A Brief History of Alternative Toxicity Testing in the U.S. Government

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FDA (retired)

June A. Bradlaw, Ph.D. 1935-2008

Tox21 Twenty Years Before There Was a Tox21 - 1986

FUNDAMENTAL AND APPLIED TOXICOLOGY **6,** 598–606 (1986)

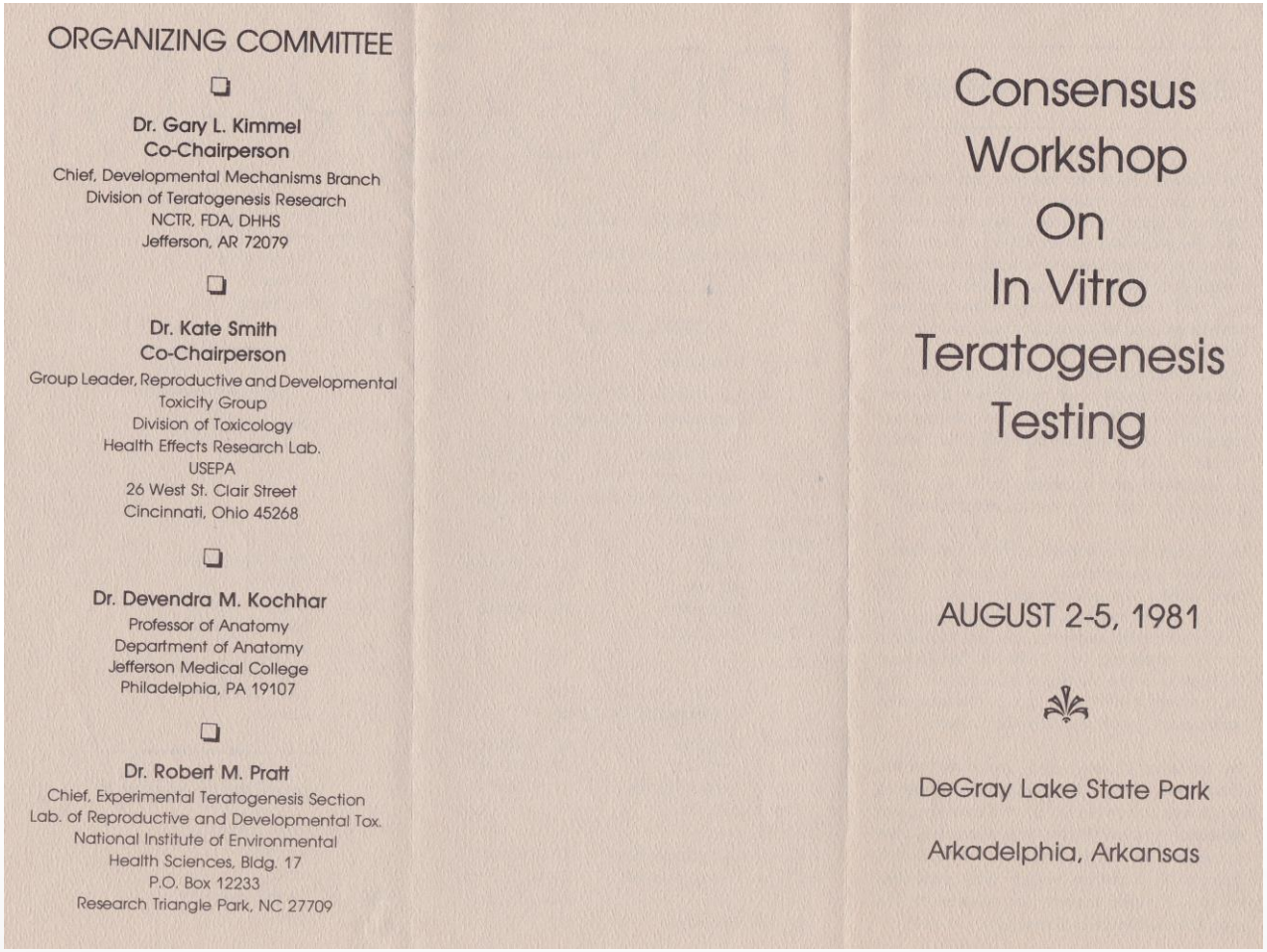
Evaluation of Drug and Chemical Toxicity with Cell Culture Systems[1]

JUNE A. BRADLAW

Division of Toxicology, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, D.C. 20204

Evaluation of Drug and Chemical Toxicity with Cell Culture Systems. BRADLAW, J. A. (1986). *Fundam. Appl. Toxicol.* **6,** 598–606. Approaches to the evaluation of drug and other chemical toxicity with mammalian cell culture systems are designed to enhance the predictability of animal models. Identification of toxic agents by *in vitro* screening tests and studies of mechanisms through which chemicals induce critical lesions at the cellular and subcellular levels help to make those predictions sooner and perhaps single out those target sites and chemicals of most concern.

In Vitro Teratogenesis NCTR - 1981



ORGANIZING COMMITTEE

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Consensus
Workshop
On
In Vitro
Teratogenesis
Testing

AUGUST 2-5, 1981

DeGray Lake State Park

Arkadelphia, Arkansas

NCTR 1981 – Conference Proceedings

TERATOGENESIS, CARCINOGENESIS, and MUTAGENESIS

volume 2 • number 3/4 • 1982

IN VITRO TERATOGENESIS TESTING

Smith et al. List Published in Teratog. Carcinog. Mutagen. 1983

- First effort to identify a consensus “gold standard” list of test agents to be used for validation of alternative teratogenicity assays
- Follow up conference sponsored by FDA/NCTR held in Charlotte, NC in 1989 where committee chaired by NCTR Director Bern Schwetz is tasked with developing a new list

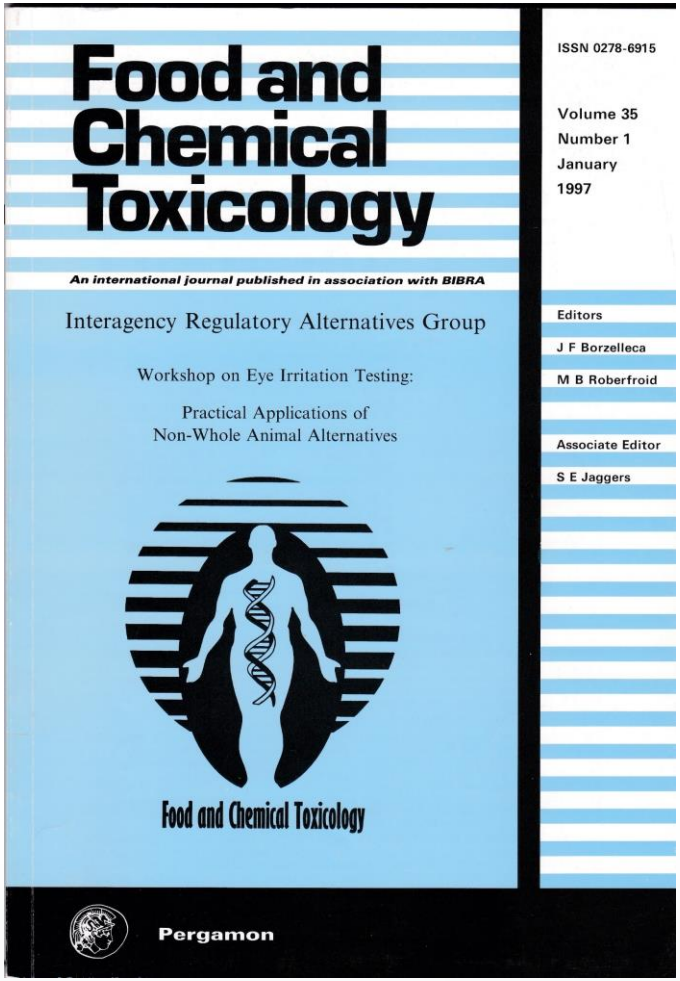
IRAG 1989

- Interagency Regulatory Alternatives Group
- *Ad hoc* committee of scientists from three federal agencies, FDA, EPA, CPSC
- Was first effort in the U.S. government to establish a process for regulatory acceptance of alternative assays
- AGT Past President Sid Green was an integral part of the IRAG process

U.S. Army 1992

- First U.S. Army biennial conference on Alternatives held at Edgewood, MD
- AGT Past President Harry Salem is the key organizer of these conferences

IRAG Workshop November 1993



NIH Revitalization Act of 1993

- Directed the NIH/NIEHS to establish an applied toxicological research and testing program
- Directed NIEHS to: “(a) establish criteria for the validation and regulatory acceptance of alternative testing methods, and (b) recommend a process through which scientifically validated alternative methods can be accepted for regulatory use”

NIH Revitalization Act of 1993 (continued)

- Creation of an *ad hoc* Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
- Consisted of representatives from 15 Federal regulatory and research agencies

Draft FDA/CFSAN Redbook II 1993

Draft

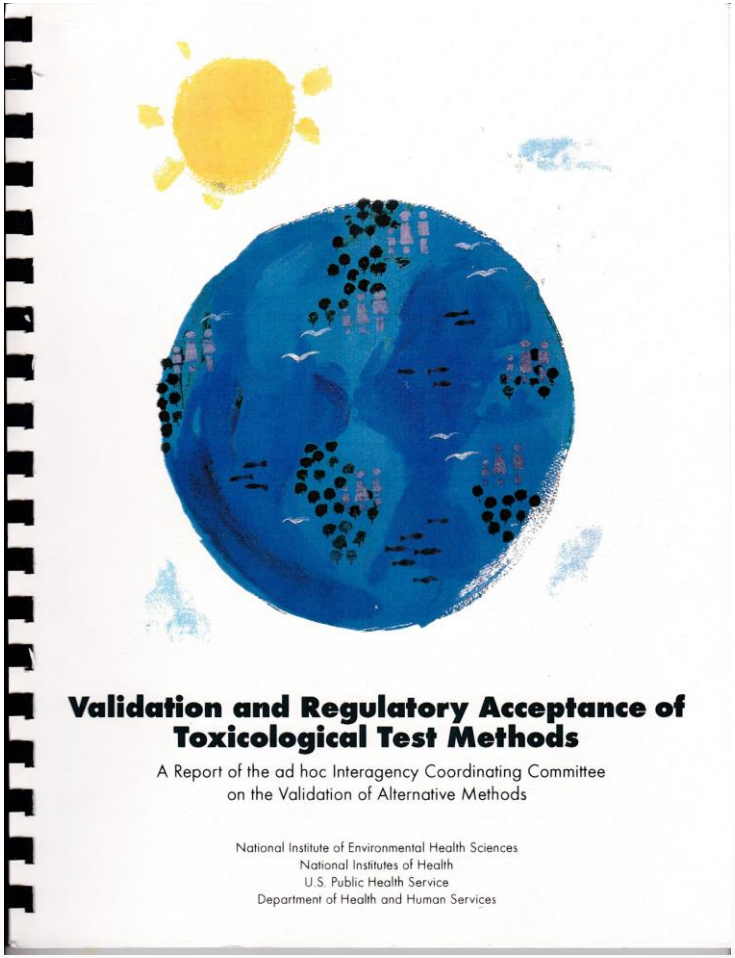
VII F. Advances in the Development of Alternatives to Whole Animal (Vertebrate) Testing

Because animal experimentation has become an emotional issue, it is important to recognize the growing impact of *in vitro* toxicology on the practice of toxicology. Although the field is often termed "alternative," experimental models have been applied to the three "R's" of Russel and Burch:[1] to replace animal models, to reduce the number of animals used, or to refine test methods to minimize stress and suffering to animals.

This section is not intended as a guideline but serves to identify a future direction in methodology. In the context of this document, "alternatives to whole animal (vertebrate) experimentation" refers to *in vitro* tests for potential toxicity that substitute for or replace *in vivo* (whole animal) studies. "*In Vitro*" literally means "in glass", and is interpreted to mean "in a test tube" or "outside of the body".[2] Alternative tests include short-term tests using isolated cells, tissues, and organs and studies involving mathematical modelling, epidemiology, or the use of human volunteers; short-term tests for genetic toxicity (see Chapter IV C 1) are excluded.

Note: This chapter is not included in Redbook 2000

ICCVAM Report 1997



ICCVAM Authorization Act of 2000

- Made ICCVAM permanent
- Codified participating agencies: (1) Agency for Toxic Substances and Disease Registry; (2) Consumer Product Safety Commission; (3) Department of Agriculture; (4) Department of Defense; (5) Department of Energy; (6) Department of the Interior; (7) Department of Transportation; (8) Environmental Protection Agency; (9) Food and Drug Administration; (10) National Institute for Occupational Safety and Health; (11) National Institutes of Health; (12) National Cancer Institute; (13) National Institute of Environmental Health Sciences; (14) National Library of Medicine; (15) Occupational Safety and Health Administration; (16) Any other agency that develops, or employs tests or test data using animals, or regulates on the basis of the use of animals in toxicity testing.

International Society of Regulatory Toxicology and Pharmacology 2005

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Regulatory Toxicology and Pharmacology xxx (2006) xxx–xxx

Regulatory Toxicology and Pharmacology

www.elsevier.com/locate/yrtph

Report of an ISRTP Workshop: Progress and barriers to incorporating alternative toxicological methods in the U.S.

Richard A. Becker [a,*], Christopher J. Borgert [b], Simon Webb [c], Jay Ansell [d], Sara Amundson [e], Christopher J. Portier [f], Alan Goldberg [g], Leon H. Bruner [h], Andrew Rowan [i], Rodger D. Curren [j], William T. Stott [k]

[a] *American Chemistry Council, Arlington, VA, USA*
[b] *Applied Pharmacology and Toxicology, Inc., Gainesville, FL, USA*
[c] *The Procter and Gamble Company, Strombeek-Bever, Belgium*
[d] *Yves Rocher North America, Inc., Exton, PA, USA*
[e] *Doris Day Animal League, Washington, DC, USA*
[f] *National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA*
[g] *Johns Hopkins University, Center for Alternatives to Animal Testing, Baltimore, MD, USA*
[h] *The Gillette Company, Needham, MA, USA*
[i] *The Humane Society of the United States, Washington, DC, USA*
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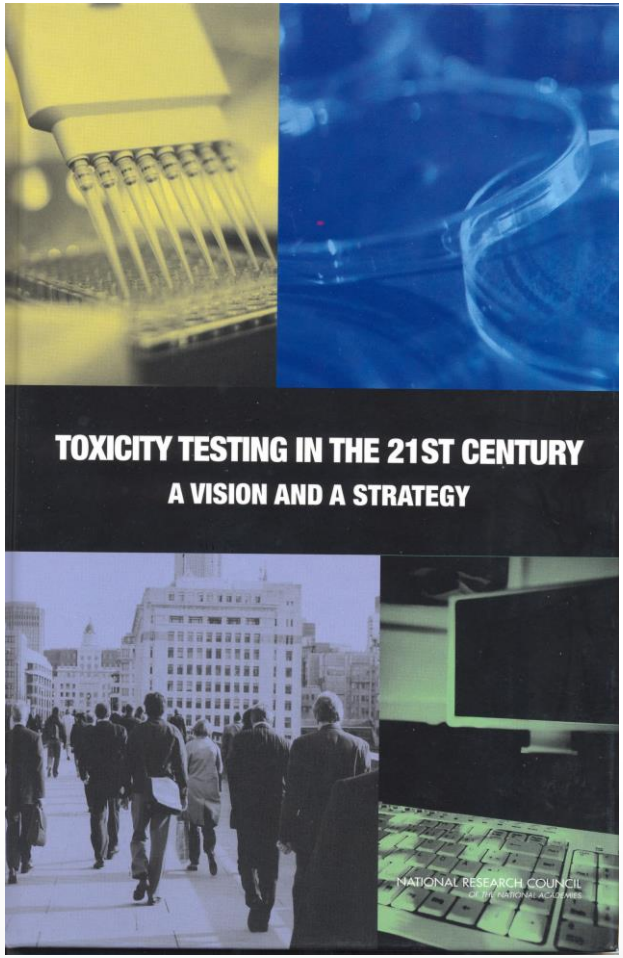
Received 6 June 2006

National Academies of Science Report 2007



ToxCast (U.S. EPA) 2007

- Established a repository of chemicals for testing in high-throughput screening assays
- More recently, established a repository for high-throughput screening data

Tox21 Multi-agency MOU 2010

Place: Sofitel Washington DC Lafayette Square, 806 15th Street, NW., Washington, DC 20005.

Contact Person: Eliane Lazar-Wesley, PhD, Health Scientist Administrator, Office of Extramural Affairs, National Institute on Drug Abuse, NIH, DHHS, Room 220, MSC 8401, 6101 Executive Boulevard, Bethesda, MD 20892–8401, 301–451–4530, *elazarwe@nida.nih.gov*.

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

Name of Committee: National Institute on Drug Abuse Special Emphasis Panel 2010 NIDA Translational Avant-Garde Award Interviews (DP1).

Date: July 27, 2010.

Time: 8:30 a.m. to 6 p.m.

Agenda: To review and evaluate grant applications.

Place: Westin Grand, 2350 M Street, NW.,

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA–2010–N–0004]
[FDA–225–10–0015]

Memorandum of Understanding: Food and Drug Administration and the National Institutes of Health, National Institutes of Environmental Health Sciences, National Toxicology Program; and the National Institutes of Health, National Human Genome Research Institute, National Institutes of Health, Chemical Genomics Center; and the Environmental Protection Agency, Office of Research and Development

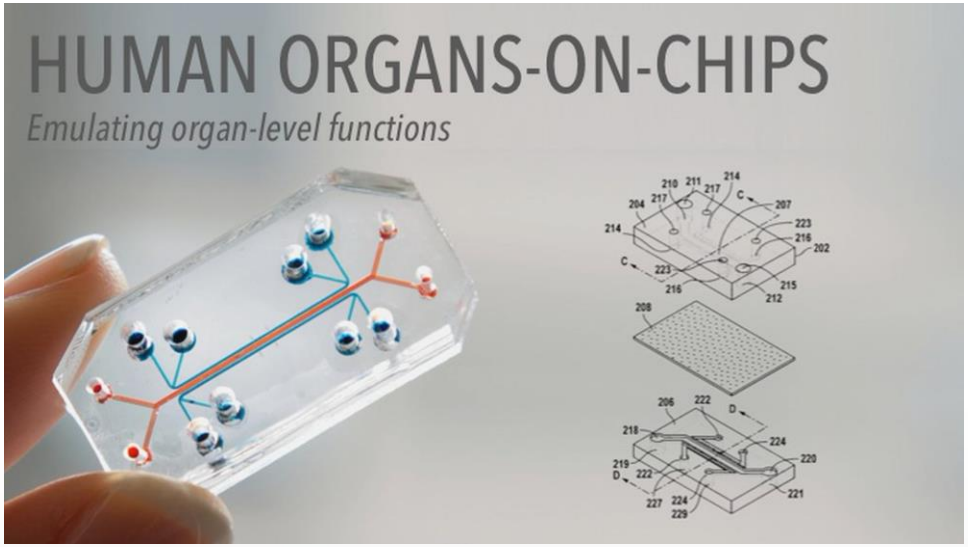
AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

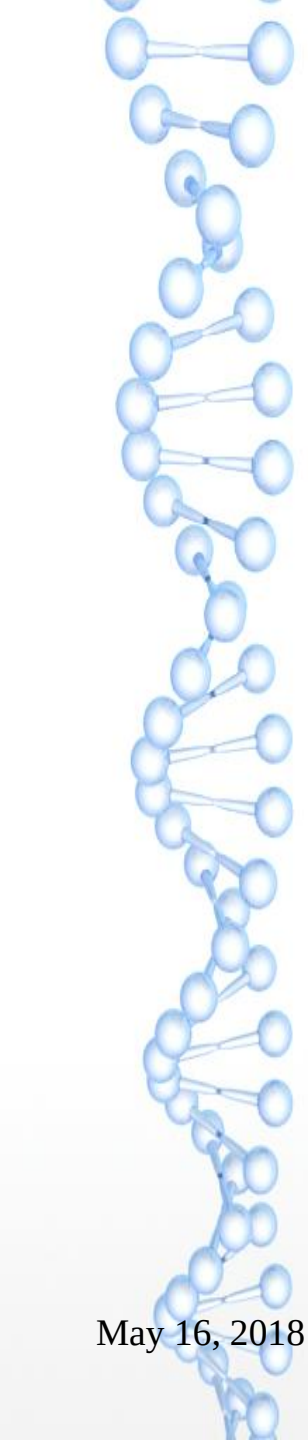
MOU is the exploration of high throughput screening (HTS) assays and tests using phylogenetically lower animal species (e.g., fish, worms), as well as high throughput whole genome analytical methods, to evaluate mechanisms of toxicity. Ultimately, the data generated by these new tools is to be provided to risk assessors to use in the protection of human health and the environment. The goals of this MOU are to investigate the use of these new tools to: (1) Identify mechanisms of chemically induced biological activity, (2) prioritize chemicals for more extensive toxicological evaluation, and (3) develop more predictive models of in vivo biological response. Success in achieving these goals is expected to result in test methods for toxicity testing that are more scientifically and economically efficient and models for risk assessment that are more

FDA CRADA with Emulate 2017

- Leverages “organ-on-a-chip” technology
- This collaborative effort has been cited in Science, Nature, and other prominent technical and non-technical journals



From: https://wyss.harvard.edu/technology/human-organs-on-chips/



Thank you.