

ECVAM ongoing activities to meet the cosmetics 2009 deadline related to acute oral toxicity

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Acute oral toxicity is one of the areas of particular concern due to the 2009 deadline set by the 7th Amendment of the Cosmetics Directive (76/768/EEC), which introduces a testing and marketing ban of cosmetic products with ingredients tested on animals. The scientific community is putting considerable effort into developing and validating *in vitro* and *in silico* alternative methods in this area. The large Integrated Project ACuteTox, funded by the European Commission's 6th Framework Programme, started in 2005 with the aim of developing and pre-validating a testing strategy to fully replace acute oral toxicity testing *in vivo*. As a follow-up to the international validation study on the prediction of acute toxicity by cytotoxicity assays and taking into consideration the high prevalence of non-toxic substances in the New Chemicals Database (87% with LD50 > 2000 mg/kg) the European Centre for the Validation of Alternative Methods (ECVAM) has commissioned a validation study to test 57 industrial chemicals (30% cosmetic ingredients) to assess the predictive capacity of the validated 3T3/Neutral Red Uptake (NRU) cytotoxicity assay to discriminate between toxic/hazardous (LD50 < 2000 mg/kg) and non-toxic (LD50 > 2000 mg/kg) substances. Since the test was established on the robotic testing facility at the Institute for Health and Consumer Protection the automated version of the validated protocol is under evaluation using the same set of chemicals. A third laboratory in the US is assessing an abbreviated version of the validated 3T3/NRU protocol using the same chemicals, which is less costly and more industry-friendly. Despite all these efforts, it is unlikely that validated and regulatory accepted alternative methods and/or strategies for acute toxicity will be available in March 2009. Following the initiatives undertaken by the pharmaceutical industry to waive the acute oral toxicity testing before going to clinical studies by using information from other *in vivo* studies, ECVAM proposed an approach to identify non-toxic compounds (LD50 > 2000 mg/kg) using information from 28-days repeated dose toxicity studies. A Non Observed Adverse Effect Level threshold was set that allowed the correct identification of 63% of non-toxic compounds, while less than 1% of harmful compounds were misclassified as non-toxic. Since repeated dose toxicity studies can be performed *in vivo* until 2013, the proposed approach could have an immediate impact for the testing of cosmetic ingredients.