Taken from: ICCVAM. 2001. The Revised Up-and-Down Procedure: A test method for determining the acute oral toxicity of chemicals. NIH Publication 02-4501. National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina. (http://iccvam.niehs.nih.gov/docs/docs.htm#udp)

III. ICCVAM Test Method Recommendations

The ICCVAM agrees with the UDP Peer Review Panel that the revised UDP test guideline, with incorporation of the Panel's recommendations from the August 21st Panel Meeting, is acceptable as a substitute for the conventional LD50 test for acute oral toxicity (U.S. EPA OPPTS 870.1100, 1998; OECD, 1987) for the purpose of hazard classification and for obtaining certain information on acute toxicity. The ICCVAM also agrees with the Panel that the revised UDP Test Guideline will reduce and refine animal use. The ICCVAM concurs also with the other conclusions and recommendations of the Panel.

ICCVAM therefore recommends that the final revised UDP test guideline should: (1) replace the current OECD UDP test guideline (TG 425; OECD, 1998a) and (2) be used instead of the conventional LD50 test to determine the acute oral toxicity hazard of chemicals.

The ICCVAM also concludes:

1. The revised UDP performs appropriately and will result in a reduction in animal usage compared to the conventional LD50 test. The recommendation to use a starting dose level below the anticipated LD50 and to follow the OECD Guidance Document on Humane Endpoints (2000) will refine animal use by decreasing pain and distress.

2. The revised UDP is an appropriate method for generating a point estimate for the LD50 for use in hazard classification and in estimating a CI for the LD50 under specified circumstances. The revised UDP does not provide information about the slope of the dose-response curve for lethality. If other human health or ecological risk assessment information is desired, including hazard dose-response and slope information, a different test should be conducted.

3. Compared to the conventional LD50 procedure, the UDP will require additional time. However, it provides potential improvements in animal welfare and is the only alternative to OECD TG 401 that will generate a point estimate for the LD50 and an accompanying CI.

4. Compared to the conventional LD50 procedure, the UDP is computationally more complex. However, the UDP does provide increased statistical power with the use of sequential dosing. The publicly available statistical software will greatly simplify and facilitate efficient conduct of the UDP. The software calculates subsequent test dose levels, determines when testing is complete, estimates the LD50, and provides an appropriate and useful CI for the LD50.

5. Due to the reduction in the number of animals required when compared to the conventional LD50 test, the amount of test material needed will also be decreased.

6. The UDP may not be appropriate for chemicals causing delayed deaths (especially after five days).

7. Limit dose testing may be conducted at 2000 or 5000 mg/kg, depending on regulatory program needs.

8. For scientific purposes, the testing of three to five animals in the Limit Test is adequate. However, it is recognized that OECD stipulates utilizing five animals at 2000 mg/kg for all alternative acute toxicity methods as a way of harmonizing procedures.

9. Either sex can be used for the UDP. However, in the absence of information indicating males may be more sensitive, it is recommended that females be used based on available data showing females to be generally more sensitive.

10. Statistical methods are evolving rapidly, thereby providing reason to consider revisiting the UDP test design in the future.

11. A practicability assessment of the revised UDP should be considered.

12. *In vitro* data may be helpful in estimating an appropriate starting dose level for UDP studies. This approach may further reduce the number of animals needed, especially if the results indicate a Limit Test may be appropriate. Further guidance can be found in the "Guidance Document on Using *In Vitro* Data To Estimate *In Vivo* Starting Doses for Acute Toxicity", NIH Publication 01-4500 (ICCVAM, 2001a).

Adopted by ICCVAM:
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