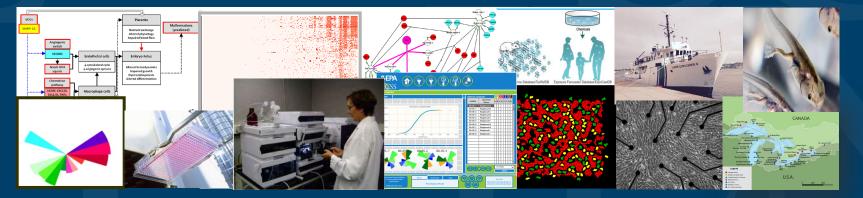
EPA Overview for the NAS Committee on Variability and Relevance of Current Laboratory Mammalian Toxicity Tests and Expectations for NAMs for use in Human Health Risk Assessment



NAS Committee Public Meeting

July 28, 2022

Rusty Thomas Director Center for Computational Toxicology and Exposure

The views expressed in this presentation are those of the presenter and do not necessarily reflect the views or policies of the U.S. EPA



Key Components in the NAS Committee Statement of Task

- Comprehensive literature review on the variability and human relevance of current laboratory mammalian toxicity tests as well as approaches to validation and establishing scientific confidence in using NAMs.
 - The variability considered in terms of reliability, qualitative and quantitative reproducibility
 - Relevance considered in terms of biological relevance and overall concordance of the results in humans.
- Recommendations on:
 - Variability of laboratory mammalian toxicity tests and concordance with human adverse responses.
 - How the variability in traditional mammalian toxicity test results and concordance with adverse effects in humans can be used to inform benchmarks in evaluating the scientific quality of NAMs.
 - Key components in a fit-for-purpose validation paradigm or scientific confidence framework for NAMs where there is no existing standard test, the standard test is not relevant to the human response, or the standard test has not been benchmarked against human responses.



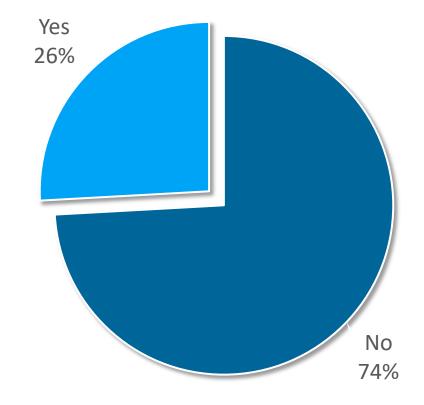
The Lack of Toxicity Testing Data is a Historical and Current Challenge

1984 NAS Report

Toxicity Testing Strategies to Determine Needs and Priorities Steering Committee on Identification of Toxic and Potentially Toxic Chemicals for Consideration by the National Toxicology Program Board on Toxicology and Environmental Health Hazards Commission on Life Sciences National Research Council Major challenge is too many chemicals and not enough data Total # chemicals = 65,725 Chemicals with no toxicity data of any kind = $\sim 46,000$

NATIONAL ACADEMY PRESS Washington, D. C. 1984

Percentage of Non-Confidential Active TSCA Inventory with Repeat Dose Toxicity Study in 2019

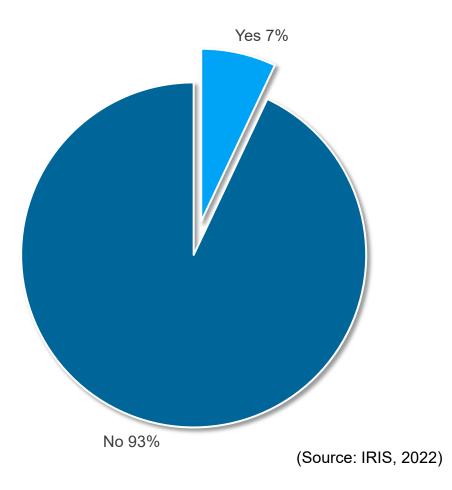


(Source: ToxVaIDB, 2019)



Current Chemical Assessments Frequently Rely on Mammalian *In Vivo* Toxicity Tests

Percentage of IRIS Non-Cancer Chemical Assessments with Human-Derived Critical Effect



Center for Computational Toxicology & Exposure



Understanding the Reliability and Relevance is a Practical and Statutorial Requirement

	6	Unclassified	ENV/JM/MONO(2005)14
tt		Organisation de Coopération et de Développement Economiques Organisation for Economic Co-operation and Development	18-Aug-2005
11 1		ENVIRONMENT DIRECTORATE JOINT MEETING OF THE CHEMICALS COMMITTEE AND	English - Or. English
ENV/JM/MONO(2005)14 Unclassified		JOINT MEETING OF THE CHEMICALS COMMITTEE AND THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BI	IOTECHNOLOGY
		OECD SERIES ON TESTING AND ASSESSMENT Number 34 GUIDANCE DOCUMENT ON THE VALIDATION AND INTERNA OR UPDATED TEST METHODS FOR HAZARD ASSESSMENT	ATIONAL ACCEPTANCE OF NEW
English - C		Patric AMCOFF Tel: +33 (0)1 45 24 16 19; Fax: +33 (0)1 44 30 61 80; Email: patr	ric.amcoff@oecd.org
-		JT00188291	

- OECD definition of "validation" as a "process based on scientifically sound principles (5)(6) by which the reliability and relevance of a particular test, approach, method, or process are established for a specific purpose. Reliability is defined as the extent of reproducibility of results from a test within and among laboratories over time, when performed using the same standardised protocol. The relevance of a test method describes the relationship between the test and the effect in the target species and whether the test method is meaningful and useful for a defined purpose, with the limitations identified."
- But... also suggested that "the validation process should be flexible and adaptable", performance must be "demonstrated using a series of reference chemicals", and "evaluated in relation to existing relevant toxicity data."



Understanding the Reliability and Relevance is a Practical and Statutorial Requirement

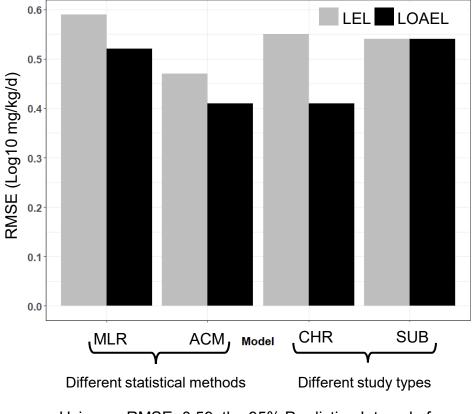
H. R. 2576	
	One Hundred Fourteenth Congress of the United States of America
	AT THE SECOND SESSION
	Began and held at the City of Washington on Monday, the fourth day of January, two thousand and sixteen
	An Act
	To modernize the Toxic Substances Control Act, and for other purposes.
	Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, SECTION 1. SHORT TITLE, TABLE OF CONTENTS. (a) SHORT TITLE.—This Act may be cited as the "Frank R. Lautenberg Chemical Safety for the 21st Century Act". (b) TABLE OF CONTENTS.—The table of contents of this Act is as follows:
	Sec. 1. Short title; table of contents.
	TTLE I-CHEMICAL SAFETY Sec. 2. Findings, policy, and intent. Sec. 3. Definitions. Sec. 4. Testing of chemical substances and mixtures. Sec. 5. Manufacturing and processing notices. Sec. 6. Prioritization, risk veriluation, and negulation of chemical substances and Sec. 7. Imminent hazards. Sec. 8. Reporting and retention of information. Sec. 9. Relationship to other Federal laws. Sec. 10. Exports of elemental mercury. Sec. 12. Penalties. Sec. 13. State-Federal relationship. Sec. 14. Judicial review. Sec. 15. Citters' civil actions. Sec. 19. State programs. Sec. 19. Conforming amendments. Sec. 19. Conforming amendments. Sec. 20. No retractivity. TTLE II-RURAL HEALTHCARE CONNECTIVITY
	Sec. 201. Short title. Sec. 202. Telecommunications services for skilled nursing facilities.
	TITLE I—CHEMICAL SAFETY
	SEC. 2. FINDINGS, POLICY, AND INTENT. Section 2(c) of the Toxic Substances Control Act (15 U.S.C. 2601(c)) is amended by striking "proposes to take" and inserting "proposes as provided". SEC. 3. DEFINITIONS. Section 3 of the Toxic Substances Control Act (15 U.S.C. 2602) is amended—

- Section 4(h) in amended TSCA law requires the identification of – "...alternative test methods or strategies the Administrator has identified that do not require new vertebrate animal testing and are scientifically reliable, relevant, and capable of providing information of equivalent or better scientific reliability and quality to that which would be obtained from vertebrate animal testing"
- In order to evaluate alternative test methods or strategies based on this standard, EPA must characterize the reliability and relevance of vertebrate animal testing models.



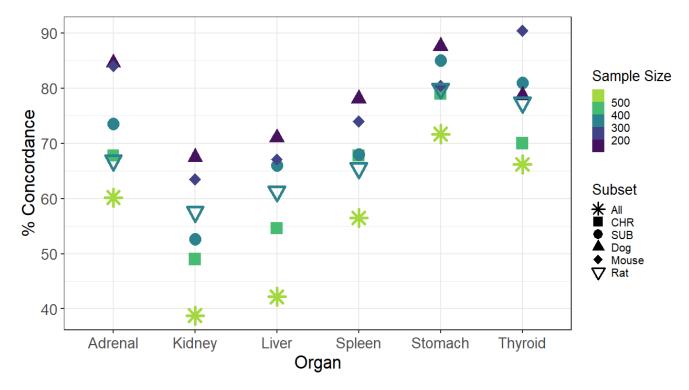
EPA Has Been Using Highly Curated Databases of Legacy Toxicity Studies to Evaluate Variability

Evaluating LEL/LOAEL Variability in Traditional Toxicity Studies to Set Expectations for NAMs



Using an RMSE=0.59, the 95% Prediction Interval of an LEL/LOAEL is +/- 10-fold (e.g., 1 mg/kg/day, 0.07 – 14)

Evaluating Qualitative Concordance of Organ Toxicity



Paul-Friedman, Unpublished

Center for Computational Toxicology & Exposure Pham et al., Comp Toxicol., 2020



Studies in Drug Development Provide an Estimate of Concordance Between *In Vivo* Toxicity Studies and Human Responses

Regulatory Toxicology and Pharmacology 32. 56–67 (2000) doi:10.1006/rtph.2000.1399, available online at http://www.idealibrary.com on DEA Concordance of the Toxicity of P in Humans and in Anii	harmaceuticals	Toxicology and Applied Planmacology 334 Contents lists available at Scie Toxicology and Applied H FUSEVIER Journal homepage: www.elsevier.	Pharmacology
Harry Olson, ¹ Graham Betton, ² Denise Robinson, ³ Karluss Thon Patrick Lilly, ³ James Sanders, ⁶ Clenn Sipes, ⁷ William Bracken, Peter Smith, ¹¹ Bruce Berger, ¹² and Al ¹⁹ Piner, Inc., Grone, Connecticut, ³ AstraZorea, Pharmae-wideals, Maccledidid, Englan & Upchen, Kalamaza, Mchagar, ⁵ Berlinger, Tagdheim Parmaewickas, Ridgher Pennsylvania: 'University of Arizona, Tuzson, Arizona, 'Mosanto-Sander Laboratories, Mober Laboratories, Mober Laboratories, ¹⁸ Janssen Research Foundation, Beerse, Belgium: 'Monsanto-Sander Laboratories, Pennsylvania: and ¹⁹ Bayer Corporation, West Har Received January 22, 2000	Michael Dorato, ⁸ Koen Van Deun, ¹⁰ en Heller ¹¹ <i>i</i> ¹ ILS JHESL Washington, D.C. 2020s, ¹ ¹ Pinnarda d. Cannettuer, ¹ ¹ Pinne Tohese Externer, Caligorithe ark, Illinois, ¹² ¹ ¹ ILII and G.C. Gronnled, Indiana; Koki, Illinois, ¹² ¹ ¹ Eard Sand Sandhall, ne., Malvern,	Current nonclinical testing paradigm enables safe clinical trials: The IQ consortium nonclinical to cl database Thomas M. Monticello ^{1,4} , Thomas W. Jones ⁵ , Donna M. Damba Michael W. Bolf, Maggie Liu ¹ , Douglas A. Keller ² , Timothy K. I ¹ compared indepts of 1466 Stress, Ampr. Tesmal Ods, CA 9122, USA	linical translational
This report summarizes the results of a multination of the second	data compiled from 150 compounds with 221 human toxicity events reported. The results showed the true positive human toxicity concordance rate of 71% for rodent and non-rodent species, with non-rodents alone being predictive for 63% of human toxicity and rodents alone for 43%.	* Setty Aurany, Grannen, San Bar Parcino, CA 1905, USA * "ing Setty Parama Interleaves Parama Control (Control (Cont	While nonclinical studies can demonstrate great value in the PPV for certain species and organ categories, the NPV was the stronger predictive performance measure across test species and target organs indicating that an absence of toxicity in animal studies strongly predicts a similar outcome in the clinic.



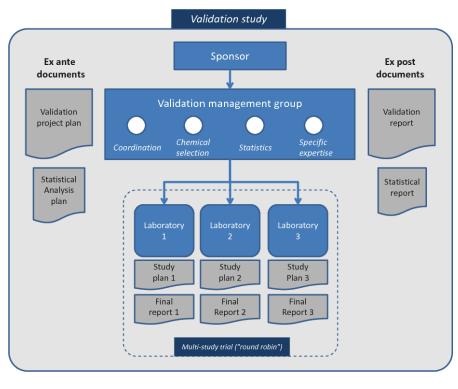
There are a Number of Other Studies That Have Also Looked at These Questions...

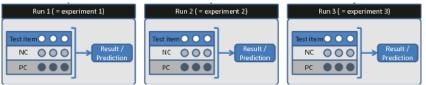
JORMAL OF TOXICOLOGY AND INVRIGNMENTAL HEALTH, PART 8 2009, VOL.22, NOC. 7-4, 208-208 http://dds.org/10.1080/100370412015.1042586	Jonathan T. Hamm, ¹ and Warren M. Gasey ² Jonathan T. Hamm, ¹ and Warren M. Gasey ² Integrated Laboratory Systems, in support of the Natio Toxicological Methods (NICEATM), Reason: Triangle Program, National Institute of Environmental Health Sci Research Triangle Park, North Carolina, USA	Are Constraints of the second	A big data approach to the concordance of the animals and humans al, 'Grace F 	e and 0/7 Potentials and limitations for predicting clinical adv analysis of 142 a Chihiro Tamakl ¹³ , Takashi Nagayan Masanori Hizuo ³ , Hiroshi Koda Voshiharu Takashima ³ , Yanato Shigeru Hisada ^{1,a} , Takako 'Non-Clinical Evolution Eyer Committen. Pre- <i>Anachatian, Japan Regulary A</i> <i>T-151 Mondaka</i>	The second	Accepted 19 September 2011 Accepted 19 September 2011 Published order in WW9 Other Library 20 October 2013 (wileycentinetSbarry.com) DCI 10:102/jat/2949 New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis [†]
Data Quality in Predictive Toxicolog Carcinogenicity Experiments Eva Gottmann, ¹² Stefan Krame, ³ Bernhard Pfahring ¹ Institute for Cancer Research, and ³ Institute for Environmental H Machine Learning Lab, University Freiburg, Freiburg, Germany, ⁴ We compared 121 epilicate indext carcinogenicity aways from the	Chemical Research in Toxicology	OXFORD SOCIET for the Evolution of Attention	Texisology in Vero 34 (2016) 205-222 Conterns lists available at Sci Toxicology in V	*Development Research, Michilds Pharmacoult *DSRD-Takyo, Pfair Japan Inc. 1 SSID-Takyo, Pfai	area tai I BEGELATORY TOXICOLOCY AND PHARMACOLOCY 23, 225–232 (1996) ARTICLE NO. 0046 Concordance between Rats and Mice in E	Environmental Hallk Perspectives Vol. 61, pp. 55-67, 1885
Institute/Suitomal Texicology Program and Iteration() of the Cere (CPDB) or estimate the relational biologic interaction from both improve substitutially when additional biologic information force and the substitutiant of the substitutional biologic information force dealbet than pervised respective, an effect that biolad be considered ture—scriptory relationsing models and the rick assessment process. machine learning, predictive toxicology, quality assurance, strue <i>Environ Exist Theoper</i> (1995) 541 (2001) (2006) 545 of genumerichaters <i>Environ Exist Theoper</i> (1995) 541 (2001) (2006) 545 of genumerichaters <i>Environ Exist Theoper</i> (1995) 541 (2001) (2006) 545 of genumerichaters <i>Environ Exist Theoper</i> (1995) 541 (2001) (2006) 545 of genumerichaters <i>Environ Exist Theoper</i> (1995) 541 (2001) (2006) 545 of genumerichaters importance in predictive toxicology and this parts of chemical astructure-archity rela- ingent of chemical astructures and there is magnetized of chemical astructures and there is measured as the substitute and the substitute of the substitute of chemical astructures and there is measured as the substitute as the substitute of the substitute of the substitute of the substitute of the substitute of the substitute of the substitute of the	Samantha J. Hughes, and Andreas Bender ^a Cate This Own Re. Twiced. 2021, 34, 438–451 ACCESSI Jan Matters & More I ANTRACT. To improve our ability to entrapolate toxicity to humans, there is a need to understand and op concordance of adverse events (AE) between animal field divide adverse events (AE) between adverse adverse adverse adverse events divide adverse events (AE) between adverse adverse adverse adverse events divide	Negative Predictors of Carcin Environmental Chemicals Thomas Hill III,* Mark D. Nelms,* Stephe Richard Judson,* J. Christopher Corton,* Oak Ridge Institute for Science and Education participant Research Ladonstroy. Office of Research and Development Triangle Park, North Carolina, *National Health and Brive Research and Development. U.S. Buylorg International Research and Development. U.S. Buylorg International Research and Development. U.S. Buylorg International Protection	Analysis of the Local Lymph Node Assay (LLNA) M the prediction of skin sensitisation potential and with non-animal approaches Coralie Dumont, João Barroso, Izabela Matys, Andrew Worth, S Jac Roward, Corres, European Correstino, Isona Martine Le Lin P o ARTICLE LIN P O ARTICLE LIN P O The Insulation of the Industric Imputer for	achine Learning of Toxicologi ead-Across Structure Activity utperforming Animal Test Reg omas Luechtefeld,* [†] Dan Marsh, [†] Craig Ro ne Hopfane University, Bloomberg School of Public Health, ¢ 71, Baltimore, Marying 2105; Toxrrack, Baltimore, Mary	DAVID A. FREEDMAN.* LOIS S. GOLD,† *Dpartment of Statistics, University of California, Brechely, California 047 and Life Sciences Drivin, Larrowce Beekley Laboratory Universit and Uppartment of Statistics, University of California, Received February 12, 199 According to current policy, chemicals are evaluated (details o for possible cancer risk to humans at low dose by test. ing in bioassays in which high doses of the chemical are given to rodents. Thus, risk is extrapolated from than the accu- general p	Species Sensitivities and Prediction of Tetratogenic Potential by James L. Schardein,* Bernard A. Schwetz,† and Michael F. Kenel*
reporters with their totaciologic effects and earlies used for the precision of adverse effects at dominals, but they are also value diffic interest (g.s., totaciologic mechanisma). Earls SAR sudy nearly heaving in the precision most investigations. Few systemic studies we ch. That write the presents of inclusions shout the reliability of totaciologic data in SAR upper (f), we covered the identification and paper (f), we covered the identification and the should be defined at the systemic and paper (f), we covered the identification and the should be defined at the systemic and the systemic of deniral investment of the systemic of the systemic and the systemic and models and risk assessment. In a previous paper (f), we covered the identification and the systemic of deniral investment of the systemic of the systemic and the systemic and the systemic and the systemic of the systemic and the systemic and the systemic and the systemic of the systemic and the systemic and the systemic and the systemic of the systemic and the systemic and the systemic and the systemic of the systemic and the systemic and the systemic and the systemic of the systemic and t	drugs reported in the PharmaPendum dambase of which new associations between tracities, encoded by differe Dictionary for Regulatory Activities terms across species deviced associations, sections species the species control po- genes index do both a precision of the grantice or strap by genes index do both a precision from the analysis is more which novel candidate of leager drugs activities could be led clinical tracerosmana and occasas reasman, for association which novel candidate of leager drugs activities could be led clinical tracerosmana and occasas reasman, for association total of 7% of hornon safety targets corredpt parted in in for investigation as future safety targets for different clinis typened All terms maching, the results of which can be use	and 'National Center for Computational Toxicology, Offic Protection Agency, Research Triangle Park, North Carolin To Winn arreguestic wold be address in UKD 2005, 0, 100 T.W. Aleas CC7070, E-mail wool.charlendepa.gov ABSTRACT Recent International efforts have led to proposals for modified on biotetre-term studies. The main goal of the current study was to e toxicity indicators on carcinogenkity study outcomes and cancer D. Survionmeral Protection Agency (PLP), Althology data wen	Nacied 21 Stocowie 215 yourst-feed evelopment of alientationon- lical lymph Morkaw (JLMA) areas Call lymph Morkaw (JLMA) areas Nacide color bit 2,02 (SLMA) 2016 inclal lymph Morkaw (JLMA) areas Call lymph Morkaw (JLMA) areas Available color bit 2,02 (SLMA) 2016 inclal lymph Morkaw (JLMA) areas To we have strained a strain analys LTM workship formed: considering the slower to alient strain GRC(P) Show that the market discretion to alient strain Moreover, it can be concluded that strain Workship Formed: considering the slower that the market discretion to alient show that the market discretion to alient strain the wariability of the reference disk were of alient of alient strain (GRC) Formed: considering the slower that the market show that the market discretion to alient strain the wariability of the reference disk were of alient of alient strain (GRC) Formed: considering the slower that the market show that the market discretion to alient strain the wariability of the reference disk were of alient of alient strain strain the strain the strain the market strain the strain strain the strain the st	Higence, Underwriters Laboratories (UL), Northbrook, Illino T-Europe, Konstanz 78464, Germany hem correspondence abouide saddeessel. Fac: +1410614 287; I:E mail: Tilartur: STRACT er we created a chemical hazard database via natural language pro mical Agency with approximately 10000 chemicais. We identified re vate oral and dermal taxistic, yee and skin irritation, mutagerid ty a the probability that on COCD paideine enrimin test wood output til sitivity 50%-57%. An expanded database with more than 866 000 ch to model health hazards and chemical properties. The constructed re to model health hazards and chemical properties. The constructed re to model health hazards and chemical properties. The constructed re to model health hazards and chemical properties. The constructed re to model health hazards and chemical properties. The constructed re to model health hazards and chemical properties. The constructed re to model health hazards and chemical properties. The constructed re to model health hazards and chemical properties. The constructed re to model health hazards and chemical properties. The constructed re to model health hazards and chemical properties. The constructed re to model health hazards and chemical properties. The constructed re to model health hazards and chemical properties. The constructed re to model health hazards and chemical properties. The constructed results and the constructed results and the model paid hazards and chemical properties. The constructed results and the model paid hazards and chemical properties. The constructed results and the model hazards and chemical properties. The constructed results and the model health hazards and chemical properties. The constructed results and the model health hazards and chemical properties. The constructed results and the model health hazards a	racy of these extrapolations is generally unvertifiable because data on humans are limited. However, it is generics effective extrapolations from mice to rats. If mice and rats are similar with first extra in favor of interspecies extrapolations conversely, if validity of extrapolations from mice to humans. One measure of interspecies extrapolations conversely, if validity of extrapolations from mice to humans. One measure of interspecies agreement is concrotance, the known h percentage of chemicals that are classified the same way as to carcinogenicity in mice and rats. Observed empirical Toxicology Program hioasays is about 75%, which Mereove	spects will accepted as human treatogenes have been shown to be terratogenic in one or more laboratory species. Yet, an single species has called utility distinguished that has been grower advantageous in the detection constrainty model the human restation, but the rabbit is resultied to the species to give a false positive finding. Among species loss commonly used for testing, primites differed is higher level of predicability member of concordant defects, but they also were responsible for the most nearescreatary responses as well. Since no other species is leastly more predictive of the human response, it is concluded that latefut decisions about be haved on all reproductive and developmental toxicity data is light of the agent's known parametabilities are functioning arguments. Introduction The extrapolation of animal data to the human in the
The database wand for our investige The database wand for our investige terror from long term in Pitre contingentity appartments for 1.288 structurally diverse formcourse provide the contagent of the terror form long term in Pitre contagent form contagent of activity of the structurally terror for the structural of the structural form contagent of the structural form of the structural terror form the system terror for the system terror form the system terror for the system terror form the system terror for the system terror form the system terror for the system terror for the system terror for the system terror form terror form the system terror form terror form terror form terror form terror form terror form terror form terror form terror form terror form terror form terror form terror form terror	■ INTRODUCTION Testing new chemical entities (NCEs) in azimal models regulatory requirement for tucidy assessment before adu titration of a drug to humans in chinal takis. However, d induced animal toristry and drug-induced human tucity d abory correlatory, which can lead to either unwarrant attituin ² or increased coms and risk to human health. The second second second second second second second predicted from simular alock ¹ , however, outanous neurological buciches translate lean well across species. Fu an analysis of the attitution of drug candidates from pharmacoutical compassies, it was found that 40% of candidates were terminated due to nonchinical tucid finding and 11% due to clinical asity finding. ² Safety fromd to the bucipater contributor to attriton in b preclinical and phase I studies. ² In an AstrZancea se- found that of the drug projects translet of preclinicity, it were due to tucity. ² Furthermore, of those dag projects with spaced into Conta Jusia, 25%, 35%, 304, 129% of them with the second particle second	hubchnoic (2)-month) and carcinogenicity studies in the U.S. EPA and evidence of hormonal perturbation in sub-chronic rat studies man evidence of hormonal perturbation in sub-chronic rat studies more and 25N-MPV for cancer disadistications not requiring quar- notations and 20N-MPV for science disadistications not requiring quar- buttown and 20N-MPV for science disadistications not require quar- turbations and 20N-MPV for science disadistications not require Additional data streams are needed to further refine these model Key words: carcinogenicity, chemical, testing; predictive value; p presistence (2R)-MPV (4P) art 30A, promisent component of this testing is the long-term robotic cancer biosaway (0EC), organications (2R)-MPV is the absence of equileonidopic data (Huff, presistence disadistication) in the absence of equileonidopic data (Huff, presistence (2R)-MPV is the absence of equileonidopic data (Huff, presistence (2R)-MPV is the absence of equilionidopic data (Huff, presistence data). This precision (2R), song with related	Linconduction The homowedge, of the biological instantion leading to the induct. The homowedge, of the biological instantion leading to the induct. The homowedge, of the biological instantion leading to the induct. The homowedge, of the biological instantion leading to the induct. The homowedge, of the biological instantion leading to the induct. The homowedge, of the biological instantion leading to the induct. The homowedge instantion leading to the induct instantion leading to the induct instantion. The homowedge is the horizet typeling leage version leading to the induct instantion. The homowedge is the horizet typeling leage version leading to the induct instantion. The homowedge is the horizet typeling leage version leading to the horizet typeling leading to the horizet typeling leage version leading to the horizet typeling leading to thorizet typeling leading to thorizet typeli	to model results hazards and chemical properties. The constructed menical classification. The novel models called ARAM set of the set of the hirty merican dia used to derive faiture vectors for supervised law of RAAMS—emiles and "Data Harms" vectors for supervised law clicing hazard from chemical analogs with honow hazard data. The feature vectors from all available porty data mather than only the swall daton achieve 70%-60% balanced accuracies with constraints: ARs show balanced accuracies in the 80%-56% range across 9 health minimum data and the set of the set of the set of the set of the set of the set of the set of the set of the set of the minimum data and the set of the set of the set of the results for larger parts of the chemical aniverse, whether of structure activity relationships has therefore been by limited to so called read across, in the programitic com- tors 1 of the windlike the supposed products at discuss age about the validity of the approach products at a supervised to so called read across, in the programitic com- tors 1 of the set of the approach products at discuss age about the validity of the approach products at a support the validity of the approach products at the set of the set of the set of the set of the set of the set of the set of the set of the set of the set of the set of the set of the set of the set of the set of th	closely related species tested under the same experi- mental conditions. However, bere da concordance surment error in the bioassays—a possibility demon- tions from test of the sume extrapole in observed concordance can be either positive or neg- ative: an observed concordance of 75% can arise if the starts are observed concordance of 75% can arise if the starts are observed concordance of 75% can arise if the starts are observed concordance of 75% can arise if the starts are observed concordance of 75% can arise if the starts are observed concordance of 75% can arise if the starts are observed concordance of 75% can arise if the starts are observed concordance of 75% can arise if the starts are observed concordance of 75% can arise if the starts are concordance is anything between 20 and 100%. In NIRRODUCTION According to current regulatory policy, chemicals are starts of car are exposed to near-toxic doses of the agent being tested. High doses are needed in order to demonstrate a statistically significant response with a starts of an arise. I however, there is an upper	In the SXTEpolation of animal data to the numan is the protect on one Sirvy surve. As well be shown, they will be abown, they will be abown. They will be abown they will be abown. They will be abown, they will be abown. They w
Environmental Health Perspectives • vouue 109 NAMER 5 May 2001	respectively, ⁷ showing that also in the clinical phases (and e	Published by Oxford University Press on behalf of the Society of Toticology 2016 This work is written by US Covernment employees and is in the public domain i	This i http://dx.doi.org/10.1016/j.tiv.2016.04.008	Anthorigh 2018. Published by Oxford University Press on bohalf of the Society of T is an Open Access article distributed under the terms of the Credite Commons. Heldy activity, Julie pression accessible pression and repeated and endowy activity, Julie pression accession accession accession accession memorial re-use, please contact journals permissions@oxp.com	bound: If the dose level is set too high, animals will not Being m live long enough to develop cancer. Thus, chemicals are study; us 225	Triangle Tark, NO 27706. In the second secon

Center for Computational Toxicology & Exposure



The Current Validation Process is Unsustainable and Not Necessary for All EPA Decision Contexts





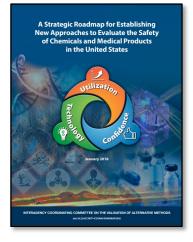
Lambris and Paoletti, Adv Exp Med and Biol, 2016

- Traditional validation process in toxicology has focused on one-for-one replacement of a reference method using a ring trial design
 - Time frame (idealized): 3 years for trial, 2 years for review/publication (Altex 27:253, 2010)
 - Costs highly dependent on method being validated
- Challenges associated with the traditional approach:
 - Time and resource intensive
 - Accommodating rapidly changing technology and methods;
 - Lack of human data for most endpoints;
 - Many original reference methods were not themselves "validated";
 - Limited reference chemicals for some endpoints/responses;
 - Difficulty in comparing overlapping, but not identical methods.
 - Expectation that individual methods that are part of integrated assessment and testing approaches (IATAs) are validated singly and in combination

Center for Computational Toxicology & Exposure



ICCVAM Roadmap and National Academy Report Support Transition to Fit-for-Purpose Validation





NICEATM/ICCVAM Strategic Roadmap

- Promotes use of efficient, flexible practices to evaluate fitness for purpose and establish scientific confidence in new methods
- Emphasizes separating testing requirements from context of use
- Highlights need to establish confidence based on human biology and mechanistic relevance rather than comparisons with existing models

NAS Report

- Emphasizes importance in defining purpose and scope of the NAM
- Recognizes challenges in validating a NAM where there is no "gold standard" or against assays that have not themselves been validated
- Suggests establishing performance standards for data quality
- Recognizes that ring-trial design is not necessary for all purposes
- Emphasizes need for reporting standards and transparency



Recent EPA Documents Have Generally Adopted the Fit-for-Purpose Approach

€PA	United States Environmental Protection Agency	EPA Document# EPA-740-R1-8004 June 22, 2018 Office of Chemical Safety and Pollution Prevention
	1 to Promote the Developme ative Test Methods Within 1	
	June 22, 2018	

- Outlined general framework for establishing scientific confidence in NAMs for TSCA-related decisions
- Important elements in evaluating relevance
 - Fit for purpose and utilization
 - Considers both NAM and integrated NAMs
 - Flexibility for use in qualitative or quantitative predictions and as part of WOE
- Important elements in evaluating reliability
 - Evaluation of inter-laboratory reproducibility is not required for all NAMs and depends on context of use
 - Incorporates performance-based approach
- Criteria for establishing scientific confidence include:
 - Clear decision context
 - Mechanistically and/or biologically relevant where possible. If not, the chemical domain of applicability clearly defined
 - Reference chemicals adequately referenced
 - Reliability considered within the context of intended use and best practices
 - Transparently described and information available to the public (except TSCA CBI)
 - Characterize uncertainty
 - Evaluation and implementation by third parties must be possible (i.e., assays commercially available or protocols)
 - Independent scientific review



NAS Study in the Context of the EPA NAM Work Plan

	A MARCAN	ECT POWER METODE SERVICE
Whee States Unitedian Agency	EPA 600/X-21/209 November 2021	
	lew Approad	ch 📕
U. Of	S. Environmental Protection Agene ffice of Research and Development ffice of Chemical Safety and Pollut	cy
No	ovember 2021	
		4

- Five objectives to increase the scientific rigor and sophistication of Agency assessments using NAMs while reducing the reliance on vertebrate animals to test chemicals.
 - Evaluate Regulatory Flexibility
 - Develop Baselines and Metrics
 - o Establish Scientific Confidence and Demonstrate Application
 - Develop NAMs to Address Information Gaps
 - Engage and Communicate with Stakeholders
- The Committee's Statement of Task help inform two strategies
 - Characterize scientific quality and relevance of traditional toxicity tests Due 2023
 - Develop a scientific confidence framework to evaluate the quality, reliability, and relevance of NAMs Due 2024
- Useful recommendations will..
 - Focus on evaluating the variability and relevance of the traditional *in vivo* mammalian toxicity testing models and not the variability and relevance of the NAMs.
 - Build on recommendations on validation and scientific confidence frameworks covered by previous NAS and OECD committees but tackle difficult issues of what to do when there is no standard test, the standard test is not relevant to the human response, or the standard test has not been benchmarked against human responses.
 - Accommodate the broad range of regulatory decisions the Agency needs to make



We Look Forward to the Committee's Input on These Difficult Issues...



The National Academies of SCIENCES • ENGINEERING • MEDICINE

