Presentation by
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Stakeholder-input meeting on EFSA's draft protocol for BPA hazard assessment

Brussels, 14 Sept. 2017
Biochemistry: hundreds of simultaneous different eukaryotic signals are sent in close proximity: so only low strength signaling could evolve to handle that noise.

Ergo, low dose toxicity is the norm.
Fas protein (APO-1) is for **Programmed Cell Death**. Implicated in various malignancies & immune diseases.

http://www.sabiosciences.com/pathway.php?sn=Fas_Signaling

**ERK Signaling**

The MAPK (Mitogen-Activated Protein Kinase) pathway is one of the primordial signaling systems that nature has used in several permutations to accomplish an amazing variety of tasks. It exists in all eukaryotes, and controls such fundamental cellular processes as Proliferation, Differentiation, Survival and Apoptosis. Mammalian MAPK can be divided into four groups based on their structure and function: ERKs (Extracellular signal-Regulated Kinases), p38MAPKs, JNKs (c-Jun NH2-terminal Kinases) and ERK5 (Extracellular signal-Regulated Kinase-5) or BMK. Activation of these MAPKs occurs through a cascade...

http://www.sabiosciences.com/pathway.php?sn=ERK_Signaling

http://www.genengnews.com/Media/images/Article/UGENWebsitepictures2010GEN20_Nov1510DimondSignalingCellSignaling.jpg
So biology is driving the acceleration of low dose findings
(I estimate 8,000+ published papers of low dose vertebrate toxicity are published).

Vandenberg '14 finds 20%+ of all biochemistry signals show non-monotonic response,
stronger at low than high dose (admittedly a small sample: most vitamin studies, all bPA in vitro findings);

Of the above ~8,000, perhaps ~1,000 are in vivo bPA alone!
So, c. 1,000 bPA in vivo low dose academia vs. … one (Tyl '08) still used by EFSA

Tyl '08 did test low doses. But it is unstated if its pathologists were blinded
–crucial given its huge financialCoI risk of bias (among other weaknesses, especially
the biased prostate weights; and the negative controls with larger prostates that were in the
lab with the polycarbonate fire, vs. the neg. controls shipped in from off-site).

In sum, science & biology prove that CEF must tear itself from Tyl '08
to use rigorous systematic review (SR) to look objectively
at academia's ~1,000 low dose in vivo bPA findings.

So kudos to EFSA, the first known regulator to begin using SR,
but it is time to ensure the subjective privileging of industry's insensitive
(including not even testing low doses)Test Guideline toxicity studies stops.

E.g. the failure in EU's EDC criteria, they rely centrally on EFSA's terrifically flawed
pesticide Art. 8(5) Guidance.
For example, CEF's 2015 bPA RA had very useful summary graphs of each low-dose bPA study evaluated.

But note below the green-shaded x-axis of these summary tables: two logrhythmic scales.

Thus the lowest dose toxicity findings were, with no justification, classed lower quality
(VU = 'Very Unlikely', etc.)

Figure 10: Summary plot for the effects of BPA exposure on the proliferative changes in the mammary gland: Ductal hyperplasia (including TEBs), intraductal hyperplasia (relative number of ducts lined by three or more layers of stratified epithelial cells) and epithelial cell proliferation (proliferative index as measured by BrdU, Ki67 or PCNA labelling). The left hand text indicates the exposure route (oral or subcutaneous, SC). The left hand pane shows the experimental design with the horizontal bars showing the timing and duration of exposure (while the up-arrows show when the measurements/assessments were made. The central pane shows the study results, based on the x-axis showing the human equivalent dose (HED) depending upon species, age and route of exposure. The lightly shaded boxes on the x-axis show the uncertainty assessment (very unlikely=VU, unlikely=U, as likely as not=ALAN, likely=L and combinations thereof). The central pane also shows the sex and species of the