Conflicting communications by scientists: Does endocrine disruption really require a special approach in toxicological risk assessment?

Dan Dietrich
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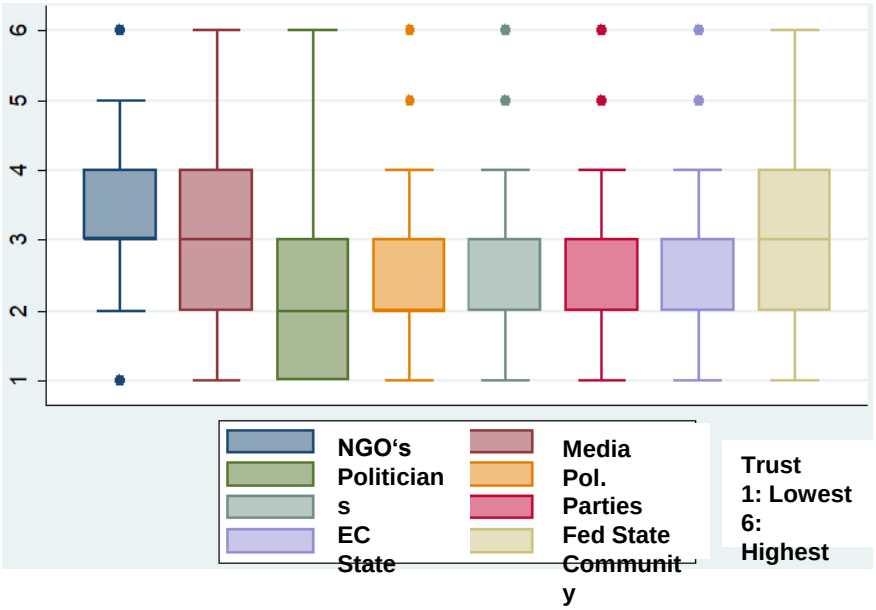
University of Konstanz

The Chasm Between Scientist and the Public

„There is a wide opinion gap between scientists and the general public in the United States when it comes to their attitudes about the state of science and science-related policy....“ Alan Leshner CEO of AAAS and Executive Publisher of Science, Science JANUARY 2015 • VOL 347 ISSUE 6221

“Speaking up for the importance of science to society is our only hope...”

Public Trust in Institutions



Prof. J. Tosun , Uni Tübingen, 2018

Scientists and Media Limelight?

CJD: experts fear 100,000 new cases

Nature **volume 385**, pages 197–198 (16 January 1997) Scientists warn today that there remains the potential for an **epidemic** of new variant **Creutzfeldt-Jakob disease**, approaching **100,000** cases, even though only four cases have been confirmed since last March.

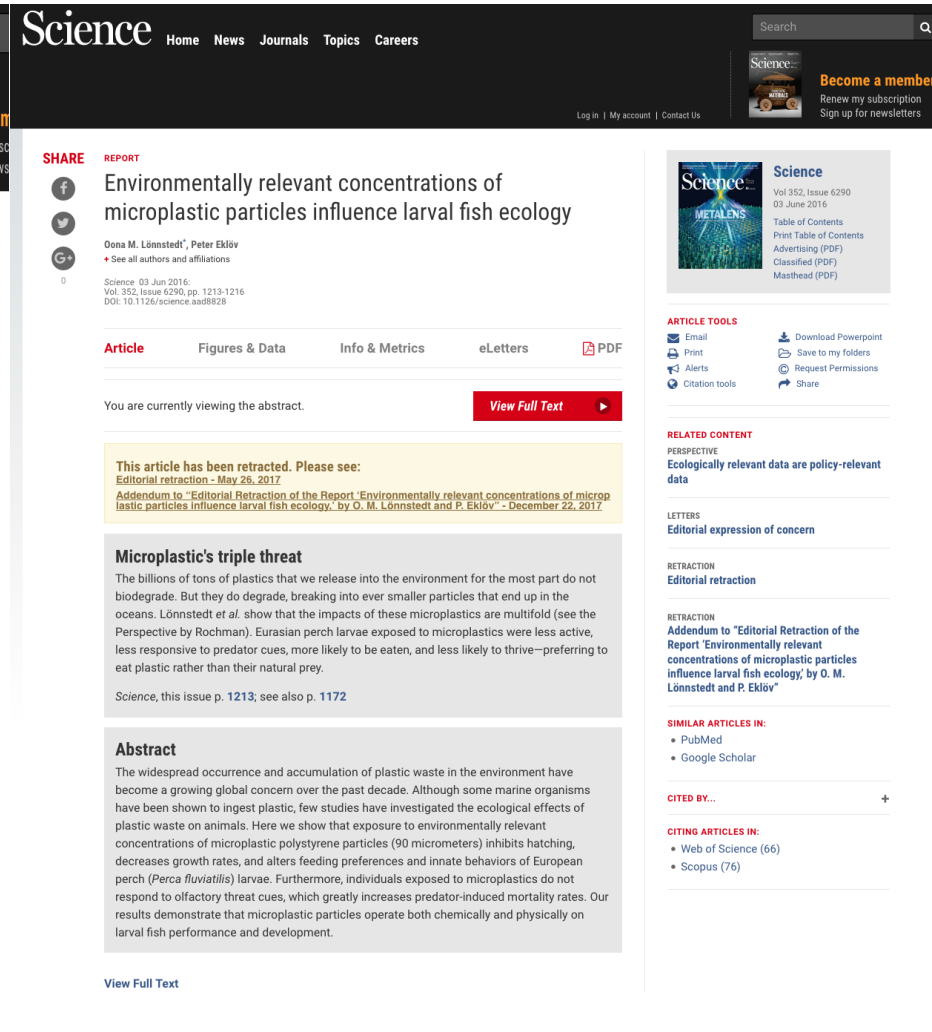
Predicting the CJD epidemic in humans

Nature Vol 385 16.1.96 p197 (rejected by The Lancet)

Epidemic or false alarm?

Nature vol 385 17.1.96 p200

Role of the Science Media?



Accession date: 03.11.2018, 15:03

Environmental Health News
Published by Environmental Health Sciences

Scientists clash over BPA: Do low doses really harm people?

Are people exposed to doses of bisphenol A in their canned foods and other consumer products that can harm them? Or are the amounts too low to cause any harm? This is the crux of a vehement debate that is being waged as federal officials are trying to decide whether the chemical, known as BPA, should be regulated. A group of toxicologists, including some who work for federal agencies, is questioning the likelihood that BPA is harming human health. But biologists studying the chemical's health effects disagree, saying that what's been detected in people is comparable to amounts that have harmed lab animals. BPA is arguably the most controversial chemical in consumer products. It is used to make polycarbonate plastic as well as food and beverage can liners and some paper receipts and dental sealants. What is widely agreed upon is that exposure is nearly ubiquitous. More than 90 percent of Americans tested have traces of BPA in their bodies.

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There is "not sufficient evidence on which to make claims that humans are at risk at current exposure levels." *-Justin Teeguarden, Pacific Northwest National Laboratory*

„D

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journal

Editorial

Scientifically unfounded pr
recommendations on EDC
well-established science ar

We, the undersigned editors of prominer
cology and toxicology, are drawing your atte
decisions by the European Commission to
framework for so-called endocrine disrupt
The currently drafted framework is based
ignorance of all well-established and taught
cology and toxicology, of opinions raised by t
sions own competent expert authority
statements made by member countries, wh
support from the European Commission's
committees.

As a statement, and as emphasized by oth
disruption" is not a toxicologically defined
of-action that may or may not result in ad
the mode-of-action concept implies the ne
threshold as experimentally proven for num
toxic agents including EDC's. Moreover, end
fundamental role in the physiological respo
environment with the aim of keeping an orga
the homeostatic space. It is the task of toxi
distinction between those effects that are
range and effects that go beyond the bou
and thus can be called adverse. Such ac
observed in adequately designed and perfor

While we agree that a concern for possibl
important, we also think that the identifica
such substances should depend on (a) the de
fects that are relevant to whole human or
not to isolated test systems of unknown hor
and (b) on a characterization of real-life pot
thresholds of concern.

In contrast, the currently drafted EU fran
sees *a priori* regulation of agents that may sh

Dietrich et al 2

Nature editorial 'exploits public anxiety' on endocrine disruptors

Geoffrey Kabat | Genetic Literacy Project | December 15, 2016

Prof. of Epidemiology, Albert Einstein College of Medicine in New York City

In December 2016, the European Union member states will vote on proposed legislation that would mandate an ambitious program to identify and regulate "endocrine-disrupting chemicals (EDCs) in the environment. On November 22, the journal *Nature* carried an editorial entitled "Stand firm on hormone disruptors" by NYU pediatrician Leonardo Trasande. Rather than laying out the scientific issues relevant to consideration of the problem of chemicals in the environment and their

ia"

ptor chemicals (EDCs) that possibly
call for restrictions, regulatory toxi-
lemned the "scientifically unfounded
oks at the ongoing scientific battle

betes, low sperm quality in young men (up to 40% in some countries), earlier onset of breast development in girls and neurobehavioural disorders associated with thyroid disruption in children.

The **second** line of evidence is the observation of endocrine-related effects in wildlife populations that are closely associated with chemical pollution.

And **finally**, laboratory studies have identified chemicals with endocrine disrupting properties that can be linked to observed diseases.

However, understanding the complexity of the endocrine systems themselves, let alone how the EDCs may be affecting them, is proving to be a major scientific challenge. It's an alarming fact that the common moc-

"***These chemicals are everywhere – in food, personal-care products, electronics and furniture – and are widely detected in human blood and urine at levels known to affect health.***" L. Trasande, Nature 539, 469 (24 November 2016) doi:10.1038/539469a

Who to believe / trust

- *„Frankly, I can‘t really say what and whom to believe!“*
- *Julie Girling MEP, October 26, 2017, European Parliament Endocrine Disruption Panel*

Human Cost Burden of Exposure to Endocrine Disrupting Chemicals:

"**Health effects from ED exposures cost the EU over 157 Billion € each year**"

Endocrine Society Letter to Commissioner Vytenis Andriukaitis

October 2015

EDC Cost Estimates

Table 1 Summary of findings from studies estimating societal costs attributable to EDC exposures (Trasande et al. 2015; Bellanger et al. 2015; Hauser et al. 2015; Legler et al. 2015; Hunt et al. 2016; Attina et al. 2016)

Exposure	Outcome	Strength of epidemiology evidence	Strength of toxicological evidence	Probability of causation, %	Base estimates of annual costs	
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BPA	Childhood obesity	Very low-to-low	Strong	20–69	1.5	2.4
PBDEs	Testicular cancer	Very low-to-low	Weak	0–19	0.85	0.08
PBDEs	Cryptorchidism	Low	Strong	40–69	0.13	0.04
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Phthalates	Low T, resulting in increased early mortality	Low	Strong	40–69	8.0	10.6
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Multiple exposures	ADHD	Low-to-moderate	Strong	20–69	1.7	0.70
Multiple exposures	Autism	Low	Moderate	20–39	0.20	2.0

ADHD attention-deficit hyperactivity disorder

Current guideline Values Chlorpyrifos

- US-EPA (2011):
  - Acute adjusted population dose (aPAD) based on blood and brain ChE Inhibition in PND 11 and 17 rats. $BMLD_{10}$ in male rats of 0.36 mg/kg bw chosen as POD and a Safety Factor of 100: 3.6µg/kg bw.
  - Acceptable Daily Intake (ADI): based on neuroteratogenicity study in pregnant rats with a $BMLD_{10}$ of 0.03 mg/kg bw and a Safety Factor of 100: chronic population adjusted dose (cPAD) 0.3µg/kg bw.
- US-EPA/EDSP (2017): no further testing for EDC based on lack of interaction with estrogen, androgen and thyroid hormone signalling pathways

CPF: What is the human situation?

- Current epidemiologic data: insufficient evidence that human developmental exposures to CPF produced adverse neuro-behavioural effects in infants and children (status 2013)
- Reiss et al (Critical Reviews in Toxicology 45, 2015) Systematic review of epidemiologic studies related to low-level non-occupational exposures to organophosphorus (OP) insecticides.
  - Most of the studies assessing exposure based on urinary levels of OP insecticide metabolites used only one or two measurements during pregnancy.
  - The potential for exposure misclassification with this method is largely due to (1) preformed metabolites that are ingested with food, (2) the short elimination half-life of OP insecticides, and (3) lack of specificity to particular OP insecticides for many of the metabolites.
  - The OP insecticide levels measured in the epidemiologic studies are too low to cause biologically meaningful acetylcholinesterase inhibition, the most widely used metric for OP insecticide toxicity.
  - Overall, the available evidence does not establish that low-level exposures to OP insecticides cause adverse birth outcomes or neurodevelopmental problems in humans.

PBDE low dose: Hazard Assessment-I

National Academy of Sciences: Low-dose Phthalates and PBDE toxicological evaluation
21.7.2017 – I Epidemiology & Animal Data

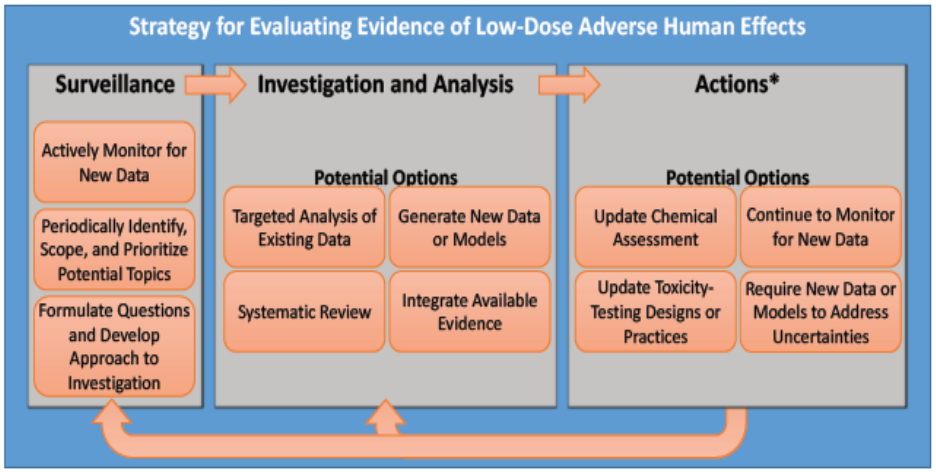
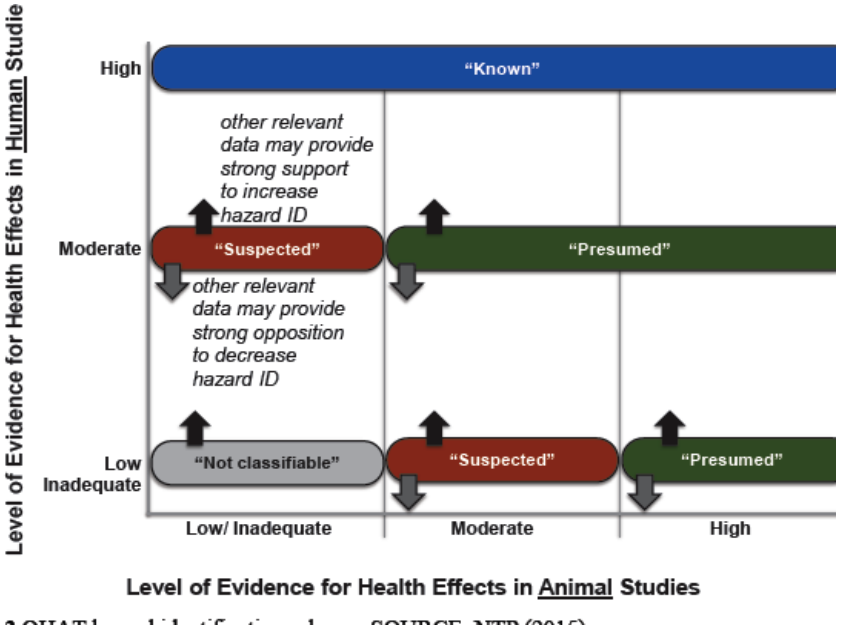


FIGURE S-1 Strategy for evaluating evidence of adverse human effects from low-dose exposure to chemicals. The strategy includes three broad phases: surveillance, investigation and analysis, and actions. Each phase includes multiple options that may be employed alone or in combination. The order in which the options appear does not indicate a hierarchy or a sequence that should be followed. *Recommendations for this phase of the strategy were outside of the committee's charge.

Low-Dose Panel:
- all stakeholders (total: 11)
- external peer-reviewers for protocol (7) and results (14)

Envtl. Studies and Toxicology Panel:
- all stakeholders (total: 20)
- external peer-reviewers for protocol (7) and results (14)



PBDE low dose: Hazard Assessment-II

National Academy of Sciences: Low-dose Phthalates and PBDE toxicological evaluation
21.7.2017 – I Epidemiology & Animal Data

Effects of PBDEs on Neurobehavioral Function

BOX S-3 Example 2

Question: Is developmental exposure to PBDEs associated with effects on neurobehavioral function?

Example chemical examined: BDE-47

Example end point examined: Learning in animals and intelligence in humans

Level of evidence conclusions: There is a moderate level of evidence that exposure to BDE-47 is associated with decrements in learning in rodents and decreases in IQ in humans.

Hazard classification conclusion: Overall, the evidence supports a conclusion that BDE-47 is a presumed hazard to humans with respect to effects on intelligence. This conclusion means that there was sufficient animal and human evidence to allow the committee to conclude that BDE-47 is a potential hazard to human health. Identifying the potential of a chemical to cause particular forms of toxicity in humans does not indicate whether the substance poses a risk in specific exposed populations. Such a determination requires the completion of a risk assessment that takes into consideration exposure of a given population; a risk assessment was not performed by the committee.

[6]A full analysis of other BDEs and end points is presented in Chapter 4. The hazard conclusions reached on the other congeners and end points were either equivalent to or weaker than the one reached for BDE-47 and learning in animals and intelligence in humans.

Current guideline Values PBDE

- US-EPA (2017): chronic oral reference doses (RfDs) based on neurotox :
  - decaBDE-209: 7µg/kg bw/d
  - octaBDE congener: 3µg/kg bw/d
  - pentaBDE congener: 2µg/kg bw/d
  - tetraBDE-47: 0.1 µg/kg bw/d*
  - hexaBDE-153: 0.2 µg/kg bw/d*
  - pentaBDE-99: 0.1 µg/kg bw/d* **

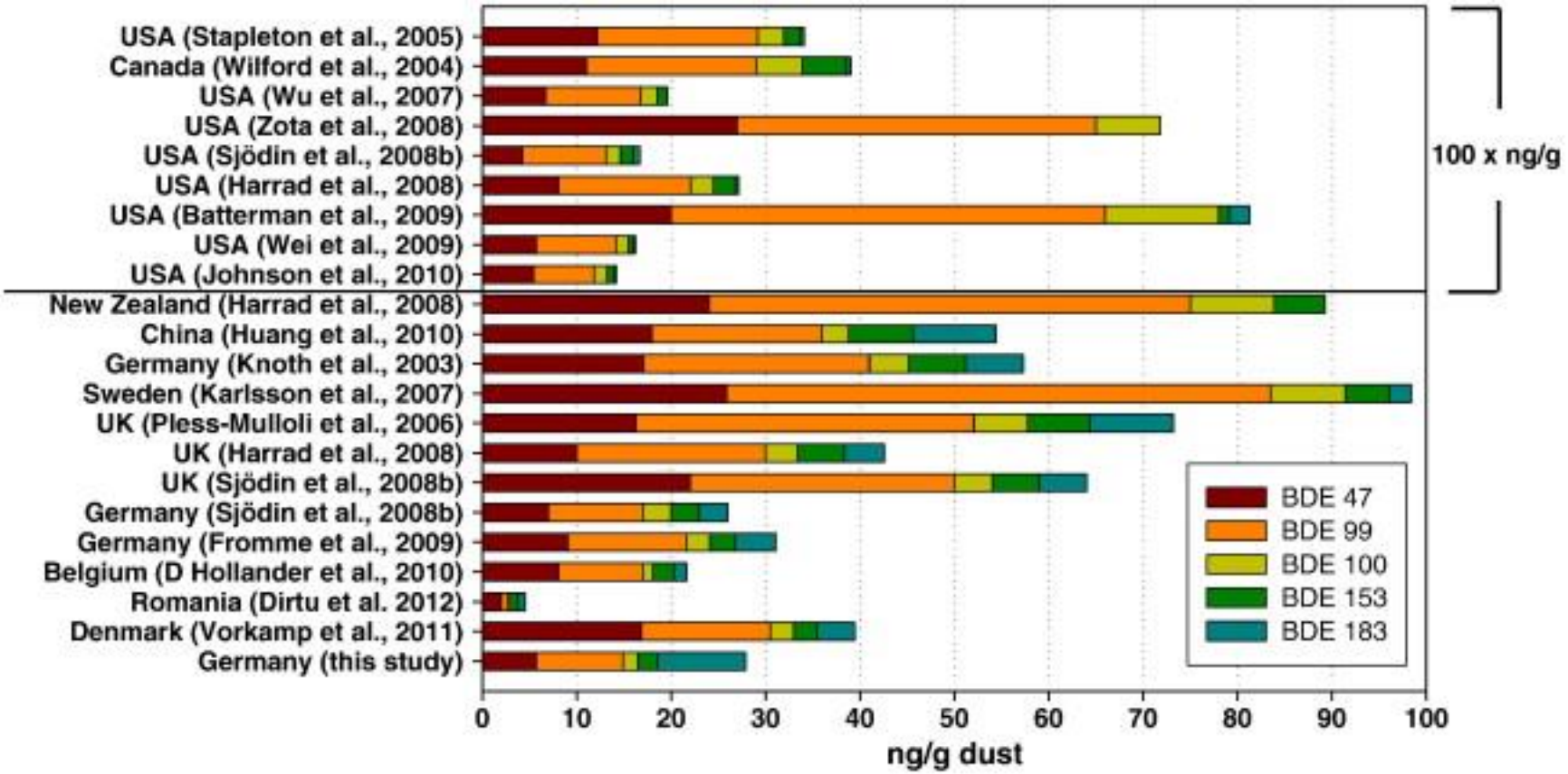
  *Safety Factors: 3000; **0.29mg/kg bw BMDL single dose after birth mouse neurotox (behavioural)

- EFSA CONTAM (2011): $BMDL_{10}$s established based on neurotox
  - decaBDE-209: 1700µg/kg bw
  - tetraBDE-47: 309 µg/kg bw
  - hexaBDE-153: 83 µg/kg bw
  - pentaBDE-99: 12 µg/kg bw

EFSA-CONTAM Panel 2011

- Refrained from setting ADI‘s due to limitations and uncertainties in the database, specifically with regard to rodent:human differences in excretion kinetics.
- However, using a Margin of Exposure (MOE) approach EFSA and body burden suggested that for:
  - BDE-47, -153 and -209 current dietary exposure in **adults** in the EU does not raise a health concern
  - for BDE-99 there is a potential health concern

PBDE in house dust (2014)



- High house dust intake scenarios would translate to 0.1% (addults) and 0.7% (toddlers) of the US-EPA RfD of tetra and hepta PBDE summed.
- MOE calculations using the LOAEL of 0.9 mg/kg bw in mice (learning and memory) fom Erikssson et al 2006) and highest intake scenario (95th percentiles) for toddlers is approx. **100‘000**.

Fromme et al Environment International 2014, 64:61-68

What are recent exposure situations?

- Bjermo et al (Chemosphere 2017, 167:485-491):

Risk assessment of BDE-47, BDE-99 and BDE-153, based on calculated body burdens from serum levels analyzed in the present paper. Margins of exposure are produced with reference to the EFSA risk assessment on PBDEs (EFSA, 2011).

Congener [a]	Median/max.	Serum level [b]	Calc. body burden (BB) [c,d]	BB $BMDL_{10}$ (EFSA data) [c]	MOE (BB $BMDL_{10}$/BB)
BDE-47	Median	0.49	0.098	232	2367
	Maximum	44	8.8	232	26
BDE-99	Maximum[e]	6.1	1.2	9	7.5
BDE-153	Median	1.2	0.24	62	258
	Maximum	7.0	1.4	62	44

[a] BDE-209 not included due to lack of BB $BMDL_{10}$ data.
[b] In ng/g lipid.
[c] In μg/kg body wt.
[d] Body burden values were achieved by assuming 20% body fat (fat adjusted serum levels × 0.2).
[e] Only maximum level of BDE-99 due to few levels above LOD, making median level uncertain.

*„**Based on our results, current BFR body burdens among adults give sufficient MOEs in relation to body burdens causing negative effects in animals**.“*

Non Monotone Dose Response Relationships (NMDR)

- in vivo NMDR are rare or inexistent: Varret et al TAAP 339: 10-23, 2018
  - Analysed 179 in vivo studies
  - 10 of which appeared to have an NMDR
  - Replication of these 10 studies would be required to eliminate procedural issues during the in vivo study that could have been the basis of the presumed NMDR

Human cost burden of exposure to endocrine disrupting chemicals. A critical review.

(Bond and Dietrich, Arch Toxicol (2017) 91:2745-2762 DOI 10.1007/s00204-017-1985-y)

- Reviewed methodology used and conclusions developed:
  - modified DELPHI Method for multiple iterations of opinions formed
  - GRADE (GEPHI) Method for evaluating epidemiologic data
  - IPCC method for evaluating probability of causation
  - Used health deficits (e.g. lowered IQ and intellecutal disability) to calculate estimated costs attributed to different EDCs.

Associations where epidemiology evidence was judged at least Moderate

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Based on WoE approaches the strength of toxicological evidence should have been „**Moderate**“ (see NAS 2017)

Based on GRADE methodology Trasande panels should **not** have judged any epidemiology evidence stronger than **Low**

Human cost burden of exposure to endocrine disrupting chemicals. A critical review.

(Bond and Dietrich, Arch Toxicol (2017) 91:2745-2762 DOI 10.1007/s00204-017-1985-y)

- Major conclusions from reviewing the cost estimates:
  - Issues with: Role of Steering Committee, Literature search, selection of underlying scientific studies, Weight of evidence analysis, Evaluation of animal toxicology evidence, Evaluation of human epidemiology evidence, Framework for assessing probability of causation
  - **Causal relationships between putative exposures to EDCs and selected diseases**, e.g., “loss of IQ” and “increased prevalence of intellectual disability,” were **assumed** but **were not established via thorough evaluation of strengths and weaknesses of underlying animal toxicology and human epidemiology evidence**.
  - Consequently, assigned disease burden costs are **highly speculative** and **do NOT serve to inform the public in a balanced manner**.

HOWEVER!

- The hazard assessment by the NAS and the RA/RM by US-EPA and EC primarily look at SINGLE COMPOUNDS
- Similarly epidemiological studies often look at asociations between body burdens /exposures and health outcomes considering single compounds or classes.
- Currently we DO NOT sufficiently consider
  - additive or antagonistic activity of compounds
  - associations of health effects resulting from co-occurring natural compounds (flavonoids, BPF, etc.)

Indeed, Mixtures matter!

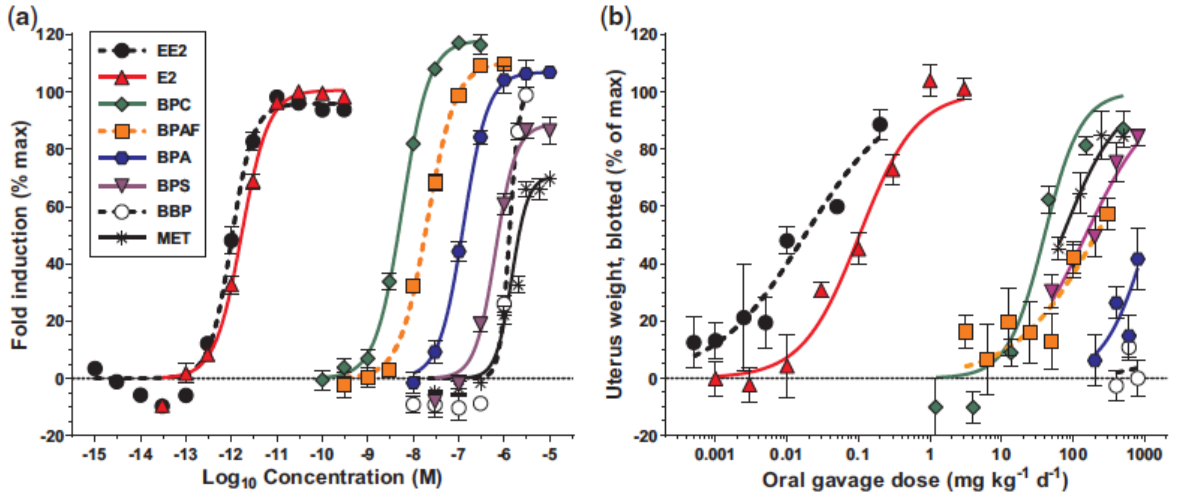
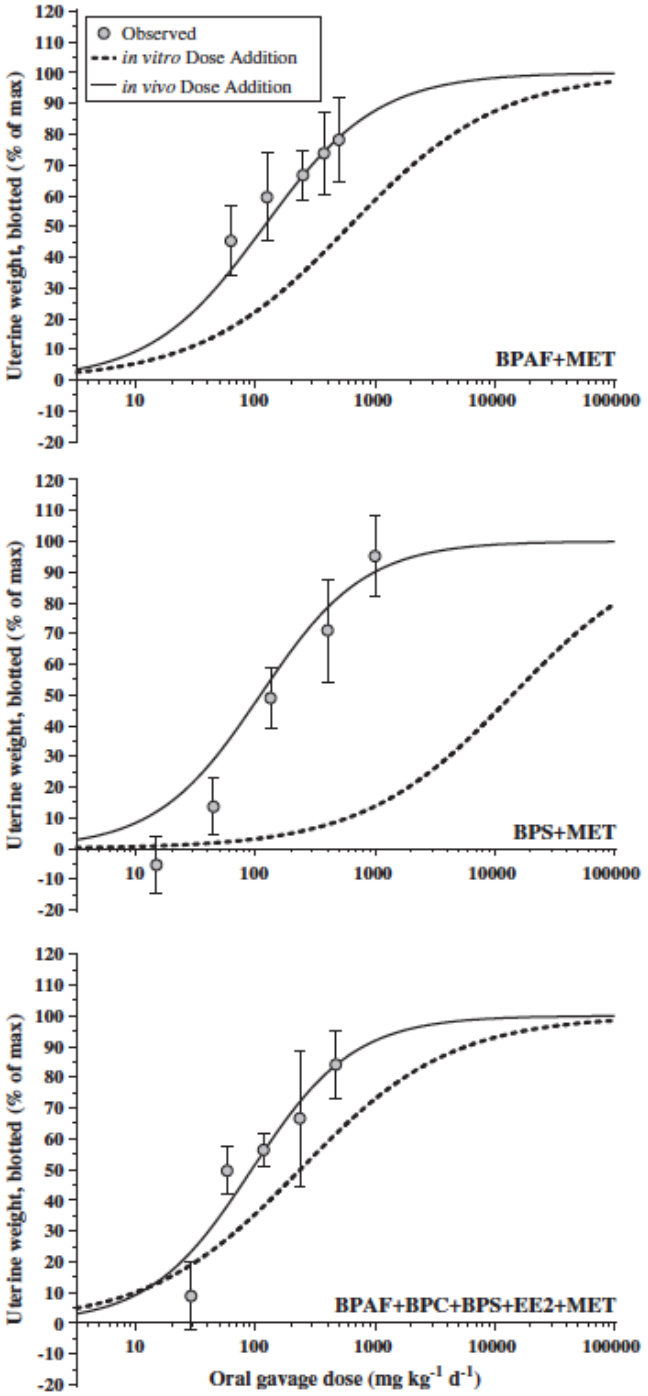


FIG. 2. Individual chemical *in vitro* (T47D-KBluc assay, panel a) and *in vivo* (ovariectomized rat uterotrophic, oral administration, panel b) dose response
Symbols and error bars represent mean ± standard error, dashed horizontal line indicates zero baseline. Color version available in online version of manuscript

From: Conley et al Tox Sci 153(2): 382-395,2016



Observed data (gray circles) versus dose addition (DA) models of binary (BPAF.MET; BPS.MET) and multi-chemical (BPAF.BPC.BPS.EE2.MET) mixtures in the ovariectomized rat uterotrophic assay (oral gavage). DA models were generated using individual compound in vitro (T74D-Kbluc, black dashed lines) and in vivo (black solid lines) response data. Observed data represent mean±95% CI; statistical significance based on model predictions overlapping the observed 95% CI.

Conclusions

- EDCs as single compounds, at least in the current scientific setting, appear to follow typical dose-response relationships toxins and thus have a threshold where no adverse effects can be observed
- Mixtures, agonists, antagonists, competitors, should be considered more thoroughly (e.g. BPDE additivity, competition for elimination etc.)
- Scientists and science media need to be much more prudent and responsible in their communication with mainstream media and politicians especially with regard to simplifications and in how far new findings can be extrapolated to the broader context
- Stakeholders (Industry, Gov. Authorities) should embrace a much more **proactive** approach, rather than doing the „just required“ in order to provide for the „safety and reasurance“ the public seeks.

“What is the harm if the costs of EDCs are grossly exaggerated?

- Everyone loses when the scientific method, which demands a level of impartial objectivity, is not met.

THANK YOU