Retrospective analysis of the statutory requirements, study requests, and research utilization in OCSPP and ORD

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Introduction

- Office of Chemical Safety and Pollution Prevention (OCSPP): mission is to protect you, your family, and the environment from potential risks from pesticides and toxic chemicals.
  - OCSPP implements the:
    - Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA),
    - Federal Food, Drug, and Cosmetic Act (FFDCA),
    - Toxic Substances Control Act (TSCA),
    - Pollution Prevention Act, and portions of other statutes.
  - OCSPP includes:
    - Office of Pesticide Programs (OPP)
    - Office of Pollution Prevention and Toxics (OPPT)
    - Office of Science Coordination and Policy (OSCP)
- Office of Research and Development (ORD) is the scientific research arm of EPA. Its leading-edge research informs Agency decisions and supports the emerging needs of EPA stakeholders, including the Agency's state, tribal, and community partners.
  - ORD research is organized into six programs

USEPA Administrator Memo Prioritizing Efforts to Reduce Animal Testing, September 10, 2019

- EPA will reduce its requests for, and our funding of, mammal studies by 30 percent by 2025
- EPA will eliminate all mammal study requests and funding by 2035. Any mammal studies requested or funded by the EPA after 2035 will require Administrator approval on a case-by-case basis.
- Form a working group of agency experts in this field who will provide a work plan within six months.
- https://www.epa.gov/environmental-topics/administrator-memo-prioritizing-efforts-reduce-animal-testing-september-10-2019

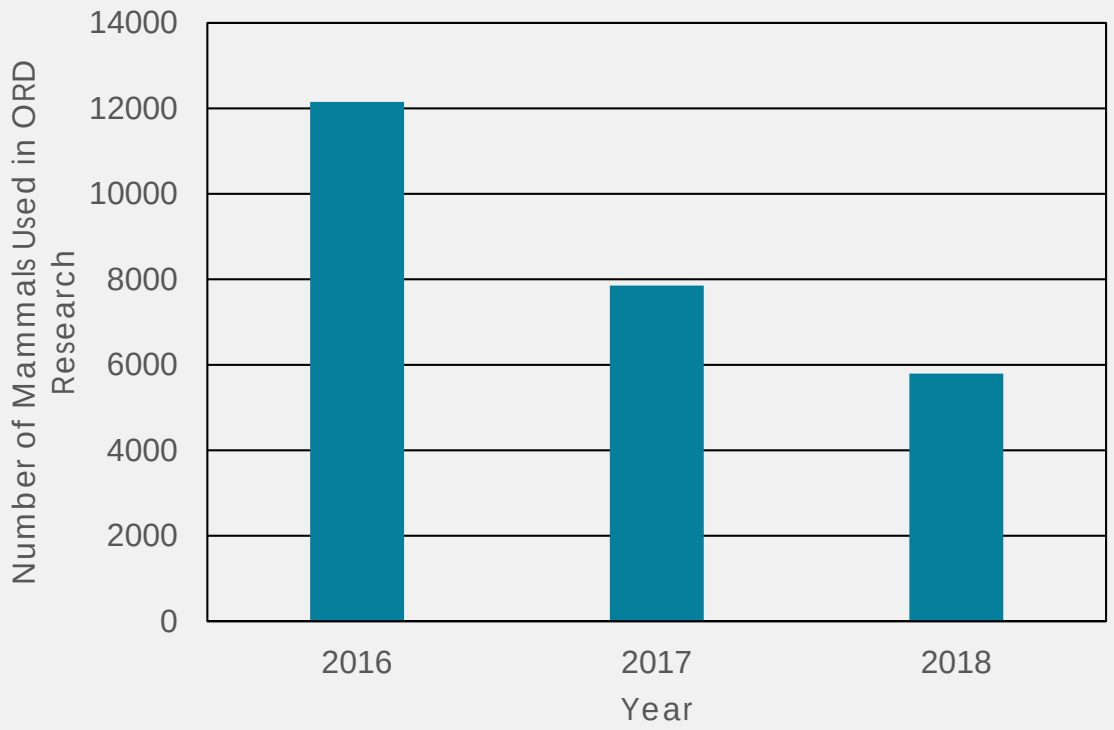
EPA Administrator Memo Prioritizing Efforts to Reduce Animal Testing, September 10, 2019

- This plan will include:
  - Validation to ensure that NAMs are equivalent to or better than the animal tests replaced;
  - Demonstration that NAMs are applicable for use in risk assessment and that new decision-making approaches are as protective of human health and the environment as existing approaches;
  - Recognition that statutory and regulatory requirements for animal testing currently exist and that a plan to adopt more flexible requirements should be developed;
  - Outreach to all stakeholders to incorporate their knowledge and address concerns; and
  - Establishment of baselines, measurements and reporting mechanisms to track the agency's progress.
- EPA will hold a joint annual conference on NAMs for presentations by leading scientists in the NAMs field, with the first conference to be held in 2019.

Office of Research & Development

- EPA's ORD has been working for over a decade to build a scientific foundation for predictive and computational toxicology
- ORD has provided global scientific leadership for the development, testing and application of new approach methodologies
  - Examples: CompTox Chemicals Dashboard, ToxCast, ECOTOX, QSAR modeling, read across, high-throughput toxicokinetics, adverse outcome pathways
- The results of ORD's research efforts are informing the Agency's use of new approach methodologies as part of implementing TSCA, FIFRA and the FQPA.
  - Example: Endocrine Disruption Screening Program (EDSP)

Use of Mammals in ORD Research



- Use of mammals in ORD research has decreased ~50% over the past three years
- A significant investment in development and application of NAMs in FY19 – 22 research plans should continue the downward trend
- An additional 30% reduction by 2025 is readily achievable

The Frank R. Lautenberg Chemical Safety for the 21st Century Act (Amended TSCA in 2016)

- Added New Section (Section 4(h) – Reduction of Testing on Vertebrates
  - 4(h)(1) - prioritizes looking at alternatives before asking for testing in vertebrate animals need to "Scientifically valid test methods and strategies that
  - 4(h)(2)(A) - develop a strategic plan to promote the development and implementation of alternative test methods and strategies to reduce, refine, or replace vertebrate animal testing (Posted on June 22, 2018)
- In its ***Strategic Plan to Promote the Development and Implementation of Alternative Test Methods***, the EPA has identified current/ near-term (<3 years) and intermediate-term (3-5 years) regulatory and research needs and activities.

Pesticide Testing

- FIFRA requires registration of new products and uses and provides for the ability to issue data call-ins
- Pesticide testing requirements for human health & ecological effects can be found:
  - https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/test-guidelines-pesticide-data-requirements
- Laboratory animal testing is conducted on a variety of species (e.g., rat, mouse, rabbit, dog, bird, fish) and health outcomes such as cancer, chronic toxicity, and reproductive and developmental toxicity based on the type of pesticide and its use pattern.

Pesticide Testing

- The number of laboratory animals used for a new pesticide varies substantially.
  - A new biopesticide with low toxicity may be tested on 100-1000 vertebrates.
  - A new conventional pesticide with complex biology may be tested on 4000-9000 laboratory vertebrates.
- The number of new pesticides submitted to EPA for review each year varies but a reasonable approximation of the total number of vertebrates used in toxicology studies submitted to EPA annually ranges from 20,000 over 100,000.
- Flexibility in implementing Part 158 data requirements (§158.30):
  - Waivers may be granted as permitted by 40 CFR Part 158.45;
  - Additional data beyond the 158 data requirements may be important to the risk management decision (§158.75), alternative approaches can be accepted, and other data can be used.

Summary of HASPOC Waivers December, 2011 through May 2018										
		Waiver Review Summary			Study Execution (Savings to the Registrant)				Study Report Review (Savings to EPA)	
Type of Study	OCSPP guideline	Waiver Requests	Waivers Granted	Required Studies	# animals/ study	Total # animals saved	Cost/ study	Total cost savings	Price to review study per contract	Total Cost Savings
Subchronic Inhalation	870.3465	296	233	63	80	18,640	$576,000	$134,208,000	$3,426	$798,258
Neurotoxicity (ACN and SCN)	870.6200	330	306	24	80	24,480	$211,550	$64,734,300	$6,441	$1,970,946
21/28-Day Dermal	870.3200	62	55	7	80	4,400	$114,100	$6,275,500	$3,426	$188,430
Developmental (rat and rabbit)	870.3700	44	39	5	80	3,120	$155,800	$6,076,200	$5,162	$201,318
DNT	870.6300	21	19	2	1,100	20,900	$771,600	$14,660,400	$10,326	$196,194
Subchronic dog	870.3150	15	13	2	32	416	$259,900	$3,378,700	$7,743	$100,659
Reproductive	870.3800	38	34	4	2,600	88,400	$432,000	$14,688,000	$12,354	$420,036
Immunotoxicity	870.7800	229	223	6	16	3,568	$71,200	$15,877,600	$8,075	$1,800,725
Chronic/Cancer	870.4300	25	23	2	480	11,040	$1,773,400	$40,788,200	$11,314	$260,222
Subchronic rat	870.3100	15	12	3	80	960	$173,000	$2,076,000	$7,743	$92,916
CTA	non-guideline	20	15	5	1800	27,000	$550,000	$8,250,000	$12,354	$185,310
Totals		1095	972	123		202,924		$311,012,900		$6,215,014

https://www.sciencedirect.com/science/article/pii/S0273230019302454

Office of Science Coordination and Policy: Endocrine Disruptor Screening Program

- In a June 19, 2015, Federal Register Notice, EPA announced the intention to "pivot" towards the use of HT assays and computational models to evaluate and screen chemicals for potential bioactivity in the estrogen, androgen, or thyroid hormone biological pathways.
- Tier 1 battery:
  - >200 mammals plus fish & amphibian embryos
  - Costs >$600,000

EDSP Tier 1 Battery of Assays (current)	High Throughput Assays and Computational Model Tier 1 Battery Alternatives
Estrogen Receptor (ER) Binding	ER Model (alternative)
Estrogen Receptor Transactivation (ERTA)	ER Model (alternative)
Uterotrophic	ER Model (alternative)
Androgen Receptor (AR) Binding	AR Model (Near Future)
Hershberger	AR/STR Model (Future)
Aromatase	STR Model (Future)
Steroidogenesis (STR)	STR Model (Future)
Female Rat Pubertal	ER, STR , THY Models (Future)
Male Rat Pubertal	AR, STR , THY Models (Future)
Fish Short Term Reproduction	ER, AR, STR Models (Future)
Amphibian Metamorphosis	THY Model (Future)
EDSP Tier 2 Tests	**High Throughput Assays and Computational Model Tier 2 Battery Alternatives**
Rat 2-gen/EOGRT	ER, AR, STR, THY (Future)
Medaka Extended 1-Gen Reproduction	ER, AR, STR (Future)
Larval Amphibian Growth & Development	THY (Future)
Avian Multi-Generation Reproduction	ER, AR, STR, THY (Future)

Areas for NAM Development

- OPP is already actively engaged with stakeholders to conduct retrospective analyses and to develop or implement NAMs. Some key on-going projects:
  - "6-pack" initiative (acute lethality, skin sensitization, skin irritation, eye irritation)
  - Retrospective analysis of *in vivo & in vitro* dermal absorption data
  - Waiver guidance development for rodent chronic/carcinogenicity
  - Use of 3D lung tissue methods for inhalation risk assessment of irritants & corrosives
  - Non-mammalian retrospective analyses (e.g., avian, fish)
  - Etc.
- OPPT is near completion of a retrospective analysis of TSCA available, requested, and required Information (ATARI)
- Areas identified for NAM development or retrospective analyses:
  - Developmental & reproductive toxicity
  - Inhalation route of exposure leading to systemic toxicity
  - Repeat dose toxicity


scientific tools
partnerships
share resources
promote health
computational tools
best science
cost effective
agency capacity
competitiveness
share expertise
National leadership
decision-making
technology transfer
regulatory science
sustainable
encourage adoption
quality
modernize toxicology
relevance
rigorous
NEW APPROACHES
efficient
transform understanding
collaboration
new information
improvements
overcome bottlenecks
risk management
validated tools
working cooperatively
innovation
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science
early identification
technology
specificity
solutions
better predict
global adoption