

ICCVAM Workshop Series on Best Practices for Regulatory Safety Testing: Assessing the Potential for Chemically Induced Allergic Contact Dermatitis (ACD)

Introduction and Public Health Impact of Chemically Induced ACD

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Welcome to NIH: The Nation's Biomedical Research Agency

- Mission: Science in the pursuit of fundamental knowledge about the nature and behavior of living systems, and the application of that knowledge to extend healthy life and to reduce the burdens of illness and disability
- 27 Institutes and Centers
- 31.2 \$ Billion Budget (FY10)
 - 83% awarded in 50,000 grants
 - 3,000 universities, medical schools, international research organizations
 - All 50 states and 90 countries



What is NICEATM?

- The National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods
- A Center of the U.S. NTP, headquartered at the National Institute of Environmental Health Sciences (NIEHS), NIH, DHHS
 - NIEHS is one of the 27 NIH Institutes and Centers
 - NIEHS is the headquarters for the NTP, which coordinates toxicology testing programs across the federal government
 - Located in Research Triangle Park, North Carolina
- Administers and provides scientific support for the **Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)**
- Conducts international validation studies



What is ICCVAM?

- The Interagency Coordinating Committee on the Validation of Alternative Methods was established by the NIEHS in 1997
- Members represent the heads of 15 U.S. Federal regulatory and research agencies
- Duties include:
 - Advising on test method development and validation
 - Conducting technical reviews of new safety testing methods
 - Transmitting formal recommendations to Federal agencies
 - Promoting regulatory acceptance of valid methods
 - Fostering national and international harmonization
- Began as ad hoc committee, 1994
- Standing committee, 1997
- ICCVAM Authorization Act of 2000
 - Permanent committee under NICEATM



ICCVAM
NICEATM



The 15 ICCVAM Member Agencies

Regulatory Agencies (7)

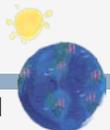
- Consumer Product Safety Commission
- Department of Agriculture¹
- Department of the Interior¹
- Department of Transportation
- Environmental Protection Agency¹
- Food and Drug Administration¹
- Occupational Safety and Health Administration

Research Agencies (8)

- Agency for Toxic Substances and Disease Registry
- National Institute for Occupational Safety and Health-CDC
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Library of Medicine
- National Institutes of Health
- Department of Defense
- Department of Energy



¹ Also has research component



ICCVAM's Mission¹

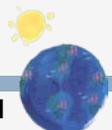
- *To facilitate and promote development, validation and regulatory acceptance of new and revised regulatory test methods that*
 - *Reduce, refine, and replace the use of animals in testing*
 - *Maintain and promote scientific quality and the protection of human health, animal health, and the environment*
- Critical role in translating science from the bench to public health practice
- Together with NICEATM, provides the translation infrastructure for validation, evaluation, and regulatory acceptance



¹Adopted by ICCVAM February 2004. All of ICCVAM's activities are grounded in the U.S. Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training. <http://grants.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples>

NICEATM and ICCVAM Progress

- 37 alternative safety testing methods accepted/endorsed by U.S. regulatory agencies since 1999
- Recommendations for R&D, translation, and validation activities to further advance methods
- International guidances
 - Five new or updated test guidelines for ocular safety and ACD testing adopted by OECD 2009-2010
- International partnerships:
 - International Cooperation on Alternative Methods (ICATM): Japan, Europe, Canada, and Korea



NICEATM-ICCVAM Five-Year Plan: 2008-2012



- Areas of Emphasis:
 - Priority test method activities with the greatest 3Rs impact
 - ACD testing
 - Ocular safety testing
 - Biologics testing
 - Acute toxicity testing
 - Application of new science and technology
 - Partnerships
 - International cooperation

Available at <http://iccvam.niehs.nih.gov/docs/5yearplan.htm>

Why Evaluate the Skin Sensitization Potential of Chemicals and Products? - 1

- ACD is a significant public health problem
 - ACD accounts for more than 7 million outpatient visits each year¹
 - 12% (8.9 million) of children in the United States had ACD in 2009²
 - More than 3700 substances have been identified as contact allergens³



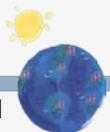
ACD photo – Medline Plus⁴

¹Allergy Principles and Practice. 5th Edition, 1998. See http://www.aafa.org/display.cfm?id=9&sub=30#_ftn4

²National Center for Health Statistics. 2010. Available at <http://www.cdc.gov/nchs/fastats/allergies.htm>

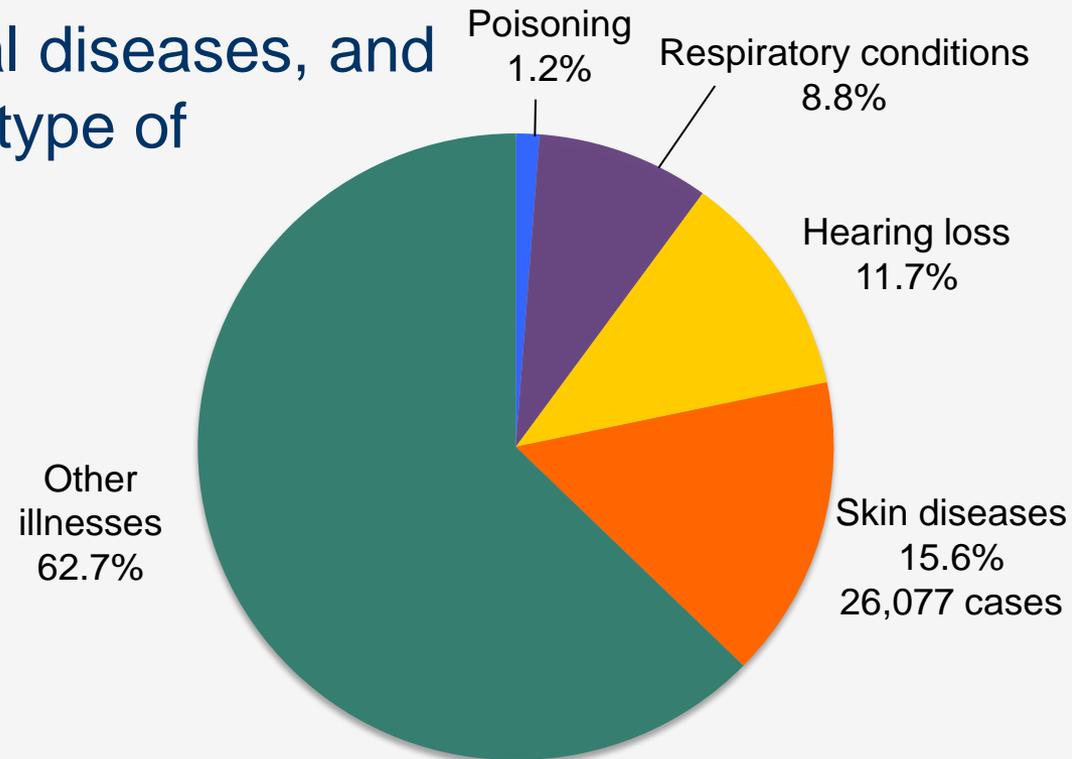
³Ann Allergy Asthma Immunol. 2006. 97:S1-S38. See <http://www.aaaai.org/media/statistics/allergy-statistics.asp#skinallergies>

⁴NLM. 2008. Available at <http://www.nlm.nih.gov/medlineplus/ency/imagepages/2387.htm>



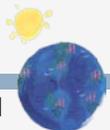
Why Evaluate the Skin Sensitization Potential of Chemicals and Products? - 2

- Occupational skin diseases, including ACD, comprise at least 15% of all reported occupational diseases, and is the most common type of occupational illness¹
 - 20% of occupational skin dermatitis cases are ACD²



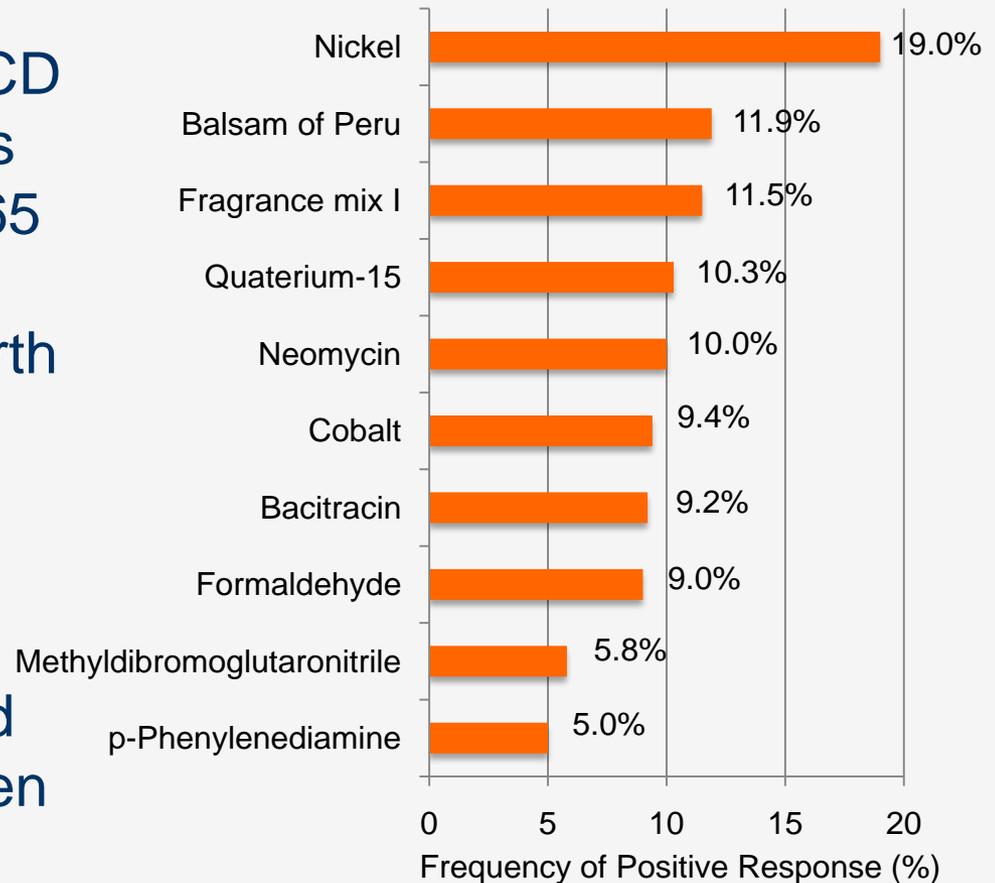
¹ BLS. 2010. Available at <http://www.bls.gov/iif/oshwc/osh/os/charts2009/charts.htm#Figure3>

² NIOSH. 2010. Available at <http://www.cdc.gov/niosh/topics/skin/>



Common Allergens

- Most frequent positive ACD reactions in 4454 patients with suspected ACD for 65 substances tested in 13 dermatology centers (North American Contact Dermatitis Group 2005-2006)
- American Contact Dermatitis Society named neomycin Contact Allergen of the Year in 2010



¹Zug et al. 2009. Patch-test results of the North American Contact Dermatitis Group 2005-2006. *Dermatitis* 20: 149-160.



Why Regulate Products That Cause ACD?

- Prognosis may be poor¹
 - Thus, prevention of ACD is crucial
- Regulatory authorities worldwide require testing for ACD potential and appropriate hazard labeling to prevent exposure



¹Hogan et al. 1990. The prognosis of contact dermatitis. J Am Acad Dermatol 23: 300-307.

Legislation and Regulatory Protocol Requirements for Skin Sensitization Testing

Agency	Regulated Products	Legislation	Regulatory Protocol Requirements
United States			
CPSC	Consumer products	FHSA	No specific protocol; Animal Testing Policy – 49 FR 22522 (1984)
EPA	Chemicals	TSCA	40 CFR 716
	Pesticides	FIFRA	40 CFR 158
FDA	Pharmaceuticals	FD&C Act	No specific protocol; 21 CFR 314.50 requires all available safety information to market new drugs
	Cosmetics		No specific protocol: 21 CFR 740.10 requires substantiation of safety or otherwise label before marketing
OSHA	Chemicals	OSHA Act of 1970	No specific protocol: 20 CFR 1910.1200 requires labeling of hazards
Europe			
EU	Chemicals and mixtures	Council Directive 67/548/EEC Commission Directive 2001/59/EC Directive 2001/58/EC	Method B.6 in Council Directive 96/54/EC (Skin sensitization) ¹ Method B.42 in Council Directive 2004/73/EC (Skin sensitization: Local Lymph Node Assay) ¹

Abbreviations: CFR = Code of Federal Regulations; CPSC = U.S. Consumer Product Safety Commission; EC = European Commission; EEC = European Economic Community; EPA = U.S. Environmental Protection Agency; FDA = U.S. Food and Drug Administration; FHSA = Federal Hazardous Substances Act; FIFRA = Federal Insecticide, Fungicide and Rodenticide Act; EU = European Union; OPPTS = Office of Prevention, Pesticides, and Toxic Substances; OSHA = U.S. Occupational Safety and Health Administration; TSCA = Toxic Substances Control Act.

¹Council Directives that contain the testing methods of Annex V to Council Directive 67/548/EEC.



Guidelines for Skin Sensitization Testing

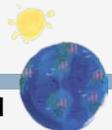
Agency/Group	Guideline	Test Requirements/Description
EPA	Health Effects Test Guidelines OPPTS 870.2600 Skin Sensitization (2003)	The Office of Chemical Safety and Pollution Prevention provides guidelines for skin sensitization testing that harmonizes EPA test guidelines under TSCA and FIFRA. Includes LLNA, guinea pig maximization test (GPMT), and Buehler test (BT)
ISO	ISO 10993-10 (2010)	Harmonized test methods described in <i>Biological Evaluation of Medical Devices: Tests for Irritation and Sensitization</i> Includes LLNA, GPMT, and BT
OECD	TG 406 (1992)	<i>Skin Sensitisation</i> Includes GPMT and BT
	TG 429 (2010)	<i>Skin Sensitization: Local Lymph Node Assay</i>
	TG 442A (2010)	<i>Skin Sensitization: Local Lymph Node Assay: DA</i>
	TG 442B (2010)	<i>Skin Sensitization: Local Lymph Node Assay: BrdU-ELISA</i>

Abbreviations: BT = Buehler test; EPA = U.S. Environmental Protection Agency; FIFRA = Federal Insecticide, Fungicide and Rodenticide Act; GPMT = guinea pig maximization test; LLNA = murine local lymph node assay; ISO = International Organization for Standardization Organization; OECD = Organisation for Economic Co-operation and Development; OPPTS = Office of Prevention, Pesticides, and Toxic Substances; TG = Test Guideline.



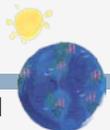
Why Seek Alternatives to Traditional ACD Tests?

- **Potential to Reduce** animal use: one of the four most commonly required chemical safety tests
 - Requires more animals per test than any other acute safety test
- **Potential to Refine** animal use: positive results in guinea pig tests (guinea pig maximization test and Buehler test) involve painful skin reactions
- **Potential to Replace** animal use:
 - To address pending EU ban on the use of animals for safety testing of cosmetic ingredients and products in the EU: 2013 deadline for skin sensitization; just extended
 - To incorporate advances in science and technology to develop more accurate and faster safety testing methods



Timeline for ICCVAM LLNA Evaluations - 1

- 1997** LLNA nominated to ICCVAM for evaluation as a stand-alone test method for ACD testing by Drs. Gerberick, Kimber, and Basketter
- Sep 1998** Public LLNA Peer Review Panel Meeting
- Apr 2002** OECD adopted Test Guideline (TG) 429 Skin Sensitisation: Local Lymph Node Assay
- Mar 2003** EPA Health Effects Test Guidelines OPPTS 870.2600 Skin Sensitization
- Jan 2007** Nomination from the Consumer Product Safety Commission (CPSC) for LLNA review activities: LLNA applicability domain, reduced LLNA, nonradioactive LLNA methods, and use of LLNA to determine relative potency
- Mar 2008** Public LLNA Peer Review Panel meeting
- 2008** NICEATM receives additional information and data relevant to the LLNA applicability domain and nonradioactive methods

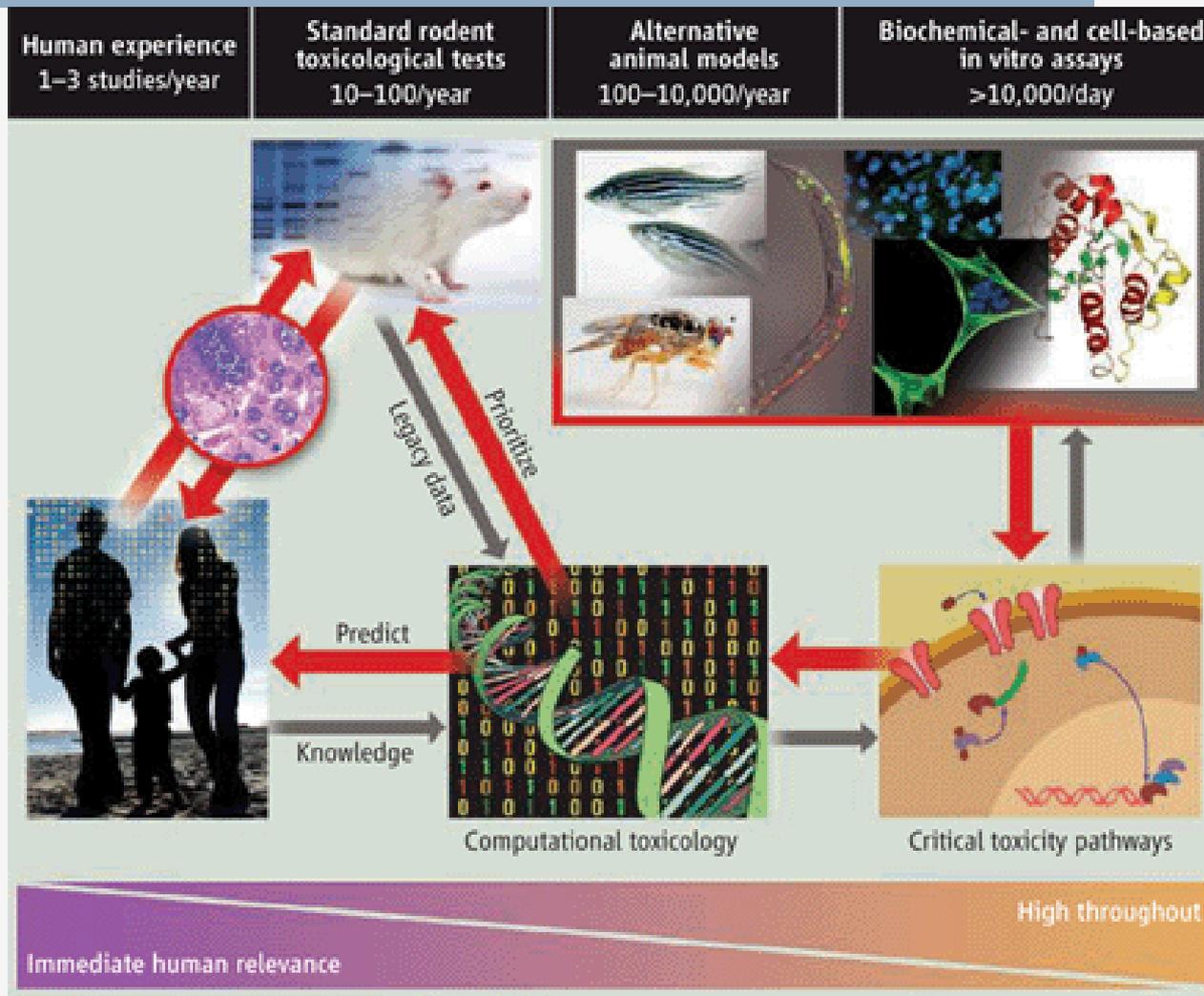


Timeline for ICCVAM LLNA Evaluations - 2

- Apr 2009** Second Public LLNA Peer Review Panel meeting
- Sep 2009** Publication of Recommended Performance Standards for the LLNA and rLLNA Test Method Evaluation Report
- Oct 2009** OECD Expert Consultation Meeting on proposed updates to TG 429 and new TG proposals for two nonradioactive LLNA methods
- Jun 2010** Publication of Test Method Evaluation Reports for the LLNA applicability domain, LLNA: DA, and LLNA: BrdU-ELISA
- Jul 2010** OECD adopts revised TG 429 for the LLNA and two new nonradioactive protocols, TG 442A for the LLNA: DA and TG 442B for the LLNA: BrdU-ELISA
- 2011** Publication of Test Method Evaluation Report for use of the LLNA to determine potency categorization of chemicals

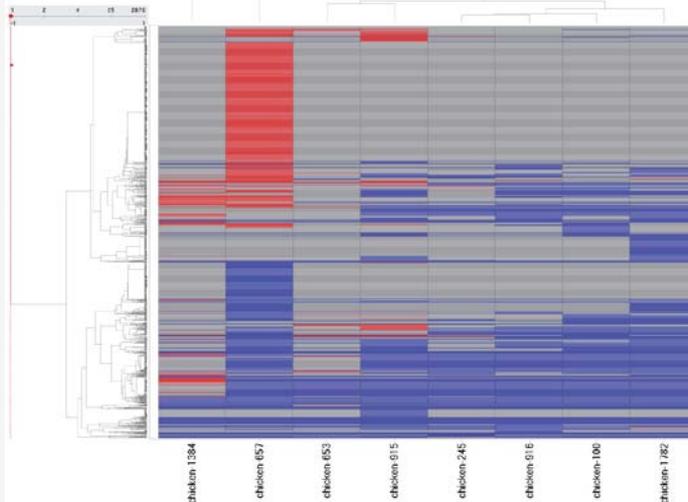


Integrating New Science and Technologies

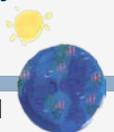


Collins FS, Gray GM, Bucher JR. 2008. Transforming Environmental Health Protection. *Science* 319: 906-07

Application of New Science and Technology: High Throughput Screening



- NIH (NIEHS and NHGRI), EPA, and FDA are collaborating to use the NIH Chemical Genomics Center: “Tox 21”
 - Robotic quantitative high-throughput *in vitro* screening (HTS)
 - ToxCast™: 600 assays
- Using 10,000 chemicals used to identify toxicity pathways
- NICEATM-ICCVAM Involvement
 - >900 ICCVAM reference chemicals nominated for inclusion
 - ACD hazard testing data for many of these reference substances
 - ICCVAM considers and nominates *in vitro* assays for HTS
 - Expect *in vitro* test methods incorporating pathway-based biomarkers to emerge for safety testing



NIH Regulatory Science Program

- Interagency partnership between National Institutes of Health and the U. S. Food and Drug Administration (FDA) to foster regulatory science
- Specialized and inter-disciplinary area of biomedical research that serves to generate new knowledge and tools for assessing experimental therapies, preventives, and diagnostics
- Accelerate development and use of new tools, standards and approaches to efficiently develop products and to more effectively evaluate product safety, efficacy and quality
- Four grants announced September 27, 2010
 - \$9.34M US awarded over 3 years
 - Co-funded by NIH Common Fund¹ and U.S. FDA

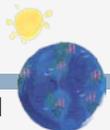


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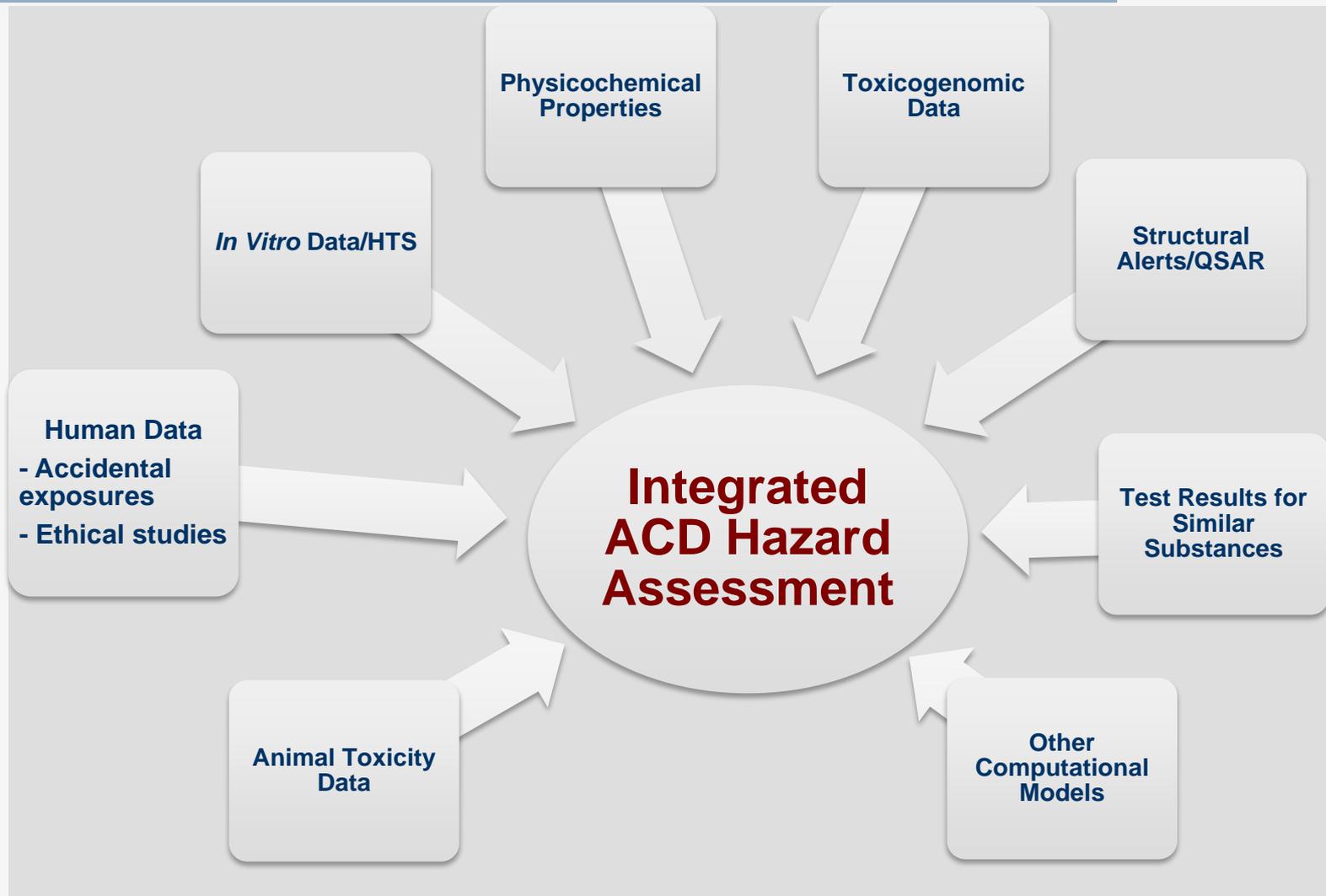


Margaret Hamburg, M.D.
FDA Commissioner

¹<http://commonfund.nih.gov/regulatoryscience/>



Future Integrated Strategies: Potential Sources of Data and Information



Source: Stokes WS, Wind M. 2010. Validation of innovative technologies and strategies for regulatory safety assessment methods: challenges and opportunities. *ALTEX* 27:87-95.



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