

New Alternative Measures: Regulatory Legal Aspects

**American Society for Cellular and
Computational Toxicology Webinar
April 27, 2021**

Gary Marchant, Ph.D., J.D .
gary.marchant@asu.edu

CENTER FOR
Law, Science & Innovation

ASU SANDRA DAY O'CONNOR
COLLEGE of LAW
ARIZONA STATE UNIVERSITY

Innovating law, policy and ethics for science & technology

What are NAMs?

- “New Approach Methodologies”
- “any non-animal technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment” (ICCVAM 2018)
- Includes new in vitro assays, QSAR, in silico assays, microphysiological systems, organs on a chip, read across, AI/neural nets

Incentives/Pressures for Regulatory Utilization of NAMs

- Inaccuracy of current animal methods
- Ethical imperative to reduce animal use
- Need for less expensive assays
- Need for faster assays
- Rapid pace of new chemical entities
- New types of endpoints (e.g., endocrine disruption)
- Need to address mixtures

Three Hurdles for Regulatory Acceptance of NAMs

- I. Confidence in validity of NAMs by agency and external scientists
- II. Willingness of agency officials to sign off on regulatory decisions based on NAMs
- III. Legal defensibility of reliance on NAMs in judicial challenge to agency decision

Example of Agency Caution:

EPA Interim Policy on Genomics (June 2002)

- Genomic data may be useful to EPA “in setting priorities, in ranking of chemicals for further testing, and in supporting possible regulatory actions.”
- “EPA will consider genomics information on a case-by-case basis.”
- Genomic data *alone* are “insufficient as a basis for decisions” at present time

Types of Potential Legal Challenges

- Agency's regulatory decision was unlawful for relying on unreliable NAMs in unjustified departure from agency's traditional reliance on animal studies
- Agency's failure to use a particular NAM in its regulatory decision was unlawful for failing to use the "best available" science

Administrative Procedure Act § 706: Judicial Review of Agency Actions

“The reviewing court shall—

(1) compel agency action unlawfully withheld or unreasonably delayed; and

(2) hold unlawful and set aside agency action, findings, and conclusions found to be—

(A) **arbitrary, capricious**, an abuse of discretion, or otherwise not in accordance with law;

(B) contrary to constitutional right, power, privilege, or immunity;

(C) in **excess of statutory jurisdiction, authority, or limitations**, or short of statutory right;

(D) without observance of **procedure required by law**;

...

Specific Legal Claims re Agency Use/Non-Use of NAMs

- 1. *Ultra vires*** – agency action inconsistent with statutory authority
- 2. *Procedural defect*** – agency failed to follow appropriate notice and comment procedures in decision to use/not use NAM
- 3. *Arbitrary & capricious*** – agency's decision to use/not-use NAMs was substantively unreasonable

1. Ultra vires – Statutory Constraints

Statutory Restrictions on Agency Use of New Risk Science

- Some statutes require agency to base decisions on factors other than risk (e.g., best available technology)
- Some statutes explicitly require agency to use “best available” science
- Relatively few specific statutory provisions regarding risk assessment methodologies

Statutes Requiring Reliance on “Best Available” Science

- Safe Drinking Water Act:
 - requires EPA to use “the best available, peer-reviewed science and supporting studies conducted in accordance with sound and objective scientific practices”
- Toxic Substances Control Act:
 - requires agency to use the “best available science” and consider “reasonably available information”
- Clean Water Act:
 - requires agency to adopt water quality criteria that accurately reflect the “latest scientific knowledge”
- Occupational Safety and Health Act:
 - requires OSHA to set occupational health standards based on “best available evidence”

Data Quality Act

- Enacted as part of Appropriations Act for Fiscal Year 2001 (PL 106-554)
- Instructed OMB to:
 - Issue guidelines for “ensuring and maximizing the **quality, objectivity, utility, and integrity** of information (including statistical information) disseminated by Federal agencies”.
 - “Establish administrative mechanisms allowing affected persons to seek and obtain **correction of information** maintained and disseminated by the agency that does not comply with the guidelines”

Data Quality Act and Judicial Review

- Data Quality Act is silent on whether an agency's compliance with Data Quality Act is judicially enforceable
 - issue will likely determine significance of statute
- On March 6, 2006, 4th Circuit Court of Appeals ruled in case brought by Salt Institute that there is no judicial review provided by Data Quality Act
 - subsequent cases confirm no judicial review

Lautenberg Chemical Safety for the 21st Century (2016)

- Requires EPA to reduce and replace “to the extent practicable” the use of vertebrate animals in chemical testing
- Among other things, requires EPA to create and periodically update a list “of particular 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”

TSCA §26

“to the extent that the Administrator makes a decision based on science,” s/he must use “scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science, and shall consider as applicable”:

- (1) the extent to which the scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate the information *are reasonable for and consistent with the intended use* of the information; ...
- (3) the degree of *clarity and completeness* with which the data, assumptions, methods, quality assurance, and analyses employed to generate the information *are documented*;
- (4) the extent to which the *variability and uncertainty* in the information, or in the procedures, measures, methods, protocols, methodologies, or models, are *evaluated and characterized*; and
- (5) the extent of *independent verification or peer review* of the information or of the procedures, measures, methods, protocols, methodologies, or models.

Legal Restrictions on NAMs

- Agency must also comply with its own regulations adopted in CFR
- EPA is currently conducting “a thorough review of existing statutes and programmatic regulations, policies and guidance to identify mammalian testing requirements that may not allow flexibility for the Agency to apply NAMs”

Table 1. Initial Survey Results of Mammalian Testing Requirements in Major Environmental Statutes

Major Environmental Statute	Statutory Requirements for Mammalian Testing	Regulatory Requirements for Mammalian Testing
Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and Federal Food, Drug, Cosmetic Act (FFDCA)	None	40 CFR Part 158 specifies FIFRA and FFDCA data requirements that include use of animals (pesticide registration, registration review, and tolerance or exemptions from the requirements of a tolerance for a pesticide chemical residue).
Endangered Species Act (ESA)	None	None
Food Quality Protection Act (FQPA) amendments to the FFDCA and the Safe Drinking Water Act (SDWA) amendments	None	None ⁶
Toxic Substances Control Act (TSCA)	None, but TSCA Section 4(h) requires reducing use of vertebrate animals in testing. ⁷	40 CFR Parts 790 through 799 apply to TSCA Section 4 test rules.
Clean Air Act (CAA)	None	Fuel and Fuel Additive Registration; ⁸ Significant New Alternatives Policy (SNAP) programs. ⁹
Clean Water Act (CWA)	None	None
Comprehensive Environmental Response, Compensation and Liability Act (CERCLA)	None	None
Emergency Planning and Community Right-to-Know Act (EPCRA)	None	None
Resource Conservation and Recovery Act (RCRA)	None	None
Safe Drinking Water Act (SDWA)	None	None

Source:
EPA NAM
Work Plan 2020

FDA Drug Approval Authority:

Vanda Pharm., Inc. v. FDA, 436 F. Supp. 3d 256 (2020)

“[T]he statutory and regulatory scheme here explicitly contemplates that the results of animal studies are predictive of the results of human trials. See, e.g., 21 U.S.C. § 355(i)(1)(A) (authorizing FDA to promulgate regulations for the “protection of the public health” that require drug sponsors to submit “preclinical tests (including tests on animals) . . . adequate to justify the proposed clinical [human] testing”); ... 21 C.F.R. § 312.23(a)(8) (requiring drug sponsors to submit “[a]dequate information” about studies “involving laboratory animals” which allow the sponsor to conclude “that it is reasonably safe to conduct” human trials). Indeed, the entire point of conducting animal studies—which the legal framework mandates—is that the results of those studies have some relevance to humans.”

II. Procedural Defects

Procedural Defects

- Favorite “gotcha” strategy of administrative lawyers
 - Agency failed to give adequate notice of its intent to rely/not rely on NAM
 - Agency failed to adequately explain/justify reasons for reliance/non-reliance on NAMs
 - Agency failed to adequately respond to public comments on NAM reliance/non-reliance

Examples of Inadequate Agency Procedure

- an agency must “examine the relevant data and articulate a satisfactory explanation for its action” *MVMA v. State Farm*, 463 U.S. 29, 43 (1983)
- an agency must give “reasoned consideration to all the material facts and issues” *Greater Boston Television Corp. v. FCC*, 444 F.2d 841, 851 (D.C. Cir. 1970), cert. denied, 403 U.S. 923 (1971)
- court should not defer to an agency that “simply has not exercised its expertise” *Public Citizen Health Research Group v. Tyson*, 796 F.2d 1479, 1505 (D.C. Cir. 1986)

III. Arbitrary & Capricious

Judicial Deference to an Agency's Scientific Conclusions

- "When examining [a] scientific determination, as opposed to simple findings of fact, a reviewing court must generally be at its most deferential." *Baltimore Gas & Elec v. NRDC*, 462 US 87, 103 (1983)
- "[S]ubstantive review of mathematical and scientific evidence by technically illiterate judges is dangerously unreliable."
 - *Ethyl Corp. v. EPA*, 541 F.2d 1, 67 (D.C. Cir. 1976)
- "In an area characterized by scientific and technological uncertainty, . . . this court must proceed with particular caution, avoiding all temptation to direct the agency in a choice between rational alternatives." *Int'l Fabricare Inst. v. EPA*, 972 F.2d 384, 389, (D.C. Cir. 1992)

“Red Flags” for Arbitrary & Capricious Review

- While arbitrary & capricious review generally deferential, some “red flags” trigger more aggressive review:
 - Failure to use most updated science
 - Unjustified departure from agency precedent
 - Failure to comply with agency guidelines
 - Disagreement with agency scientific advisory committees

Failure to Use Updated Science

- an "agency acted arbitrarily in failing to utilize the best scientific evidence available." *American Tunaboat Ass'n v. Baldrige*, 738 F.2d 1013, 1017 (9th Cir. 1984)
- regulation "must remain attuned to our rapidly expanding knowledge and technology." *EDF v. Costle*, 578 F.2d 337, 344 (D.C. Cir. 1978)
- agency must rely on data that "accurately reflect the latest scientific knowledge useful in indicating the kind and extent of all identifiable effects on public health." *Lead Indus. Ass'n v. EPA*, 647 F.2d 1130, 1157 (D.C. Cir. 1980)

But....

“The determination of what constitutes the best scientific data available belongs to the agency’s special expertise and warrants substantial deference.”

- National Family Farm Coalition v. US EPA, 966 F.3d 893 (9th Cir. 2020) (citing Santa Clara River, 887 F.3d at 924).

Judicial Scrutiny of Updated Evidence on Dose-Response Models

- EPA promulgated standards for chlorinated byproducts in drinking water based on linear, no-threshold comments
- Agency itself conceded that scientific data suggested existence of a threshold; but agency decided to follow standard LNT default assumption
- EPA's decision overturned by D.C. Circuit in *Chlorine Chemistry Council v. EPA*, 206 F.3d 1286 (D.C. Cir. 2000) (for failure to follow best available science)

Departure from Agency Precedent

- *Int. Union, UAW v. Pendergrass*, 878 F.2d 389 (D.C. Cir. 1989)
 - D.C. Circuit over-turned OSHA occupational standard for formaldehyde
 - OSHA improperly used maximum likelihood estimate (MLE) rather than upper confidence limit (UCL) to calculate risk
 - UCL but not MLE consistent with linear dose-response assumption
 - OSHA provided insufficient rationale for departing from traditional linear dose-response assumption

Judicial Enforcement of Agency Risk Analysis Guidelines

- Several court decisions have upheld agency risk assessments in part because they are consistent with the Agency's risk assessment guidelines. *E.g.*, *EDF v. EPA*, 548 F.2d 998 (D.C. Cir. 1976); *NRDC v. EPA*, 824 F.2d 1211 (D.C. Cir. 1987).
- One court struck down an agency action because the agency's decision was inconsistent with its own risk assessment guidelines. *Flue-Cured Tobacco v. EPA*, 4 F.Supp2d 435 (1998) (later reversed on other grounds)

Judicial Deference to Views of Scientific Advisory Committees

- *International Harvester Co. v. Ruckelshaus*, 478 F.2d 615, 648 (D.C. Cir. 1973) (heightened standard of explanation required to override science advisor's advice)
- *Chlorine Chemistry Council v. EPA*, 206 F.3d 1286 (D.C. Cir. 2000) (EPA's continued reliance on no-threshold assumption to set drinking water standards for chloroform reversed because in part contrary to conclusions of two EPA scientific advisory committees)
- *Asbestos Disease Awareness Org. v. Wheeler*, 2020 WL 7625445 (N.D. Cal. Dec. 22, 2020) (EPA's modeling arbitrary & capricious in part because it failed to follow advice of its Science Advisory Committee on Chemicals)
- *Murray Energy Corp. v. EPA*, 936 F.3d 597 (D.C. Cir. 2019) (EPA failed to adequately justify not following CASAC recommendations)

Conclusion

- Agencies must amend or circumvent regulations requiring animal studies
- Agencies must explain their decisions and respond to critiques from stakeholders
- Agencies must justify departures from previous precedents
- Agencies must document the quality, reliability, and relevance of NAMs
- NAM must be fit for purpose
- Endorsement of science advisory committee helpful