Beyond the Bench: Using Exposure Science to Promote Toxicology in Policy, Decision-Making, and Public Health

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Outline of Presentation

- Exposure Science:
  - Overview
  - Common approaches
  - Exposures in Toxicological vs epidemiologic research.
  - Using exposure science to better link toxicological research to studies of health across human populations (epidemiology)

Risk assessment/ policy-making:

- Role of exposure science in regulatory decision making
- Improving applicability of tox research to regulatory decision making
- Real-world examples

Framing Piece #1:
The Matrix: Better relating exposure science/ epidemiology to risk assessment/ decision-making…

Contents lists available at ScienceDirect

Global Epidemiology

journal homepage: https://www.journals.elsevier.com/global-epidemiology

Methodology article

A matrix for bridging the epidemiology and risk assessment gap☆

Carol J. Burns [a,*], Judy S. LaKind 2[b], Donald R. Mattison [c], Cecilia S. Alcala [d], Francesca Branch [e], Juan Castillo [f], April Clark [g], Jane Ellen Clougherty [h], Sally P. Darney [i], Heidi Erickson [j], Michael Goodman [k], Matthias Greiner [l], Anne M. Jurek [m], Aubrey Miller [n], Andrew A. Rooney [o], Angelika Zidek [p]

Table 1
Matrix of priority "asks" of epidemiologic studies for each risk assessment step.

Risk assessment step	Priority asks for risk assessment		
Hazard ID	Confirm outcome.	Confirm exposure.	Report methods fully and transparently.
Dose response	Include information on shape of the curve.	Evaluate concordance with previous results.	Describe direction/magnitude of error.
Exposure assessment	Describe source-to-intake pathways.	Describe complete exposure data.	Describe direction/magnitude of error.

Framing Piece #2: Exposures (doses) in Epi vs. Tox

TOXICOLOGICAL SCIENCES 97(2), 241–252 (2007)
doi:10.1093/toxsci/kfm005
Advance Access publication January 18, 2007

Can Exposure Characterization Explain Concurrence or Discordance between Toxicology and Epidemiology?

Leonard Ritter*,[1] and Tye E. Arbuckle†

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TABLE 1
Characteristics of the Exposure Assessment in Toxicological and Epidemiological Studies

Characteristic	Toxicology	Epidemiology
Design	Experimental	Observational
Study agents	Known and controlled source, vehicle, route	Can be multiple sources, routes and vehicles, not within control of investigator
Timing and duration of exposure	Known, constant and controlled; less likelihood of measurement error	Not controlled, may be of longer duration and even multigenerational and variable over observation period; higher likelihood of measurement error
Magnitude of exposure	Dose often exceeds range relevant to humans	Reflect actual range of human exposure
Exposure categorization	Dose is selected *a priori,* fixed, limited number of doses administered to groups of animals by investigator; usually one compound at a time	Estimated, commonly based on a one-time environmental (i.e., *ad libitum* exposure to contaminated air, drinking water, food) or biological (e.g., blood, urine) sampling; may or may not be categorized; evaluates mixtures to which people are exposed (although exact nature of mixture may not be well characterized)
Study groups	Homogenous (e.g., genetic, nutritional, environmental factors) both within dosing groups and between groups, except for the exposure under study	Efforts made to make the groups as homogenous as possible (within and between groups) using selection and restriction criteria for study population and/or data analysis
Relevance to humans	Species and strain selected may have metabolic pathways not representative of humans	Directly relevant if no selection biases present
Statistical analysis	Straightforward; a few select and fixed ordinal doses with a set number of animals exposed to each dose; if doses selected appropriately lends itself well to dose-response curves and threshold determinations (if applicable)	Complicated; concentrations are continuous variables, therefore can be issues such as: (1) data are not normally distributed; (2) may have high proportions of nondetectable concentrations; (3) choice of cut points to categorize data; difficult to identify sufficient numbers of truly nonexposed; choice of statistical model for dose-response curves

What do we mean by "Exposure"?

- Exposure is "contact between an agent and a target. Contact takes place at an exposure surface over an exposure period."
  - source: WHO, 2004

- *Broadly, Exposure Assessment is the systematic attempt to quantify the human-environment interface.*

- Primary Goal: To quantify exposure differences (contrasts) across human populations.
  - for purposes of understanding relationships between patterns of exposure and human health outcomes (i.e., epidemiology),
  - or to make informed decisions about human disease risk (i.e., risk assessment).

http://www.who.int/ipcs/methods/harmonization/areas/ipcsterminologyparts1and2.pdf

The Utility of Exposure Science

- Exposure science enables study of health effects of environmental contaminants
  - Epidemiology
  - Toxicology
  - Risk assessment

- And informs regulatory & other decision-making:
  - Policies & protections for environment and human health.
  - Identifying populations with disproportionate exposures/ risks.
  - Design and planning.

Hubal et al., JESEE 21:119, 2011

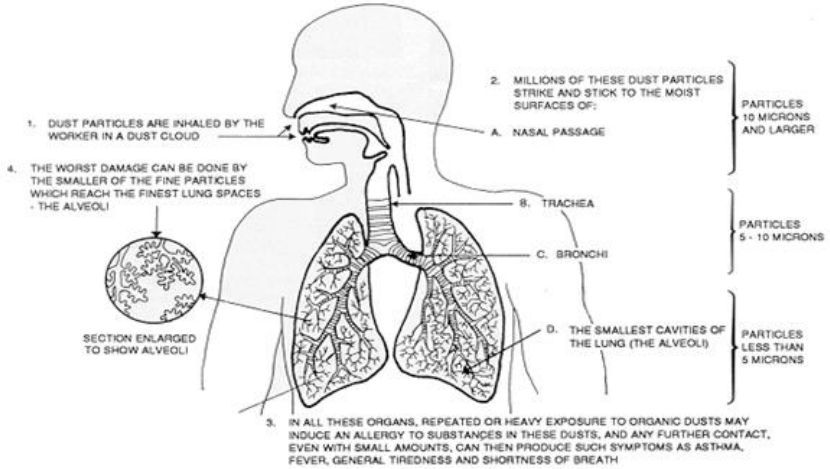
Exposure Science Paradigm:

Environmental Media (air (mg/m^3), water (mg/l), soil (% weight), food (mg/kg))

Source → Concentration → Exposure → Dose → Biologically Effective Dose → Human Health Effects

Time activity patterns

Exposure Routes
- Inhalation rates
- Ingestion rates
- Dermal absorption



Key methods in Exposure Science: Monitoring & Modeling

- Monitoring:
  - Tools & Technologies
    - To ensure the right chemical or compound, with high accuracy and reproducibility.
  - Monitoring systems/ design
    - Strategies to monitor in the right places, at the right times.
- Modeling:
  - Because it's not realistic or cost-effective to monitor everywhere, all the time, for everything…
  - To make reasonable estimates of exposure contrasts.
    - Across specific individuals or populations
    - In a given location, over a given time period.

We use a combination of monitoring & modeling methods to capture "Exposure Dimensions":

- Variability
  - Over time
  - Across space
  - Within individual
  - Between individuals
  - Between groups

- Uncertainty
  - Lack of data (e.g., statistical error in measurements)
  - Lack of understanding (e.g., wrong models or assumptions)

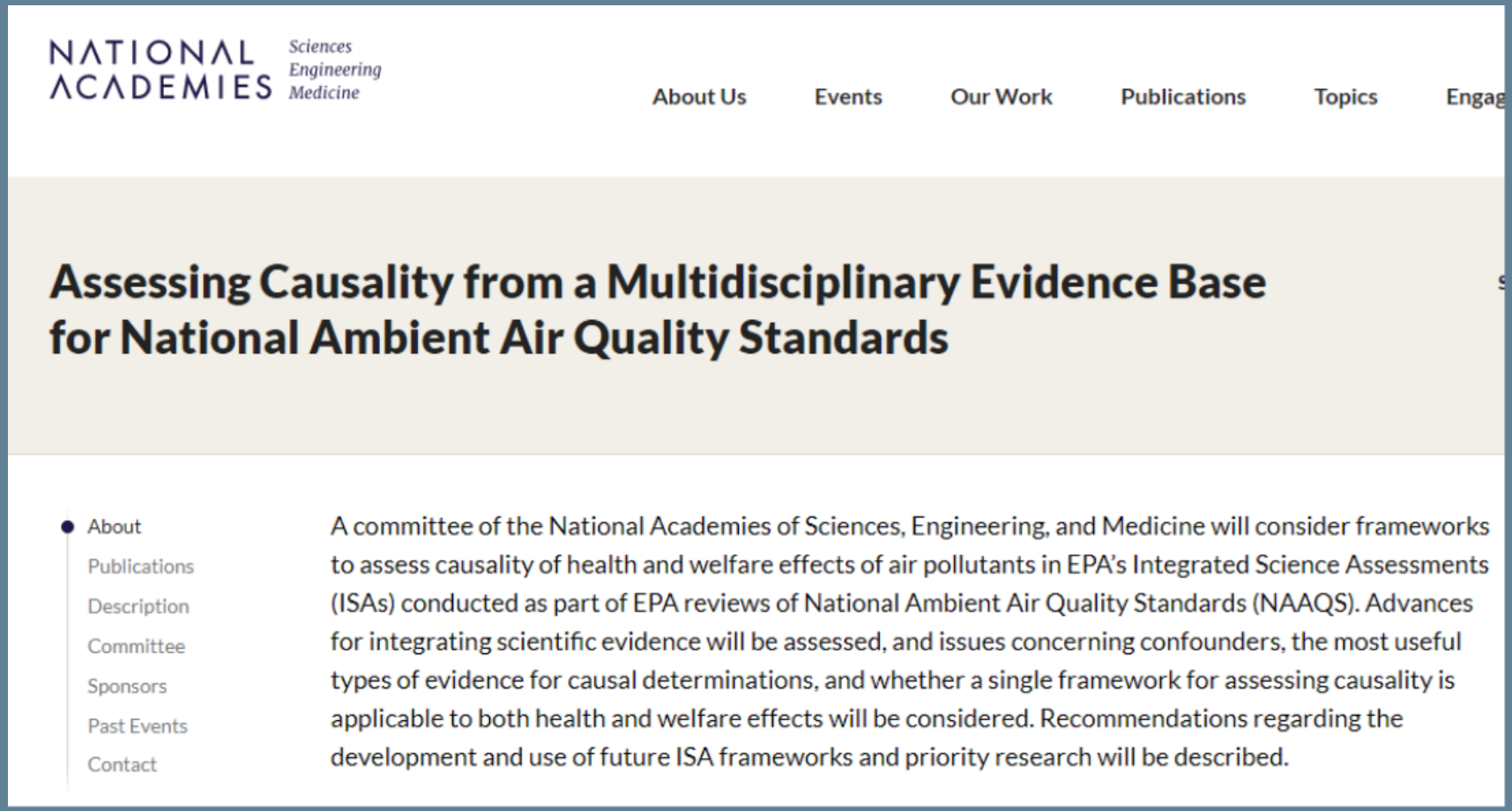
http://www.bvsde.ops-oms.org/tutorial3/fulltex/ehc214/ehc214.html#SectionNumber:1.1

Better relating toxicologic evidence to human populations…

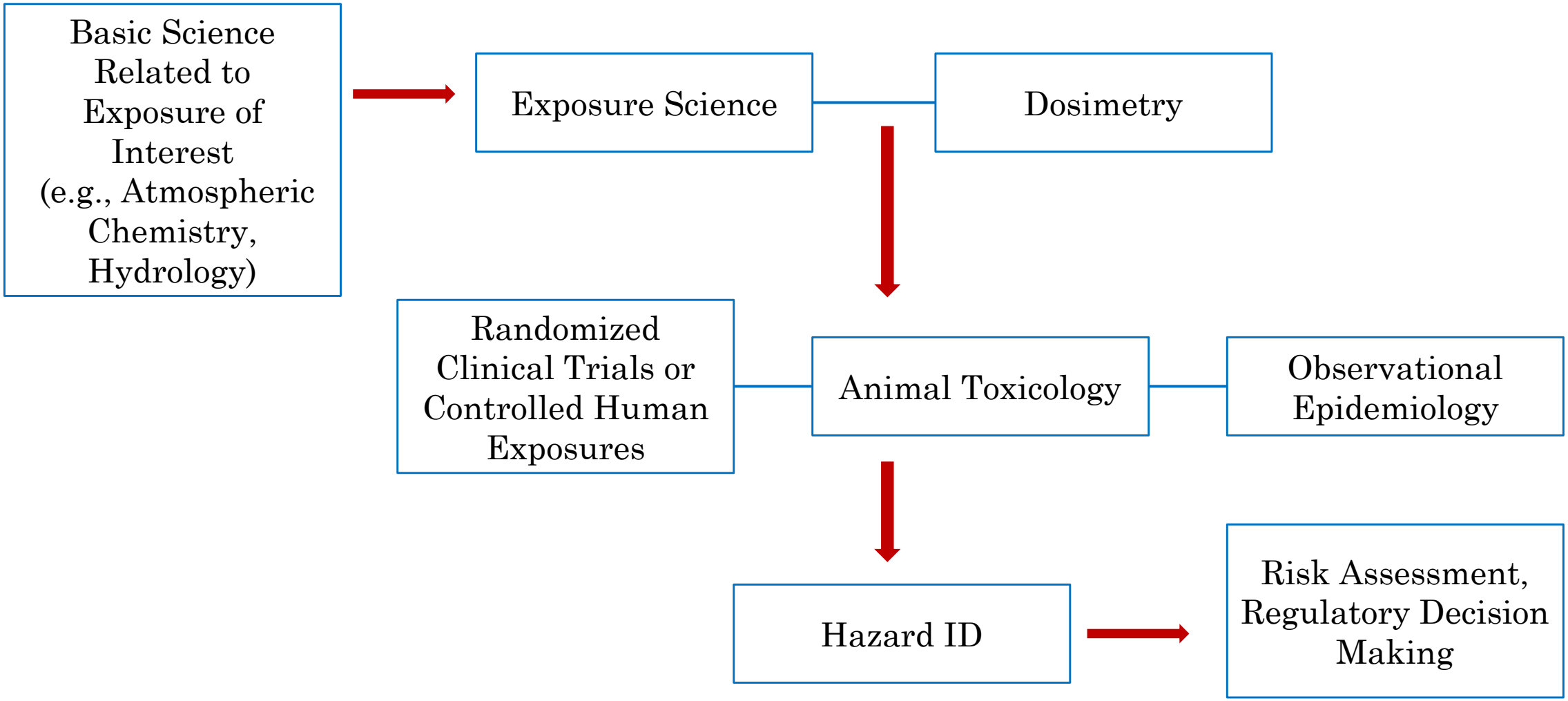
- May be achieved through an emphasis on exposures:
  - Use of realistic doses, when possible.
    - Detailed dose-response curve.
  - Attention to mode of action/ pathway/ mechanism.
  - Consider real-world exposure mixtures
    - & Effect modification.

http://www.bvsde.ops-oms.org/tutorial3/fulltex/ehc214/ehc214.html#SectionNumber:1.1

Framing Piece #3: Toxicology as part of a multidisciplinary evidence base



Role of Exposure Science in Regulatory Decision Making



Where to Find Guidance When Designing a Study

Table Annex 3-1 (Continued): Scientific considerations for evaluating the strength of inference from studies on the health effects of ozone.

Exposure Assessment or Assignment
Controlled Human Exposure:
For this assessment, the focus is on studies that use ozone concentrations <0.4 ppm. Studies that use higher exposure concentrations may provide information relevant to biological plausibility, dosimetry, or inter-species variation. Studies should have well-characterized pollutant concentration, temperature, and relative humidity and/or have measures in place to adequately control the exposure conditions. Preference is given to balanced crossover or parallel design studies that include control exposures (e.g., to clean filtered air). Study subjects should be randomly exposed without knowledge of the exposure condition. Method of exposure (e.g., chamber, facemask, etc.) should be specified and activity level of subjects during exposures should be well characterized.
Animal Toxicology:
For this assessment, the focus is on studies that use ozone concentrations <2 ppm. Studies that use higher exposure concentrations may provide information relevant to biological plausibility, dosimetry, or inter-species variation. Studies should characterize pollutant concentration, temperature, and relative humidity and/or have measures in place to adequately control the exposure conditions. The focus is on inhalation exposure. Noninhalation exposure experiments (i.e., intratracheal instillation [IT]) are informative and may provide information relevant to biological plausibility and dosimetry. *In vitro* studies may be included if they provide mechanistic insight or examine similar effects as *in vivo* studies but are generally not included. All studies should include exposure control groups (e.g., clean filtered air).
Epidemiology:

Where to Find Guidance When Designing a Study

"Finally, an additional source of uncertainty is some heterogenicity in the animal toxicological evidence. This may arise from differences in study design, such as varying exposure concentrations (0.25–1.0 ppm) and durations, differences in rodent strain, sex, or diet, or from the measurement of effects at different time points post-exposure."

- 2020 Ozone ISA, pg. 5-29

Table 5-2 Summary of changes in serum lipids from experiments conducted in male rats.

Study	Species (Stock/ Strain), Age	Exposure Details (Concentration, Duration)	Time at Measure-ment	Triglycerides[a]	Free Fatty Acids[a]	HDL[a]	LDL[a]	Total Cholesterol[a]
Miller et al. (2015)	Rats (WKY) Age: 10 weeks	1.0 ppm, 6 h	Immediately PE	-	↑	NS	NS	NS
		1.0 ppm, 6 h/day for 2 days	Immediately PE	-	↑	NS	↑	NS
		1.0 ppm, 6 h/day for 2 days	18 h PE	-	-	↑	↑	↑
Bass et al. (2013)	Rats (BN) Age: 1, 4, 12, and 24 mo	1.0 ppm, 2 days	18 h PE	-	-	↑ (12 mo old rats only)	NS	NS
Farraj et al. (2012)	Rats (SH) Age: 12 weeks	0.8 ppm, 4 h	24 h PE	-	-	↓	NS	NS
Farraj et al. (2016)	Rats (SH) Age: 12 weeks	0.8 ppm, 3 h	24 h PE	↑	-	NS	NS	NS
Vella et al. (2014)	Rats (Wistar) Age: adult (400–450 g)	0.8 ppm, 16 h	Immediately PE	NS	NS	-	-	NS

Where to Find Guidance When Designing a Study

Evaluation concern		Domain—core question	Prompting questions	General considerations
Sensitivity (continued)	Exposure methods sensitivity (continued)	**Exposure timing, frequency and duration** Was the timing, frequency, and duration of exposure sensitive for the endpoint(s)/outcome(s) of interest?	For each endpoint/outcome or grouping of endpoints/outcomes in a study: • Does the exposure period include the critical window of sensitivity? • Was the duration and frequency of exposure sensitive for detecting the endpoint of interest?	Considerations for this domain are highly variable depending on the endpoint(s)/outcome(s) of interest and must be refined by assessment teams. A judgment and rationale for this domain should be given for each endpoint/outcome or group of endpoints/outcomes investigated in the study. • **Good**: The duration and frequency of the exposure was sensitive, and the exposure included the critical window of sensitivity (if known). • **Adequate**: The duration and frequency of the exposure was sensitive, and the exposure covered most of the critical window of sensitivity (if known). • **Deficient**: The duration and/or frequency of the exposure is not sensitive and did not include most of the critical window of sensitivity (if known). These limitations are expected to bias the results towards the null. • **Critically deficient**: The exposure design was not sensitive and is expected to strongly bias the results towards the null. The rationale should indicate the specific concern(s).

Excerpt from Table 6-9 in ORD Staff Handbook for Developing IRIS Assessments, Version 1.0

Exposure Methods– Example 1 of 4

OXFORD
SOT | Society of Toxicology
www.toxsci.oxfordjournals.org
ToxSci 20 Years

TOXICOLOGICAL SCIENCES, 162(1), 2018, 189–199

doi: 10.1093/toxsci/kfx240
Advance Access Publication Date: November 7, 2017
Research Article

Early Postnatal Exposure to Airborne Fine Particulate Matter Induces Autism-like Phenotypes in Male Rats

Kang Li,*,† Li Li,* Bo Cui,‡ Zhihui Gai,‡ Qiuyue Li,* Shumei Wang,* Jun Yan,* Bencheng Lin,* Lei Tian,† Huanliang Liu,* Xiaohua Liu,†,1 and Zhuge Xi*,2

"Epidemiological studies have revealed that ambient fine particulate matter ($PM_{2.5}$) exposure is closely associated with autism spectrum disorder (ASD). However, there is a relative paucity of laboratory data to support this epidemic finding. In order to assess the relationship between $PM_{2.5}$ exposure and ASD, neonatal male Sprague–Dawley rats were chosen and exposed to $PM_{2.5}$ (2 or 20 mg/kg body weight, once a day) by intranasal instillation from postnatal day 8 to 22. "

Exposure Methods – Example 2 of 4

Chang *et al. Particle and Fibre Toxicology* (2018) 15:18
https://doi.org/10.1186/s12989-018-0254-4

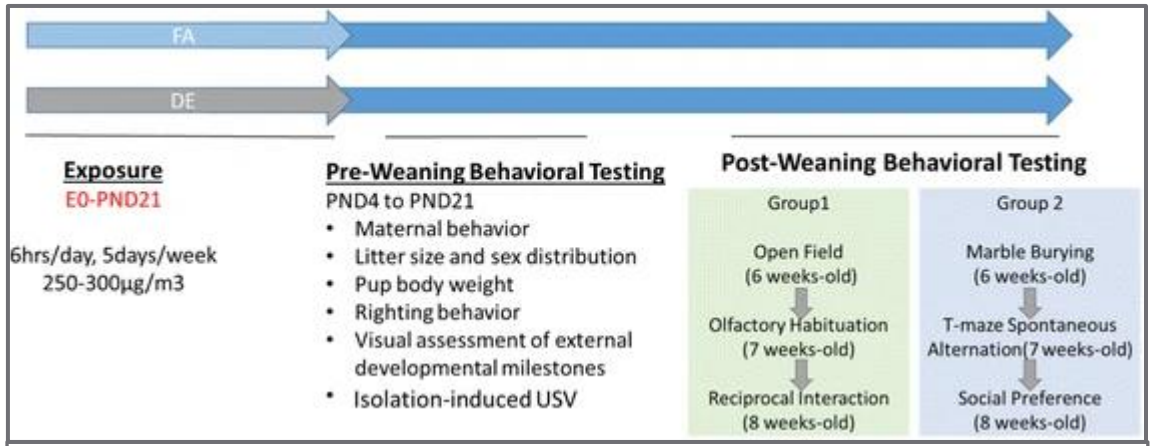
Particle and Fibre Toxicology

RESEARCH Open Access

Prenatal and early-life diesel exhaust exposure causes autism-like behavioral changes in mice

Yu-Chi Chang[1], Toby B. Cole[1,2*] and Lucio G. Costa[1,3]

"The exposure period was based on epidemiological studies in humans showing that traffic-related air pollution exposure during all three trimesters of pregnancy and during the first 9 months of infants' life is associated with increased ASD risk [5, 22, 24, 27]. The exposure duration was designed to cover key neurodevelopmental events happening during this window of susceptibility, which in mice equates to the period from E0 to PND21 [33]."



Experimental Design. C57/BL6J mice were time-mated and exposed to 250–300 µg/m³ of DE or FA from E0 to PND21 for 6/day and 5 days/week. Pre-weaning developmental assessment started on PND3. Behavioral assessment focusing on three characteristic domains of ASD started when the mice were 6 weeks old

Exposure Methods– Example 3 of 4

Environmental Research 183 (2020) 109242

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Traffic-related particulate matter affects behavior, inflammation, and neural integrity in a developmental rodent model

Benjamin C. Nephew[a,b,*], Alexandra Nemeth[c], Neelakshi Hudda[d], Gillian Beamer[e], Phyllis Mann[f], Jocelyn Petitto[g], Ryan Cali[a,b], Marcelo Febo[h], Praveen Kulkarni[i], Guillaume Poirier[b], Jean King[a,b], John L. Durant[d,j,k], Doug Brugge[l]

"Recent studies indicate that exposure to airborne particulate matter (PM) is associated with cognitive delay, depression, anxiety, autism, and neurodegenerative diseases; however, the role of PM in the etiology of these outcomes is not well-understood. Therefore, there is a need for controlled animal studies to better elucidate the causes and mechanisms by which PM impacts these health outcomes. We assessed the effects of gestational and early life exposure to traffic-related PM on social- and anxiety-related behaviors, cognition, inflammatory markers, and neural integrity in juvenile male rats. Gestating and lactating rats were exposed to PM from a Boston (MA, USA) traffic tunnel for 5 h/day, 5 days/week for 6 weeks (3 weeks gestation, 3 weeks lactation). The target exposure concentration for the fine fraction of nebulized PM, measured as PM2.5, was 200 μg/m^3."

Exposure Methods – Example 4 of 4

Berg et al. *Translational Psychiatry* (2020)10:289
https://doi.org/10.1038/s41398-020-00978-0

Translational Psychiatry

ARTICLE Open Access

Developmental exposure to near roadway pollution produces behavioral phenotypes relevant to neurodevelopmental disorders in juvenile rats

Elizabeth L. Berg[1], Lauren R. Pedersen[1], Michael C. Pride[1], Stela P. Petkova[1], Kelley T. Patten[2], Anthony E. Valenzuela[2], Christopher Wallis[3], Keith J. Bein[3], Anthony Wexler[3], Pamela J. Lein[2] and Jill L. Silverman[1]

"Epidemiological studies consistently implicate traffic-related air pollution (TRAP) and/or proximity to heavily trafficked roads as risk factors for developmental delays and neurodevelopmental disorders (NDDs); however, there are limited preclinical data demonstrating a causal relationship. To test the effects of TRAP, *pregnant rat dams were transported to a vivarium adjacent to a major freeway tunnel system in northern California where they were exposed to TRAP drawn directly from the face of the tunnel or filtered air (FA).* "

Exposure to Mixtures – Example 1

Published in final edited form as:
Toxicol Appl Pharmacol. 2020 December 15; 409: 115296. doi:10.1016/j.taap.2020.115296.

Fish Oil and Olive Oil-Enriched Diets Alleviate Acute Ozone-induced Cardiovascular Effects in Rats

Haiyan Tong[1], **Samantha J. Snow**[2,*], **Hao Chen**[3], **Mette C. Schladweiler**[2], **Gleta Carswell**[4], **Brian Chorley**[4], **Urmila P. Kodavanti**[2]

"Fish oil (FO) and olive oil (OO) supplementations attenuate the cardiovascular responses to inhaled concentrated ambient particles in human volunteers. This study was designed to examine the cardiovascular effects of ozone (O_3) exposure and the efficacy of FO and OO-enriched diets in attenuating the cardiovascular effects from O_3 exposure in rats. "

Exposure to Mixtures – Example 2

Journal of Animal Research: v.7 n.3, p. 465-470. June 2017

DOI: 10.5958/2277-940X.2017.00069.9

Study on Neuroendocrine Disrupting Potential of Cadmium in Rats and Evaluation of Role of Green Tea

Pabbathi Shivakumar*, Alla Gopala Reddy, Gangineni Aruna Kumari, Nagireddy Nalinikumari and Ramya B

P.V. Narasimha Rao Telangana Veterinary University, Rajendranagar, Hyderabad, Telangana, INDIA

**Corresponding author: P Shivakumar; Email: drshiva40@gmail.com*

Received: 27 Dec., 2016 **Revised:** 20 Feb., 2017 **Accepted:** 21 Feb., 2017

"Twenty-four weaned Sprague Dawley male rats were randomly divided into 4 groups of 6 rats in each . Group 1 served as Sham control, Group 2 was treated with CdCl2 @5mg/kg b.wt. per orally for 3 months, Group 3 was treated with Green tea extract(1.5%) and Group 4 with CdCl2 + green tea extract. The serum testosterone, Tri-iodothyronine (T3) and Thyroxine (T4) hormones were monitored at monthly interval…Treatment with green tea significantly ameliorated ($p<0.05$) toxic effects of CdCl2 by restoring biochemical and hormonal profile to normal. "

Beyond EPA and Air Pollution…

Federal Agencies

ATSDR

OSHA

FDA

National Institute for Occupational Safety and Health
NIOSH

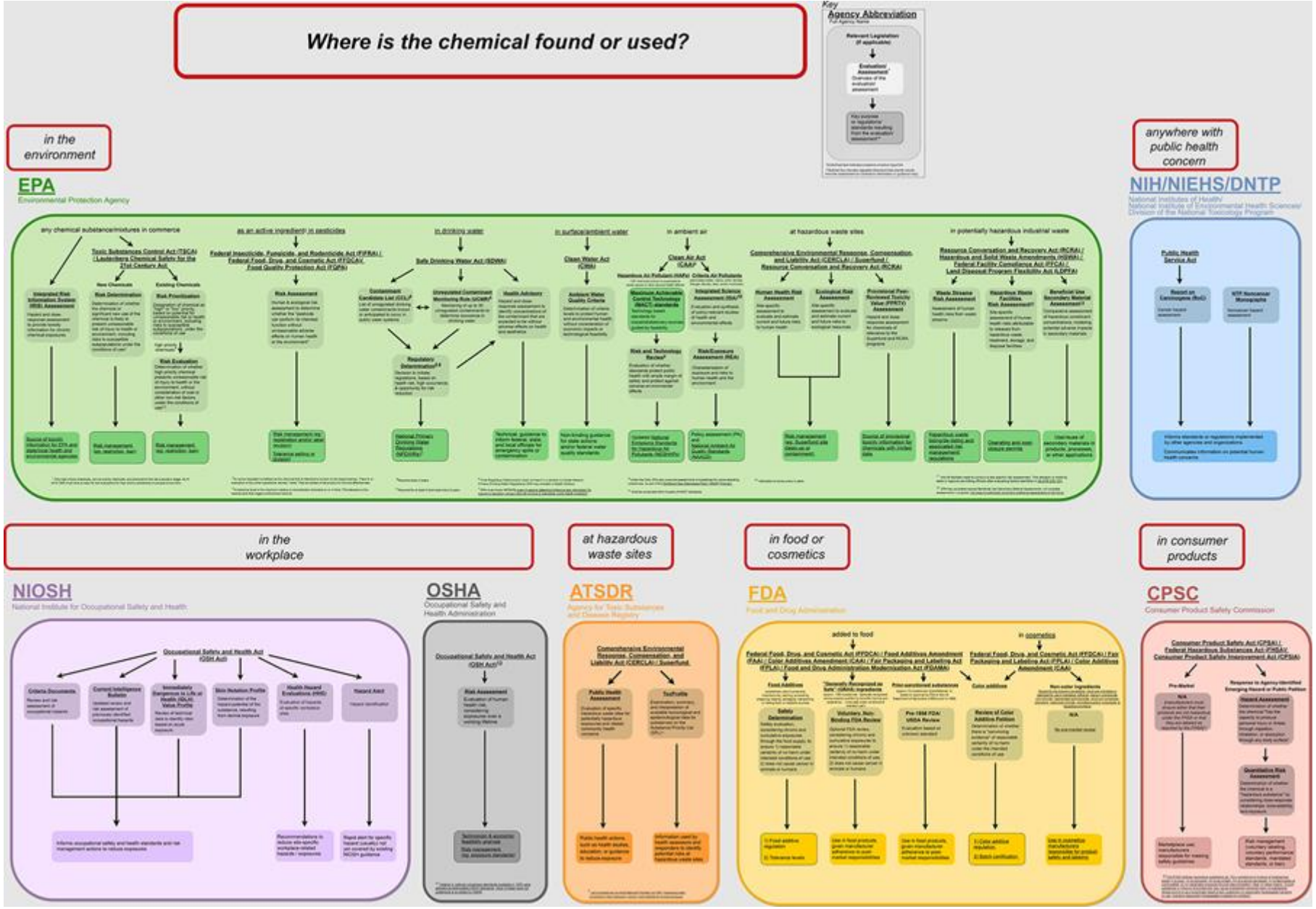
State Agencies

TCEQ

Other Entities

ACGIH®

AIHA
Protecting Worker Health



An overview of federal chemical evaluations and assessments in the United States. As indicated by the figure key, the agency abbreviation and full agency name are located in the upper left corner above each subsection. Within each subsection, arrows lead from the relevant legislation (if applicable) to the evaluation or assessment (light shaded box) and then further to the downstream purpose of each (dark shaded box). For EPA and FDA, there are additional levels of organization above each statute based on where the chemical is found. Outlined boxes at the bottom of each subsection indicate a formal regulation or standard that directly results from the evaluation or assessment; non-outlined boxes indicate non-binding guidelines or recommendations alone. Underlined text denotes active hyperlinks available for further reference in the interactive HTML version. A fully interactive version of this image is available as Supporting Information. *Environ. Sci. Technol.* 2021, 55, 16, 10923-10927 DOI: (10.1021/acs.est.1c01955)

Summary/Conclusions

- Exposure science can help to improve applicability of toxicological evidence to regulatory decision-making and improved public health protections
- Utility of “iterative” exposure science in toxicological (and other) research in building a robust evidence base to inform regulatory decision-making.
- Useful resources from EPA and other federal agencies exist that can aid in designing exposure components of future experiments.

Questions?

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