National Academies
Committee to Review Advances Made to the IRIS Process[1]
DELS-BEST-17-03
Feb 1-2, 2018

We are pleased that the National Academies is reviewing the progress made by the EPA Integrated Risk Information System (IRIS).[2] The IRIS program identifies and characterizes the potential human health impacts of chemicals and determines "acceptable" levels of exposure to a chemical or substance. IRIS assessments provide hazard characterizations and dose-response assessments for cancer and non-cancer outcomes. While IRIS assessments are not regulations, they are used by regulators – at the EPA, by local, state and regional governments, and around the world – to set health-based standards for chemicals in air, water, food or soil.

IRIS assessments are also used to inform non-regulatory initiatives pursued by forward-thinking and sustainable chemical and product manufacturers, fabricators, and retailers. For example, reliable, transparent, credible scientific IRIS chemical assessments are relied upon by members the American Sustainable Business Council (ASBC), which represents over 250,000 businesses, local and state chambers of commerce, and investors. In comments to the National Academies during its 2014 review of the IRIS program, ASBC pointed out that, "A safer marketplace helps to dispel consumer fears, spurs innovation, decreases legal liability, and increases shareholder value." [3]

The 2014 National Academies Committee review was very supportive of the IRIS program's successes in addressing previous NAS process concerns: "Overall, Review of EPA's Integrated Risk Information System Process finds that substantial improvements in the IRIS process have been made, and it is clear that EPA has embraced and is acting on the recommendations in the NRC formaldehyde report. The recommendations of this report should be seen as building on the progress that EPA has already made."[4]

It should be noted that no committee of the National Academies has ever disagreed with the scientific conclusions of IRIS assessments, but only the adequacy of the process and presentation of information.

Since the 2014 NAS review, the IRIS program has made significant continued progress towards implementing a systematic review process consistent with national and global efforts, including the systematic review developed by EPA's sister agency, the NIEHS National Toxicology Program, Office of Health Assessment and Translation (OHAT) and the Navigational Guide (NavGuide), a method developed by academic experts. Both the OHAT and NavGuide systematic review methods are designed to effectively address the full range of data relevant to environmental health assessments (e.g., human, animal, and in vitro/mechanistic studies), and include tools to assess potential bias of studies.

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[1] More information at: https://www8.nationalacademies.org/cp/projectview.aspx?key=49904

[2] http://dels.nas.edu/Upcoming-Workshop/Review-Advances-Made/AUTO-2-82-78-I

[3] ASBC comments to National Academies Joint Meeting: Committee to Review the Formaldehyde Assessment in the NTP 12th RoC and the Committee to Review the Styrene Assessment in the NTP 12th RoC, March 2013. Available here: https://www.nrdc.org/sites/default/files/hea_13032002a.pdf

[4] National Research Council. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. https://doi.org/10.17226/18764

More recently, a review of the IRIS program generated praise from EPA's own Science Advisory Board (SAB): "The program has fully adopted the principles of systematic review, and incorporated automation and publicly available software platforms to modernize the process...it is now standard practice for the [IRIS] program to engage stakeholders in an early scoping and problem formulation phase, thereby allowing stakeholders to provide important input at the very beginning of the process." [5]

While we support the progress of the IRIS program, and urge this Committee to do the same, we have two concerns: (1) the politicization of the IRIS program by shifting it from the office of science and research programs to the office of toxics programs; (2) the potential for over-confidence and therefore inappropriate use of data from alternative test methods. Our concerns are discussed below, for the Committee's consideration.

(1) We are concerned that EPA may shift the IRIS program out of the Office of Research and Development (ORD) and into the Office of Chemical Safety and Pollution Prevention (OCSPP) which regulates pesticides and toxic chemicals. This shift would move it from a science and research office to a regulatory policy office under the management of Nancy Beck, a chemical industry lobbyist prior to her recent political appointment at EPA. The chemical industry's opposition to the IRIS program is well-documented and long-standing.[6] Dr. Beck's previous foray into developing risk assessment guidelines was a failure, as evidenced by the NAS conclusion that the draft government-wide risk assessment bulletin which she authored while at the Office of Management and Budget (OMB) was "fundamentally flawed" and the unprecedented recommendation for its withdrawal (NAS 2007).[7]

We are concerned that EPA may assimilate the IRIS program within the TSCA program, as directed in the Senate FY2018 Appropriations Bill (see Minority response).[8] We are opposed to this move as it would narrow IRIS's potential scope and thwart its purpose. The TSCA Program is focused on developing risk evaluations (risk assessments) of industrial chemicals to comply with the requirements of that one law. The IRIS program, however, is intended to function more broadly (and independently) to produce information on chemicals to be used for a variety of purposes and actions pursuant to numerous statutes and other federal, state and local bodies. Policy makers and the public would be robbed of the benefits of the IRIS program if it simply subsumed into the risk assessment process for implementing TSCA.

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[5] Science Advisory Board comments on EPA's response to recommendations on the Integrated Risk Information System. September 1, 2017. EPA-SAB-17-008. Available at: https://yosemite.epa.gov/sab/SABPRODUCT.NSF/RSSRecentAdditionsBOARD/A9A9ACCE42B6AA0E8525818E004CC597/$File/EPA-SAB-17-008.pdf

[6] The Chemical Industry Delay Game: How the Chemical Industry Ducks Regulations of the Most Toxic Substances. Jennifer Sass and Daniel Rosenberg. NRDC report. 2011. Available at https://www.nrdc.org/resources/chemical-industry-delay-game

[7] Available at http://www8.nationalacademies.org/onpinews/newsitem.aspx?RecordID=11811

[8] November 2017 Senate Approps Bill for FY2018. Available at https://www.appropriations.senate.gov/imo/media/doc/FY2018-INT-CHAIRMEN-MARK-BILL.PDF

See Minority response here: https://www.appropriations.senate.gov/news/minority/summary-fy2018-interior-environment-appropriations-chairmans-mark-released

Furthermore, the OCSPP is now developing TSCA review methods that are contrary to those recommended by the NAS in its previous review of the IRIS program (NAS 2014).[9] We are particularly concerned about the potential under TSCA to adopt a policy of favoring industry-sponsored studies by establishing a preference for guideline studies and for studies conducted using Good Laboratory Practice (GLP) standards. Such a preference has long been promoted by chemical industry scientists and consultants.[10] The US Food and Drug Administration (FDA) first issued GLP standards in 1978 after a criminal investigation into chemical testing labs found evidence of widespread fraud and misconduct.[11] EPA's GLP rules for chemical regulatory tests followed shortly thereafter. While GLP requirements have been helpful in ensuring that commercial labs retain better records and not commit rampant fraud, they are not an accurate measure of study quality per se. The 2014 NAS IRIS review report pointed out the limitations of GLP standards, including that they fail to prevent flawed, unreliable or biased-by-design studies.[12] Simply put, GLP should not be relied upon to support public health decisions and placing the IRIS program under the direction of EPA's toxics office makes such an approach more likely.[13]

(2) As noted above, we are also concerned about IRIS (and other EPA assessment programs) moving toward inappropriate or premature use of information from alternative test methods (ATMs) to dismiss or disregard potentially hazardous chemicals or endpoints (false negatives). While the potential exists for alternative test methods to be used to identify toxicity and exposure potential, there are several limitations that demonstrate the need for additional research and development and avoid the potential for false negatives:[14]

Lack of metabolic capacity – The inability of current ATMs, like those used in the ToxCast™ platform, to mimic the metabolic capacity within humans (and across species) means that relying solely on ATMs could result in EPA failing to identify toxicity that would otherwise occur in an intact living system (e.g., a human body).

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[9] National Research Council. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. https://doi.org/10.17226/18764.

[10] Christopher J. Borgert, Richard A. Becker, Betsy D. Carlton, Mark Hanson, Patricia L. Kwiatkowski, Mary Sue Marty, Lynn S. McCarty, Terry F. Quill, Keith Solomon, Glen Van Der Kraak, Raphael J. Witorsch, Kun Don Yi; Does GLP enhance the quality of toxicological evidence for regulatory decisions?, Toxicological Sciences, Volume 151, Issue 2, 1 June 2016, Pages 206–213, https://doi.org/10.1093/toxsci/kfw056

Becker RA, Janus ER, White RD, Kruszewski FH, Brackett RE. Good Laboratory Practices and Safety Assessments. Environmental Health Perspectives. 2009;117(11):A482-A483. doi:10.1289/ehp.0900884.

[11] Markowitz GE, Rosner D. Deceit and Denial: The Deadly Politics of Industrial Revolution. Berkeley, CA: University of California Press; 2002.

[12] NAS 2014 IRIS report. Pages 62-63. Available at: https://doi.org/10.17226/18764.

[13] Myers JP, vom Saal FS, Akingbemi BT, Arizono K, Belcher S, Colborn T, Chahoud I, Crain DA, Farabollini F, Guillette LJ Jr, Hassold T, Ho SM, Hunt PA, Iguchi T, Jobling S, Kanno J, Laufer H, Marcus M, McLachlan JA, Nadal A, Oehlmann J, Olea N, Palanza P, Parmigiani S, Rubin BS, Schoenfelder G, Sonnenschein C, Soto AM, Talsness CE, Taylor JA, Vandenberg LN, Vandenbergh JG, Vogel S, Watson CS, Welshons WV, Zoeller RT. Why public health agencies cannot depend on good laboratory practices as a criterion for selecting data: the case of bisphenol A. Environ Health Perspect. 2009 Mar;117(3):309-15. doi: 10.1289/ehp.0800173

[14] Dr. Kristi Pullen Fedinick, NRDC. Draft Considerations for the Development of the Strategic Plan for Developing and Implementing Alternative Test Methods and Strategies to Reduce, Refine, or Replace Vertebrate Animal Testing for Chemical Substances or Mixtures. EPA Docket EPA-HQ-OPPT-2017-0559. January 10, 2018

Diminished concordance with animal systems/high false negative rate - When comparing guideline and guideline-like studies to an ATM developed for screening under the Endocrine Disruptor Screening Program, the ToxCast™-derived "ER Model" missed nearly 30 percent (15/55[15]) of the *in vivo* estrogenic reference chemicals[16] from guideline-like studies and 3 percent (1 out of 30 chemicals) of estrogenic reference chemicals from guideline studies[17]. The lack of sensitivity (high false negative rate) of the "ER Model" and similar ATMs for *in vivo* studies is problematic and leads to decreased confidence in the ability of the model to reliably identify chemicals that could disrupt biological processes in whole animal (including human) systems.

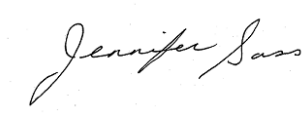
Overly narrow exposure estimates in high-throughput models – The current models used by the Agency to generate high-throughput population-level exposure estimates are severely limited in their capacity to generate values for vulnerable populations. The reliance on National Health and Nutritional Examination Survey (CDC-NHANES) data for the generation of model estimates prevents the ExpoCast program from accurately identifying exposures in vulnerable populations including children under the age of 6, highly exposed populations (e.g., workers) and vulnerable populations (e.g., pregnant women). These large uncertainties limit their use as gap-filling data.

For the potential benefits of ATMs to be realized, EPA must be encouraged by the NAS to develop and incorporate use of such methods over realistic timeframes, with a commitment to ensuring methods' effectiveness, and without a rush to eliminate use of proven existing methods for assessing toxicity and exposure.

In conclusion, the protection of EPA's scientific independence and integrity is of great concern to regulators, manufacturers, businesses, scientists, academics, health professionals, and the public. We appreciate the work of the NAS to review the progress of the IRIS Program, and we hope that its final report will provide support for the continuation of an independent chemical assessment program committed to using the best scientific methods for ensuring protection for public health and the environment.

Thank you for your consideration of these comments.

Respectfully,



Jennifer Sass, Ph.D.

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[15] For this discussion, false negatives include chemicals that were incorrectly identified as not having estrogenic activity and those with "inconclusive" results.

[16] Estrogenic *in vivo* reference chemicals missed by the "ER Model" include methylparaben, triclosan, reserpine, permethrin, octamethylcyclotetrasiloxane, and gibberellic acid. Inconclusive chemicals cannot be specifically listed due to coded identities in footnote 8.

[17] Browne, P., Judson, R. S., Casey, W., Kleinstreuer, N., & Thomas, R. S. (2015). Screening Chemicals for Estrogen Receptor Bioactivity Using a Computational Model. Environmental Science & Technology, 150612115349008. http://doi.org/10.1021/acs.est.5b02641

Senior Scientist, Natural Resources Defense Council, and
Professorial Lecturer, George Washington University,
Milken Institute School of Public Health
Department of Environmental and Occupational Health
Tel: 202.289.2362; E: jsass@nrdc.org

Academic titles and affiliations are provided for identification purposes only and do not constitute or imply institutional endorsement.

Margaret A. Adgent, MSPH, PhD
Research Assistant Professor, Department of Pediatrics
Vanderbilt University Medical Center
Nashville, TN

Alaska Community Action on Toxics
Pamela Miller, Executive Director

Alliance of Nurses for Healthy Environments
Katie Huffling, RN, MS, CNM, Executive Director

Frank S. Anastasi, PG
Principal, SCA Associates

Laura Anderko PhD RN
Robert and Kathleen Scanlon Endowed Chair in Values Based Health Care, and
Professor, School of Nursing & Health Studies
Georgetown University

David C. Bellinger, PhD, MSc
Professor, Harvard Medical School
Boston, MA

Chris Borello
Concerned Citizens of Lake Township (CCLT)
Industrial Excess Landfill (IEL) Superfund Site,
Uniontown, Ohio

Robert W. Bowcock
Integrated Resource Management, Inc.
Claremont, California

Asa Bradman, PhD, MS
Associate Adj. Professor of Environmental Health Sciences
Center for Environmental Research and Children's Health
School of Public Health/UC Berkeley
Berkeley, CA

Citizens For A Clean Pompton Lakes

Lisa J. Riggiola Executive Director

Citizens for Safe Water Around Badger - CSWAB.org
Laura Olah, Executive Director

Joseph M. Braun, MSPH, PhD
RGSS Assistant Professor of Public Health
Assistant Professor of Epidemiology
Epidemiology Master's Program Director
Brown University School of Public Health
Providence, RI

Breast Cancer Prevention Partners
Janet Nudelman, Director of Program and Policy

Erin Brockovich Foundation
Erin Brockovich
Claremont, California

Lindsey J. Butler
Environmental Health Doctoral Candidate
Boston University School of Public Health

California Rural Legal Assistance Foundation
Anne Katten, Pesticide and Work Safety Project Director

Courtney Carignan, Ph.D.
Assistant Professor, Department of Food Science and Human Nutrition
Department of Pharmacology and Toxicology
Michigan State University

Center for Biological Diversity
Nathan Donley, PhD, Senior Scientist

Center for Environmental Health
Ansje Miller, Director of Policy and Partnerships

Center for Health, Environment & Justice
A Project of People's Action Institute
Stephen Lester, PhD, Science Director

Center for Progressive Reform
Matthew Shudtz, Executive Director

Citizens' Environmental Coalition
Barbara Warren, RN, MS, Executive Director

Clean and Healthy New York

Kathleen A. Curtis, LPN, Executive Director

Clean Production Action
Mark S. Rossi, PhD, Executive Director

Coming Clean
Judith Robinson, Executive Director

Commonweal
Sharyle Patton, Director
Health and Environment Program
Bolinas, CA

Cynthia Curl, PhD
Assistant Professor
Department of Community and Environmental Health
Boise State University

Don't Waste Arizona
Stephen Brittle, President
Phoenix, AZ

Earthjustice
Tyler J. Smith, MPH
Staff Scientist, New York, NY

Jerome M. Ensminger
Agency for Toxic Substances and Disease Control
Camp Lejeune Community Assistance Panel (CAP)

Environmental Health Strategy Center/Prevent Harm
Patrick MacRoy, Deputy Director

Environmental Justice Health Alliance
Richard Moore, National Co-Coordinator
Michele Roberts, National Co-Coordinator

Environmental Working Group
Ken Cook, President
Washington, DC

Brenda Eskenazi, PhD
Jennifer and Brian Maxwell Professor of Maternal and Child Health and Epidemiology
Director, Center for Environmental Research and Children's Health (CERCH)
School of Public Health
University of California, Berkeley

Pam Factor-Litvak, PhD

Professor of Epidemiology
Associate Dean for Research Resources
Mailman School of Public Health
Columbia University

Shohreh F. Farzan, PhD
Assistant Professor of Preventive Medicine
Keck School of Medicine of University of Southern California

Steven G. Gilbert, PhD, DABT
INND (Institute of Neurotoxicology & Neurological Disorders)
Seattle, WA

Robert M. Gould, MD
Associate Adjunct Professor
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
UCSF School of Medicine
Past-President, Physicians for Social Responsibility

Green Science Policy Institute
Arlene Blum, PhD, Executive Director
Tom Bruton, PhD. Science and Policy Fellow

Alexis Jeannine Handal, PhD MPH
Associate Professor, College of Population Health
Senior Fellow - Robert Wood Johnson Foundation Center for Health Policy
University of New Mexico

Kim Harley, PhD
Associate Director for Health Effects,
Center for Environmental Research and Children's Health
University of California, Berkeley
Berkeley, California

Health Care Without Harm and Practice Greenhealth
Paul Bogart, Executive Director

Healthy Building Network
Tom Lent, Policy Director

Wendy Heiger-Bernays, PhD
Clinical Professor of Environmental Health
Boston University School of Public Health

International Center for Technology Assessment
Jaydee Hanson, Policy Director

Molly Jacobs, MPH
University of Massachusetts Lowell
Lowell Center for Sustainable Production
Lowell, MA

Amy E. Kalkbrenner
Associate Professor
Zilber School of Public Health
University of Wisconsin-Milwaukee

Margaret Karagas
Professor, Geisel School of Medicine
Dartmouth College

David Kriebel, Sc.D., Professor
Lowell Center for Sustainable Production
University of Massachusetts Lowell
Lowell MA

Philip J. Landrigan, MD, MSc, FAAP
Dean for Global Health
Professor of Preventive Medicine and Pediatrics
Arnhold Institute for Global Health
Icahn School of Medicine at Mount Sinai
New York, NY

Bruce Lanphear, MD, MPH
Professor, Simon Fraser University
Vancouver BC, Canada

Learning Disabilities Association of America
Maureen Swanson, MPA
Director, Healthy Children Project

Victoria Leonard, RN, NP, PhD
San Francisco, CA

Jianghong Liu, PhD, FAAN
Associate Professor, University of Pennsylvania
Schools of Nursing and Medicine
Philadelphia, Pennsylvania

Maryland Pesticide Network
Ruth Berlin, LCSW-C
Executive Director

Merrimack Citizens for Clean Water (NH)
Laurene Allen, LICSW, Founder

David Michaels, PhD, MPH
Professor l Department of Environmental and Occupational Health
Milken Institute School of Public Health l
The George Washington University

Midwest Environmental Justice Organization
Maria Powell, PhD, President
Madison, WI

Howard W. Mielke, Ph.D.
Department of Pharmacology
Tulane University School of Medicine

Mark Miller, MD
Assistant Clinical Professor,
University of California San Francisco

Gina Muckle
Professor, School of Psychology,
Université Laval, Canada

Susan K. Murphy, PhD
Associate Professor of Obstetrics and Gynecology
Chief, Division of Reproductive Sciences
Program Director, NICHES Children's Environmental Health and Disease Prevention Research Center
Duke University Medical Center
Durham, NC

National Hispanic Medical Association
Elena Rios, MD, MSPH, FACP
President & CEO

NJ Friends of Clearwater
Ed Dlugosz, President
Red Bank, New Jersey

Northwest Green Chemistry
Lauren Heine, Ph.D.
Executive Director
Spokane, WA

Heather B Patisaul
Professor Department of Biological Sciences
Keck Center for Behavioral Biology
Center for Human Health and the Environment
NC State University
Raleigh, NC

Jerome A. Paulson, MD, FAAP
Professor Emeritus of Pediatrics and of Environmental & Occupational Health
George Washington University School of Medicine and Health Sciences and
Milken Institute School of Public Health

Peaceful Skies Coalition
Carol Miller, MPH, President

People Concerned About Chemical Safety
Pam Nixon, President
Charleston, WV

Janet Perlman, MD, MPH
Clinical Professor of Pediatrics
University of California, San Francisco, CA

Physicians for Social Responsibility
Kathy Attar, MPH
Environmental Health Program Manager

Beate Ritz MD, PhD
Professor of Epidemiology
Center for Occupational and Environmental Health
FSPH, University of California Los Angeles

I Leslie Rubin MD
Morehouse School of Medicine
Southeast Pediatric Environmental Health Specialty Unit,
Emory University
Atlanta, Georgia

Science and Environmental Health Network
Ted Schettler MD, MPH, Science Director

Jennifer Schlezinger, Ph.D.
Associate Professor of Environmental Health
Boston University School of Public Health
Boston, MA

Peter Strauss
PM Strauss & Associates
San Francisco, CA

Evelyn O. Talbott, DrPH, MPH
Professsor, Dept of Epidemiology
University of Pittsburgh,
Pittsburgh, PA

Martha María (Mara) Téllez Rojo,
Investigadora Ciencias Médicas F,
Centro de Investigación en Nutrición y Salud,
Instituto Nacional de Salud Pública,
Mexico

The Environmental Health Leadership Foundation
Jeanne A Conry MD, PhD
President

The Marbledale Road Environmental Coalition,
Rachel Zolottev, President
Eastchester, NY

Toxics Action Center
Shaina Kasper, Vermont and New Hampshire State Director

Tribal Healthy Homes Network
Gillian Gawne-Mittelstaedt, MPA, Director

Union of Concerned Scientists
Andrew A. Rosenberg, Ph.D.
Director, Center for Science and Democracy

Dania Valvi, M.D. M.P.H Ph.D.
Research Associate, Department of Environmental Health
Harvard T.H. Chan School of Public Health
Boston, Massachusetts

Voluntary Cleanup Advisory Board
Tim Lopez, President
Denver, Colorado

W.A.T.E.R., Wake-up Alaskans to the Toxic Environmental Reality
David Berrey, President
Fairbanks, Alaska

Robin M. Whyatt, DrPH
Professor Emeritus
Department of Environmental Health Sciences
Mailman School of Public
Columbia University

Kimberly Yolton, PhD
Professor of Pediatrics
Cincinnati Children's Hospital

R. Thomas Zoeller, PhD
Professor of Biology
Director, Laboratory of Molecular & Cellular Biology
University of Massachusetts, Amherst