A recent scientific review published by EFSA could not find plausible evidence for non-monotonic dose-response for substances in the area of food safety – including for BPA.

In May 2016, the European Food Safety Authority (EFSA) published a comprehensive report investigating potential evidence for non-monotonic dose-response (NMDR) by systematically reviewing the scientific peer-reviewed literature that appeared since 2002 for substances in the area of food safety.

The key overall conclusion of EFSA is that “(...) NMDR as a common phenomenon is so far not supported for substances in the area of food safety.”

The reviewing authors from four national authorities and institutes in Europe applied a systematic, tiered review process. The procedure comprised a thorough literature search to identify relevant scientific studies based on predefined criteria, followed by a thorough statistical analysis of the most relevant studies.

For Bisphenol A (BPA) many studies have been published that describe alleged findings of non-monotonic dose-response effects, often referred to as “low-dose-effects”. In the systematic review it turned out that none of the many peer reviewed publications on BPA in this context fulfill all predefined criteria. Thus none of the many studies on BPA reporting alleged findings of NMDR could provide reliable evidence on the validity of this hypothesis.

Furthermore, the review highlights the importance of replication of study findings in order to substantiate hypothetic evidence for NMDR. However, there are no such replications yet supporting the finding of any study reporting on NMDR evidence for BPA.

In conclusion, from this comprehensive review, there is currently no plausible scientific evidence of NMDR with regard to BPA.

The report had been commissioned by EFSA and was carried out by four member state organisations:

- the Austrian Agency for Health and Food Safety GmhH (AGES),
- the French Agency for Food, Environment and Occupational Health & Safety (ANSES),
- the Dutch National Institute for Public Health and the Environment (RIVM),
- and the Swedish Institute of Environmental Medicine, Karolinska Institutet (IMM).

The four member state organisations point out that “Criteria for evidence of NMDR, evaluation of data and importance for risk assessment have to be further evaluated.” At the same time, EFSA concludes: “According to the report, considering the type (hormones and pharmaceuticals were excluded) and amount of data selected and analysed, NMDR as a common phenomenon is so far not supported for substances in the area of food safety.”
The EFSA documents can be found here:

Background about the evaluation

Systematic methodology, transparent criteria
A systematic review methodology was applied. This included a review of previous reports published on the issue of NMDRs, followed by a thorough literature search to identify relevant in vivo, in vitro and epidemiological/human studies. These had to include at least five dose groups in addition to a control. The reviews were performed by up to three reviewers at each step.

Starting with more than 10,000 identified studies, relevant and reliable studies were selected using predefined inclusion and reliability criteria. On the 49 in vivo, 91 in vitro and 2 epidemiological studies that fulfilled the initial criteria, six checkpoints addressing random and non-random errors were applied to evaluate possible evidence of NMDR to dose-response results. The plausibility of NMDRs was assessed based on the number of fulfilled checkpoints. The report found that “In most of the in vivo datasets, the apparent NMDR might have been caused by a single outlying dose group. In total, only 10 out of the 179 in vivo datasets fulfilled all six checkpoints. The latter datasets included studies on the substances quercetin, resveratrol, alpha-benzene hexachloride, and methyl-mercury.” The 10 datasets fulfilling all 6 checkpoints related to only 4 studies.

Quotes from the report about the need for basic scientific criteria to be considered when assessing the results of any toxicological studies (bold typo highlights not in the original quote):

- “The hypothesis that the DR [dose response] is non-monotone is a more complex hypothesis than the hypothesis that the DR is monotone. Therefore, monotonicity will be the working hypothesis for a given dataset, until the evidence is strong enough to reject monotonicity (as a general principle in science, from two hypotheses that are able to explain the data the more simple one wins; this is also referred to as Occam’s razor). The burden of proof is on the side of the non-monotone hypothesis.”

- “A second general consideration is that convincing evidence of NMDR can never be based on a single study. Confirmation of the claimed NMDR by another study (performed in another laboratory) is always needed.”

- “Claims of NMDR expressed in a given paper or report cannot be taken for granted, and in each case a re-evaluation of the DR dataset would be needed. As experimental data always contain errors, statistical evaluation is needed to reduce the possibility that biological conclusions are based on data errors rather than on biological phenomena. Data errors can either be random sampling errors, or systematic errors. The possibility of the latter type of errors is often overlooked. Although experimenters try to minimize the probability that they occur, they cannot always be avoided. In establishing an NMDR, the possibility of systematic errors plays a prominent role, since many NMDR claims are based on the response in one single dose group. In that case, it remains unclear if the DR was in reality non-monotone, or that there was one deviating dose group due to
another experimental factor"

- “The total number of checkpoints fulfilled may be considered as a relative measure of evidence for NMDR. (...) But even when they [the 6 checkpoints] are all fulfilled, this is not sufficient evidence for the existence of an NMDR. **Convincing evidence of NMDR always requires at least one other independent study, performed in another laboratory and examining the same substance-endpoint combination, which reproduces the non-monotonicity.**”