Are Low Dose Adverse Effects an Issue in Developmental Toxicology ?

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Low dose effects definition

- Effects of environmental chemicals observed within – or close to – the exposure levels normally experienced by the general population.

- Effects that occur at doses below the apparent NOEL/NOAEL found in routine experimental studies.

Why Low dose effects are a controversial matter

- **Epidemiological data**: Owing to methodological limitations inherent to epidemiology studies the evidence of association does not mean a causal relationship.

- **Experimental data**: In in vivo studies, large numbers of animals *(i.e.*, a large group size (N) and an increased number of tested doses) are needed to reveal effects in the low dose range (*i.e.*, below the apparent NOAEL).

- **Lack of reproducibility**: When a low dose effect is found it is seldom confirmed by replication studies conducted by independent researchers.

Are low dose effects a plausible hypothesis ?

- **Threshold** *vs* **non-threshold phenomena** in pathogenesis
- If we assume that pathogenetic mechanisms are triggered by a non-threshold event (*i.e.*, by a stochastic process), then we also assume that there is no NOEL/NOAEL and therefore the low dose effect notion is not applicable (*i.e.*, any exposure may give rise to an adverse effect the probability of which decreases exponentially as exposure is reduced).

Are low dose effects a plausible hypothesis ?

- So far plausibility of “low dose effects“ hypothesis has been discussed (theoretically) regarding endocrine mediated mechanisms (see Vandenberg L et al, and vom Saal F et al publications).

- As far as we are aware no mechanistic model through which in utero low dose exposures could elicit fetal structural abnormalities and / or embryolethality has been proposed.

Are low dose effects a plausible hypothesis ?

- **Non-monotonic dose-effect relationships**
- . Low dose effects are generally (but not exclusively) associated to non-monotonic dose response curves.
- That is, effects are observed in the low dose but not at higher doses, or effects in the low dose range are in one direction whereas the effects noted at higher doses are in the opposite direction.
- As far as impairment of normal embryo development is concerned, non-monotonic dose-effects remain undemonstrated by experimental studies.
- No hypothetical toxicodynamic mechanism has been proposed through which non-monotonic dose effects on embryo development might occur.

Low dose effects: Developmental toxic effects other than fetal structural abnormalities and gestation losses.

- **Vom Saal F et al. studies**
- Prostate enlargement in adult mice associated with low dose exposure to xenoestrogens , or supraphysiological β-estradiol *in utero*.

- **Soto A et al studies**
- . Pre- and/or postnatal (prepubertal) exposure to BPA alter tissue architecture and epithelial cells proliferative activity in mammary gland tissue.

- **In both cases, however, experimental findings remain undemonstrated by independent investigations.**

Conclusions:

- **Regarding birth defects (structural abnormalities) and gestational losses (embryolethality) the Low Dose Effects hypothesis has not been supported by experimental data.**

- **The is no plausible hypothesis on toxicodynamic mechanisms through which low dose in utero exposures and non-monotonic dose responses could lead to abnormal embryo development.**

- **Thank you for your attention!**