

HELPING YOU BETTER COMMUNICATE OUR CHEMICAL RISKS

**R.I.S.K.**  
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**S**cience with  
**K**nowledge

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(M.Sc. = d.s. de Science = Ls. en Ciencias = Magister)

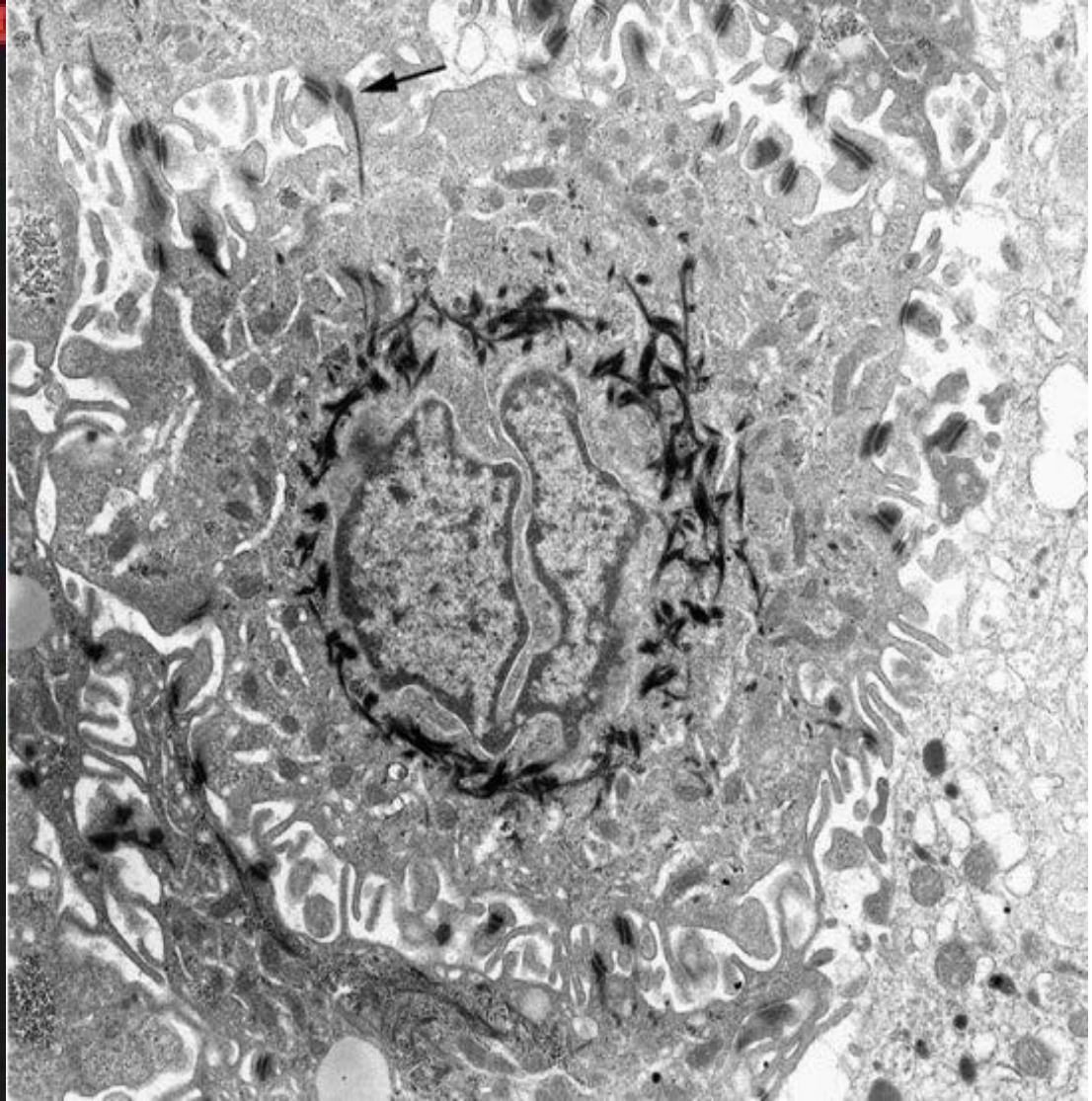
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## Presentation by

Anthony Tweedale, MS (principal):

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.*

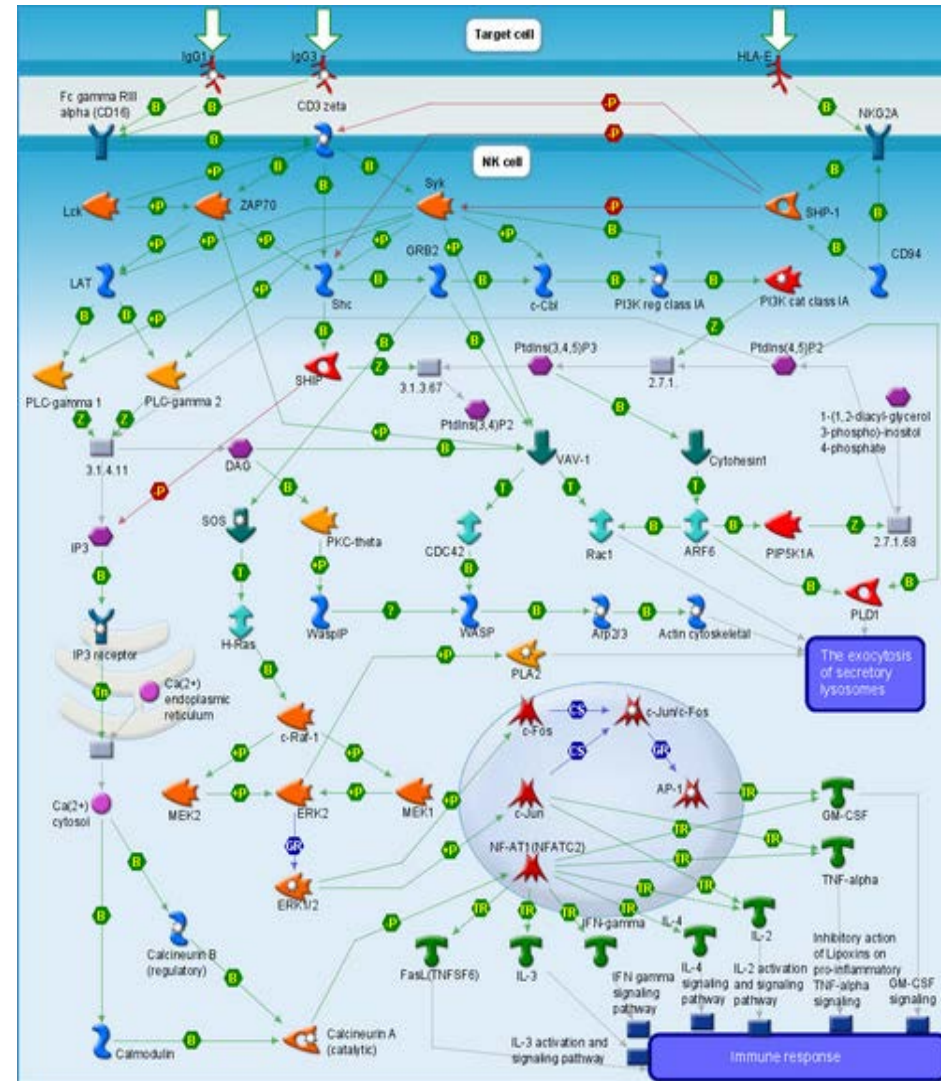
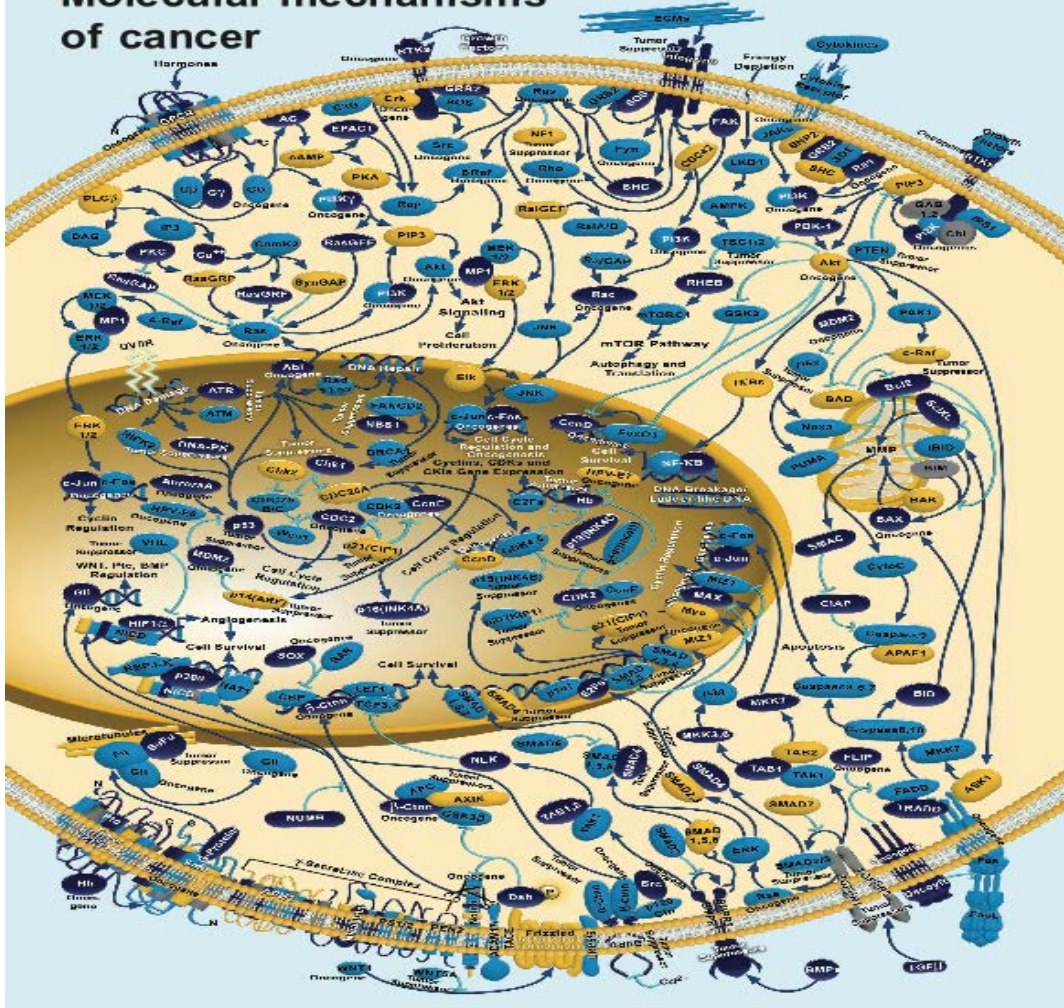


# CD16 signaling in NK cells

<https://lsresearch.thomsonreuters.com/maps/2249/>



## Molecular mechanisms of cancer

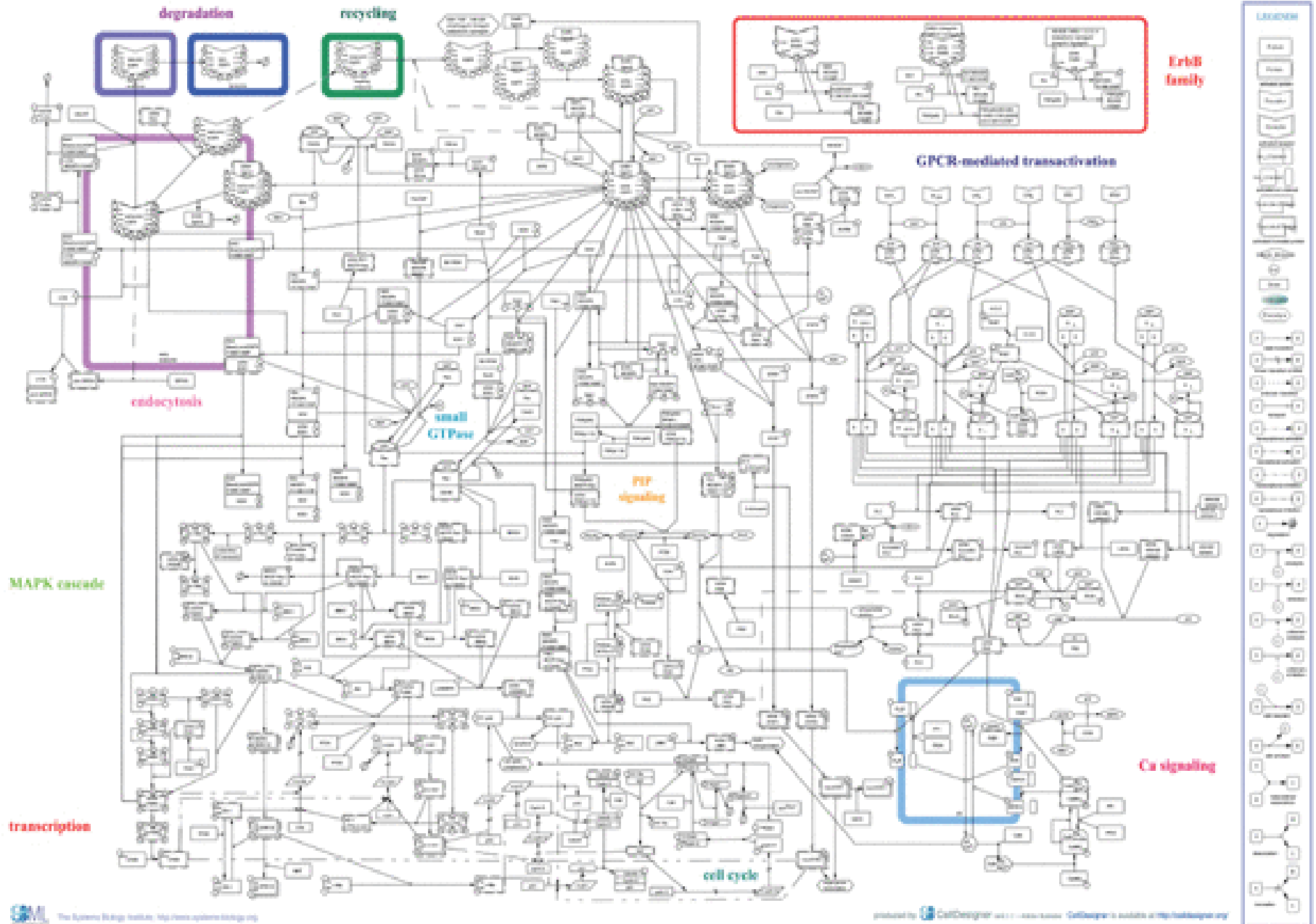


# 2005 A comprehensive pathway map of EGFR signaling

Kanae Oda, Yukiko Matsuoka, Akira Funahashi, Hiroaki Kitano DOI 10.1038/msb4100014 | Published online 25.05.2005 Molecular Systems Biology (2005) 1, 2005.0010

## Epidermal Growth Factor Receptor Pathway Map

Kanae Oda et al., Yukiko Matsuoka et al., Hiroaki Kitano et al.  
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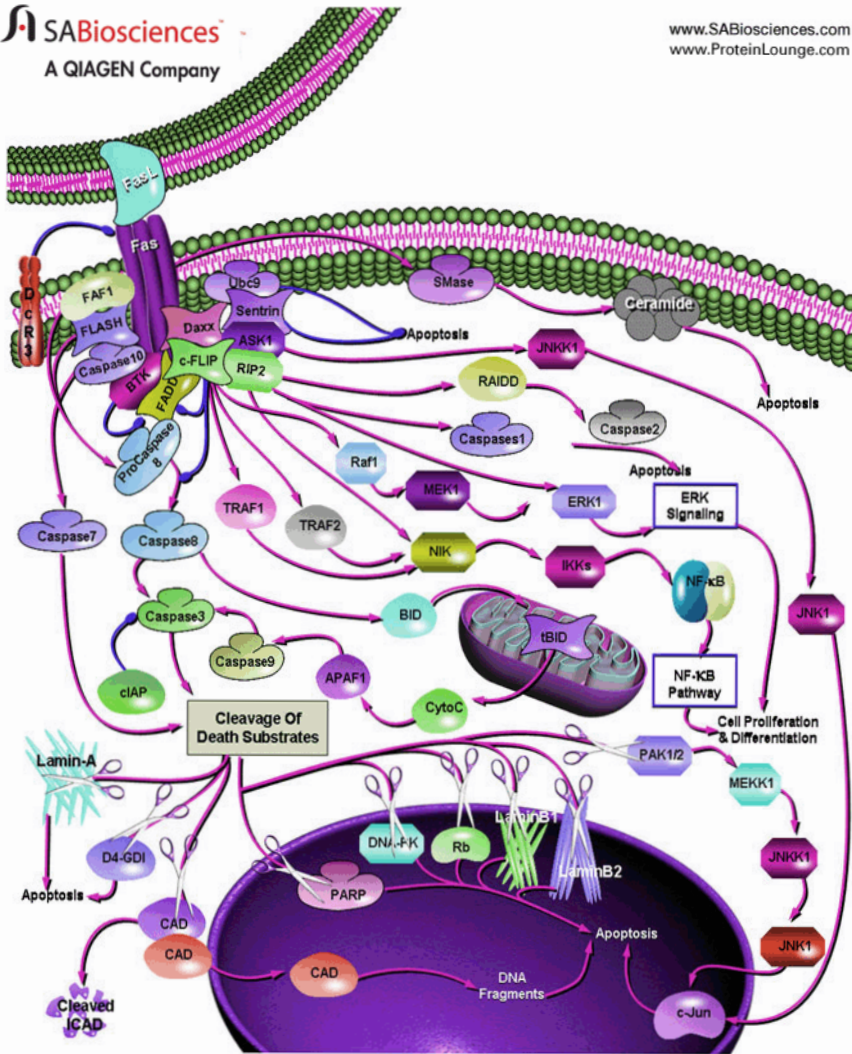




**Fas** protein (APO-1) is for **Programmed Cell Death**.  
 Implicated in various malignancies & immune diseases.  
[http://www.sabiosciences.com/pathway.php?sn=Fas\\_Signaling](http://www.sabiosciences.com/pathway.php?sn=Fas_Signaling)

**SABiosciences**  
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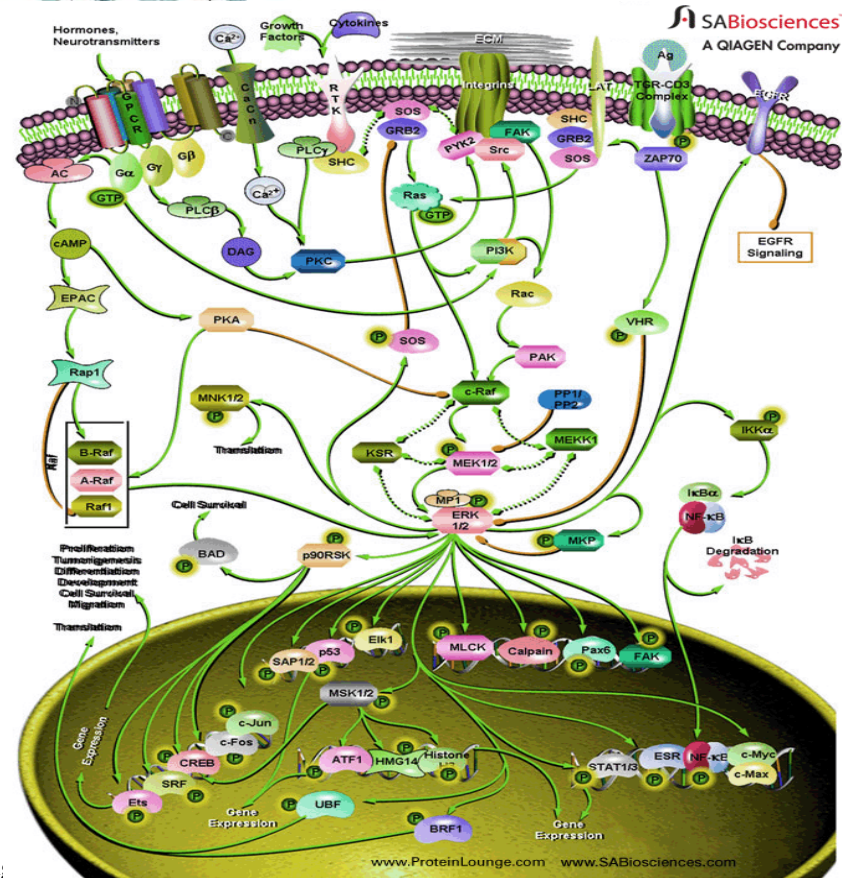
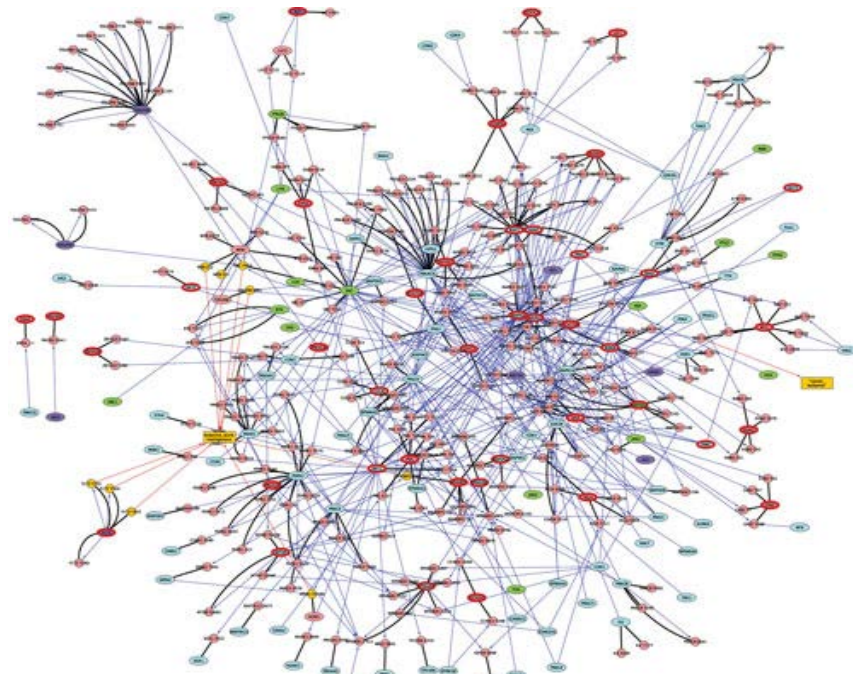
www.SABiosciences.com  
 www.ProteinLounge.com



### 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.sabiosciences.com/pathway.php?sn=ERK_Signaling)



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 financial CoI 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.

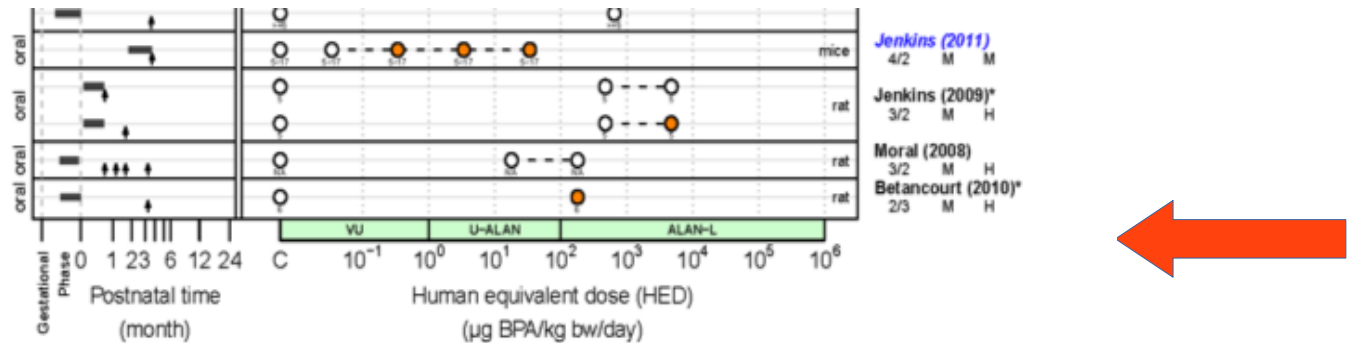
E.g. the failure in EU's **EDC criteria**, they relies centrally on EFSA's terrifically flawed pesticide Art. 8(5) Guidance.



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* logarithmic 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