal Register of May 10, 1985 *(50 FR 19675))*, eliminating the requirement of the "classical" LD 50 test for batch comparison of three antitumor antibiotics and providing for nonbiological alternative means of assessing batches of these antibiotics.

For several years, FDA has initiated or participated in activities to clarify that the "classical" LD 50 test is not an FDA-required procedure for determining the safety of products regulated by the agency, and that its use is not part of agency testing policy. In 1983, the agency sponsored an Acute Studies Workshop (Ref. 1), which was open to the public, to discuss agency testing requirements including the uses of and the rationale for LD 50 tests in acute toxicity studies. The discussions at the workshop revealed that although FDA regulations require acute toxicity data for new compounds, they do not require that such data include the results of the "classical" LD 50 test.

In January 1984, the agency established a Steering Committee on Animal Welfare Issues to determine, among other things, whether FDA was indirectly perpetuating the use of the "classical" LD 50 test. The Committee's Final Report to the Commissioner, Food and Drug Administration (Ref. 2) discusses this issue in great detail. The report concludes that, in general, the agency does not directly or indirectly perpetuate the use of LD 50 determinations by statistically precise methods. The report also concludes that the "classical" LD 50 test was not required by FDA in quality control procedures (with the exception noted above), and that its use is not encouraged in agency testing policy for assessing the acute toxicity of new chemicals.

On May 15, 1986, in a citizen petition (86P-0224/CP) submitted by the American Society for the Prevention of Cruelty to Animals and 20 cosponsors, petitioners requested that FDA issue regulations to:

1. Require all FDA centers to promptly complete revisions of guideline test protocols for acute toxicity, making clear that the "classical" LD 50 test is not an FDA-required procedure for determining safety, and that data gathered from the "classical"LD 50 test will not be used or considered by FDA for determining safety of compounds, drugs, or products, after 1 year from the date of promulgation of the regulation or regulations;

2. Inform all persons submitting acute toxicity data to FDA that the "classical" LD 50 test is no longer considered scientifically necessary, wastes animal life, and is not required; and that the "classical" LD 50 test will not be used by FDA for determining safety after 1 year from the date of promulgation of the regulation or regulations;

3. Describe and define acceptable alternative testing methods to replace the "classical" LD 50 ; and

4. Prohibit FDA from using or conducting the "classical" LD 50 test within its own centers including, but not limited to, the National Center for Toxicological Research.

In a letter dated November 12, 1986 (Ref. 4), the agency denied the petition on the grounds that regulations are neither appropriate nor necessary to grant the relief requested. The agency denied petitioners' first and second requests insofar as they sought to bar FDA from accepting or reviewing data from the "classical" LD 50 test. Under the act, the agency may not refuse to accept or review data, including acute toxicity data from the "classical" LD 50 test, if they are relevant to a decision FDA must make on the safety of a regulated article. For example, the agency could not refuse to accept or review acute toxicity data showing a significant histopathological change in an internal organ resulting from the administration of one nonlethal dose of a noncorrosive compound. Thus, FDA cannot revise guideline test protocols or regulations to state that it will never use or consider any "classical" LD 50 data in making safety determinations. The agency stated, however, that it would publish in the Federal Register a notice explaining that the "classical" LD 50 test is not a required procedure for use in safety determinations within the agency. FDA further stated that it had been and would be imlementing most of the requests by policy statements, guideline modifications, and other publications, and in discussions with representatives of regulated industry, rather than by regulations.

The scientific community agrees that the "classical" LD 50 test is not necessary for determining acute toxicity. In agreement, FDA has adopted the policy that the "classical" LD 50 test is not a required toxicity study. The agency supports efforts to eliminate continued conduct of the "classifical" LD 50 test and to reduce the numbers of animals used in acute toxicity testing without sacrificing information necessary in the interest of human safety.

This policy will be further emphasized by the agency through its inclusion in the FDA Staff Manual Guide, in agency safety testing guidelines, in agency publications, and through discussions by agency officials and personnel with representatives of the regulated industry, as appropriate.

References

The following information has been placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, and may be seen by interested persons between 9 a.m. and 4 p.m. Monday through Friday.

1. "Report on Acute Studies Workshop Sponsored by the Food and Drug Administration," November 9, 1983.

2. "Final Report to the Commissioner, Food and Drug Administration, Agency Steering Committee on Animal Welfare Issues," August 15, 1984.

3. Citizen Petition 86P-0224.

4. Letter from John M. Taylor, FDA, to Barbara K. Pequet, American Society for the Prevention of Cruelty to Animals, November 12, 1986.

Interested persons may submit to the Dockets Management Branch (address above) written comments regarding this general statement of policy. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Dated: October 5, 1988.
John M. Taylor,

Associate Commissioner for Regulatory Affairs.
[FR Doc. 88-23504 Filed 10-6-88; 4:11 pm]

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