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Status of acute systemic toxicity testing requirements and data uses by U.S. regulatory agencies

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ABSTRACT

Acute systemic toxicity data are used by a number of U.S. federal agencies, most commonly for hazard classification and labeling and/or risk assessment for acute chemical exposures. To identify opportunities for the implementation of non-animal approaches to produce these data, the regulatory needs and uses for acute systemic toxicity information must first be clarified. Thus, we reviewed acute systemic toxicity testing requirements for six U.S. agencies (Consumer Product Safety Commission, Department of Defense, Department of Transportation, Environmental Protection Agency, Food and Drug Administration, Occupational Safety and Health Administration) and noted whether there is flexibility in satisfying data needs with methods that replace or reduce animal use. Understanding the current regulatory use and acceptance of non-animal data is a necessary starting point for future method development, optimization, and validation efforts. The current review will inform the development of a national strategy and roadmap for implementing non-animal approaches to assess potential hazards associated with acute exposures to industrial chemicals and medical products. The Acute Toxicity Workgroup of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), U.S. agencies, non-governmental organizations, and other stakeholders will work to execute this strategy.

Abbreviations: AEGL, Acute Exposure Guideline Level; CBER, FDA Center for Biologics Evaluation and Research; CDER, FDA Center for Drug Evaluation and Research; CDRH, FDA Center for Devices and Radiological Health; CFSAN, FDA Center for Food Safety and Nutrition; DoD, U.S. Department of Defense; DOT, U.S. Department of Transportation; FHSA, Federal Hazardous Substances Act; GHS, Globally Harmonized System of Classification and Labelling of Chemicals; ICCVAM, Interagency Coordinating Committee on the Validation of Alternative Methods; ICH, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use; OECD, Organisation for Economic Co-operation and Development; OPP, EPA Office of Pesticide Programs; OPPT, EPA Office of Pollution Prevention and Toxics; PPPA, Poison Prevention Packaging Act; TSCA, Toxic Substances Control Act

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1. Introduction

Acute systemic toxicity testing identifies the potential for a chemical to cause adverse effects distant to the entry point after exposure to a single dose. A number of regulatory agencies use acute systemic toxicity data for hazard classification and labeling of products to alert handlers and consumers to potential toxicity hazards. Data may also be used to determine acceptable human exposure limits, personal protective equipment needed for handling, and countermeasures that should be employed in the event of toxic exposures. In some cases, acute systemic toxicity data may be used to establish doses for longer-term studies, identify target organs for toxicity, and assess the hazard of accidental ingestions of chemical contaminants in food. The LD_{50} (the dose of a test substance that would be expected to kill 50% of the animals tested for oral or dermal routes) or LC_{50} (for the inhalation route) values from acute systemic toxicity tests in rodents are used to assign substances to toxicity categories that, in turn, determine the hazard warnings displayed on product labels.

The most commonly used acute systemic toxicity test designs are described in OECD test guidelines. While the LD_{50} test of 1981 used 30 or more animals per chemical, the current oral toxicity test designs, the up-and-down procedure, the acute toxic class method, and the fixed dose procedure, use five to nine animals (OECD, 2001, 2002a, 2002b, 2008). While the up-and-down procedure can yield an LD_{50} value, the acute toxic class method and the fixed dose procedure classify chemicals in acute toxicity hazard categories based on LD_{50} ranges. The fixed dose procedure uses evident toxicity rather than lethality as an endpoint. The acute dermal systemic toxicity test guideline, which previously used at least 20 animals, has recently been revised to use fewer than 10 animals (OECD, 2017a). While the acute inhalation test guideline of 1981 used at least 30 animals, the current test guideline uses at least 20 animals (OECD, 2009a). The inhalation toxicity test guideline for the acute toxic class method uses six to 12 animals per test (OECD, 2009c) while the test guideline for the fixed concentration procedure uses five to 10 animals per test (OECD, 2017b). Limit tests, which can be employed for substances expected to be of low toxicity, test three to six animals at the maximum required doses (based on regulatory needs) for each exposure route. In practice, a recent retrospective analysis of agrochemical formulations estimated that acute oral, dermal, and inhalation testing could require as few as 61 animals or as many as 112 animals for the main tests (Corvaro et al., 2016).

Alternative methods are defined as methods or approaches that reduce or replace the use of animals in acute systemic toxicity testing and may include the use of existing data (*in vivo* human or animal, or *in vitro*), *in silico* modeling (e.g., quantitative structure-activity relationships [QSAR]), or *in vitro* testing (e.g., cell-based assays). A workshop on “Alternative Approaches for Identifying Acute Systemic Toxicity: Moving from Research to Regulatory Testing” (Hamm et al., 2017) reviewed the state-of-the-science of non-animal alternatives for this testing and explored ways to facilitate the implementation of alternatives. The workshop, cosponsored by the U.S. National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), the PETA International Science Consortium Ltd., and the Physicians Committee for Responsible Medicine, was held in Bethesda, MD, on September 24–25, 2015, and attended by more than 60 experts from academic, industry, government, and nongovernmental organizations.

Workshop participants recommended development of a manuscript that would:

- Clarify U.S. federal agency needs for acute systemic toxicity information so that test method developers can identify opportunities for non-animal method development;
- Share experiences among federal agencies about how they are currently satisfying their need for acute toxicity data and what steps they are taking to reduce and replace animal use;
- Provide information on the status of existing alternative methods as a starting point for future method development, optimization, and validation efforts;
- Inform the development of a national strategy and roadmap for assessing the effects of acute chemical and medical product exposures on humans using human-predictive approaches that do not use animals.

Here, in response to that recommendation, we review and summarize six federal agencies' requirements (Consumer Product Safety Commission, Department of Defense, Department of Transportation, Environmental Protection Agency, Food and Drug Administration, Occupational Safety and Health Administration) for and uses of acute oral, dermal, and inhalation toxicity data. To aid in achieving the objectives of the workshop recommendation, we address the following specific questions regarding each agency's use of acute toxicity data:

1. What standards, test guidelines, or guidance documents are used for acute systemic toxicity testing?
2. Is there a specific requirement for animal data or is there flexibility to use alternative approaches?
3. What information from a non-animal approach will satisfy the needs for acute toxicity data (i.e., for what purposes are acute toxicity data used)? Do agencies want the alternative approach to predict rodent responses (which for most applications must then still be imperfectly translated to a human response), or instead to predict human responses?
4. What is the path to regulatory acceptance of non-animal approaches for determining acute toxicity? How often are alternative approaches accepted by agencies?

2. Overview of U.S. regulatory testing requirements for acute systemic toxicity

Acute systemic toxicity data are used by the following six U.S. agencies to satisfy various research and regulatory functions designated to them under federal laws: the Consumer Product Safety Commission (CPSC); the Department of Defense (DoD); the Department of Transportation (DOT); the Environmental Protection Agency (EPA); the Food and Drug Administration (FDA); and the Department of Labor's Occupational Safety and Health Administration (OSHA). These agencies are members of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), which was established in 2000 as a permanent committee under NICEATM (42 U.S.C. 285l-3, 2000).

ICCVAM provides a forum through which member agencies can evaluate and facilitate the use of new and revised toxicity test methods. One of ICCVAM's priorities is the regulatory implementation of non-animal methods for acute systemic toxicity testing, which is the primary focus of the ICCVAM Acute Toxicity Workgroup (Casey et al., 2015). In coordination with regulators, industry, and non-governmental organizations, the workgroup provides the technical expertise to inform ICCVAM's development of a national strategy and roadmap for incorporating new approaches into safety testing of chemicals and medical products in the United States. The specific goal is regulatory acceptance of *in vitro* and *in silico* approaches for assessing the effects of acute chemical exposures on human safety (Lowit, 2016).

Table 1 lists the ICCVAM member agencies that require or use acute systemic toxicity information for product labeling, safety assessment, or other purposes, along with the type of substances regulated and relevant legislation. Some regulations do not call for the submission, use, or consideration of acute systemic toxicity data specifically, but indicate that toxicity testing or safety assessments must be performed. The FDA Center for Drug Evaluation and Research is not included in this review because it does not request nonclinical acute systemic toxicity data. Although a guidance document for industry on single dose