

ESAC STATEMENT ON THE OECD ADOPTED TEST GUIDELINES FOR ACUTE ORAL TOXICITY TESTING

At its 27th meeting, held on 30–31 October 2007 at the European Centre for the Validation of Alternative Methods (ECVAM), Ispra, Italy, the non-Commission members of the ECVAM Scientific Advisory Committee (ESAC)¹ acknowledged the work carried out on the revision and adoption of three Test Guidelines (TGs), namely, TG 420 — Fixed Dose Procedure (FDP),² TG 423 — Acute Toxic Class Method (ATC),³ and TG 425 — Up and Down Procedure (UDP),⁴ as replacements for OECD TG 401,⁵ and unanimously endorsed the following statement:

On the grounds of all the supportive information, including the scientific publications of international validation studies of the ATC^{6–9} and the FDP,¹⁰ and the peer review panel reports of the UDP,¹¹ the ESAC considers the three methods as equivalent to scientifically validated.

The three methods were initially proposed as alternatives to the revised OECD TG 401 as reduction methods, which reduced the number of animals used per test from 25 with TG 401 to 5–9 with the alternative methods. However, in order to facilitate the international acceptance of the FDP, ATC and UDP, and eventually the deletion of OECD TG 401, the OECD organised a series of expert meetings, at which revisions to TGs 420, 423 and 425 were drafted. In 2000, the OECD Joint Meeting of the Chemical Committee and Working Party on Chemicals, Pesticides and Biotechnology, concluded that TG 401 could be deleted after adoption of the revised TGs 420, 423, and 425.¹²

At the 14th ESAC meeting (14–15 March 2000), the non-Commission Members of the ESAC endorsed a statement of concern about the progress within the OECD toward deletion of the acute oral toxicity (LD50) test, due to the USA's position on one of the alternative methods, TG 425 (UDP).

In December 2002, following the ratification of the OECD Council and a training workshop on the use of the three validated alternative methods, organised jointly by the US EPA and ICCVAM, TG 401 was finally deleted.

Common to the three methods is the administration of a single bolus dose by oral gavage, either by using a constant volume or a constant concentration. The test animals are young adult rats of one sex, unless otherwise indicated. The treated animals are observed over a 14-day period, at the end of which a necropsy is performed.

OECD TG 420 — Fixed Dose Procedure was proposed in 1984, as a new method for acute toxicity testing that replaced death of the animal as an endpoint with the observation of clear signs of toxicity developed at one fixed-dose level. An international validation study was sponsored by the Commission of the European Communities and the UK Government Department, under the patronage of the OECD, in 1988–89. The results of the study, published in 1990, showed that the method was able to produce consistent results, could rank the substances according to the EU system of classification,¹³ and could provide information on time of onset, duration and outcome of the signs required for risk assessment. The FDP procedure was adopted by OECD as TG 420 in 1992, as an alternative to TG 401, and in December 2001 as a replacement for TG 401.

OECD TG 423 — Acute Toxic Class Method was adopted in 1996 as an alternative for OECD TG 401, following the publication in 1995 of “the international validation study of the acute toxic class method (oral)”. The study was sponsored by the German Government, and was carried out under the patronage of the OECD. The results of the study showed that the method was a validated alternative to the TG 401, that it was able to rank substances in all commonly-used classification systems, in a similar or even better manner than TG 401, and that the number of the animals used was significantly reduced. In December 2001, the ATC method was adopted as a replacement for OECD TG 401.

OECD TG 425 — Up and Down Procedure, adopted in 1998 as an alternative to OECD TG 401, aims to estimate the LD50 value by testing individual animals sequentially, with the dose for each animal being adjusted up or down, depending upon the outcome for the previous animal. The US Environmental Protection Agency organised a technical Task Force to revise the UDP. In August 1999, the EPA asked ICCVAM to conduct an independent scientific peer review panel evaluation of the revised UDP. In 2001, the Peer Review Panel concluded that the revised UDP test guideline was acceptable as a substitute for the conventional LD50 test for acute oral toxicity (US EPA OPPTS 870.1100, 1998; OECD, 1987), for the purpose of hazard classification, and for obtaining certain information on acute toxicity, and that this would reduce and refine animal use. The final revised UDP Test Guideline was adopted by the OECD in December 2006 as a replacement for OECD TG 401.

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1. The ESAC was established by the European Commission, and is composed of nominees from the EU Members States, industry, academia and animal welfare, together with representatives of the relevant Commission services.

This statement was endorsed by the following members of the ESAC:

Mr Walter Pfaller (Austria)
 Ms Sonja Beken (Belgium)
 Ms Dagmar Jírová (Czech Republic)
 Mr Tõnu Püssa (Estonia)
 Mr Timo Ylikomi (Finland)
 Mr Manfred Liebsch (Germany)
 Mr Efstathios Nikolaidis (Greece)
 Ms Katalin Horvath (Hungary)
 Ms Annalaura Stamatì (Italy)
 Ms Maija Dambrova (Latvia)
 Mr Jan van der Valk (The Netherlands)
 Mr Dariusz Sladowski (Poland)
 Mr Constantin Mirciou (Romania)
 Ms Argelia Castaño (Spain)
 Mr Patric Amcoff (Sweden)
 Mr Jon Richmond (UK)
 Mr Carl Westmoreland (COLIPA)
 Ms Vera Rogiers (ECOPA)
 Ms Nathalie Alépée (EFPIA)
 Ms Maggy Jennings (Eurogroup for Animals)
 Mr Roman Kolar (Eurogroup for Animals)

The following Commission Services and Observer Organisations were involved in the consultation process, but not in the endorsement process itself:

Mr Thomas Hartung (ECVAM; chairman)
 Mr Jens Linge (ECVAM; secretary)
 Mr Juan Riego Sintes (ECB)
 Ms Susanna Louhimies (DG Environment, Unit D.1)
 Ms Barbara Mentré (DG ENTR, Unit F.3)
 Mr Nicholas Nicholson (IHCP)
 Mr Hajime Kojima (JaCVAM)
 Mr William Stokes (NICEATM, USA)
 Ms Marilyn Wind (ICCVAM, USA)

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5. OECD (1987). *OECD Guidelines for the Testing of Chemicals, No. 401. Acute Oral Toxicity* [deleted in 2001]. Paris, France: Organisation for Economic Cooperation and Development.
6. Diener, W. & Schlede, E. (1999). Acute Toxic Class Methods: Alternatives to LD/LC50 tests. *ALTEX* **16**, 129–134.
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