Bisphenol A: new immune system evidence useful but limited

New data confirm EFSA’s previous conclusion that bisphenol A (BPA) might affect the immune system in animals, but the evidence is too limited to draw any conclusions for human health.

Following a request from the Dutch Ministry of Health, Welfare and Sport, EFSA’s experts reviewed two studies by Ménard et al. (unpublished at the time of EFSA’s last comprehensive evaluation of BPA) and concluded that there were key limitations in the way they were designed and carried out. Furthermore, the data from the studies were too variable to use for setting a new tolerable daily intake (TDI) for BPA.

As stated in 2015, EFSA will review its temporary TDI of 4 micrograms per kilogram of body weight (µg/kg bw/day) after evaluating the scientific evidence on BPA toxicity published since 2012.

Prof Vittorio Silano, Chair of EFSA’s expert Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF), said: “EFSA’s new review will start in 2017 and additional immunological studies such as those by Ménard et al. would be useful contributions if the limitations we identified are addressed.”

Dr Fleur van Broekhuizen – lead author of a report by the Dutch National Institute for Public Health and the Environment (RIVM) that prompted EFSA’s appraisal of the new evidence – said: “RIVM welcomes EFSA’s confirmation of our assessment that BPA might affect the immune system. We look forward to the outcome of EFSA’s next review of scientific evidence on BPA.”

Studies by Menard et al. (2014)

The two studies by Menard et al. suggested food intolerance and reduced resistance (“impaired immune response”) to parasitic infection in rats exposed to 5 µg of BPA per kg bw/day. The doses were administered “perinatally” (i.e. before and just after birth).

EFSA set up a working group of international experts to assess the studies and the authors kindly provided the original data to EFSA for the review.

The CEF Panel concluded that the limitations in the design and conduct of these studies – particularly the use of a single dose for the majority of the tests – prevent meaningful assessment of their relevance for human health. Moreover, for the only effect tested at three BPA doses, when plotted on a graph, the data results are so scattered and variable that they do not allow identification of a reference point for the immunotoxicity of BPA and, therefore, cannot be used to set a TDI.
The main technical limitations of the studies included:

- Only one type of immune response was tested with three BPA doses – evaluating dose-response relationships is not possible below three doses.
- No positive control to account for differences between immune-deficient animals and the tested animals.
- No control for litter effect to account for possible differences between animals from different litters.
- Insufficient study reporting, for example, no information on animal body weight, BPA source, mode of oral administration, number of dams (mothers)/pups.
- Lack of statistical evaluation of the non-monotonic dose response.
- No mention of power analyses – a statistical tool to calculate the minimum effective sample size.

- A statement on the developmental immunotoxicity of bisphenol A (BPA): answer to the question from the Dutch Ministry of Health, Welfare and Sport

What’s next?

In December 2014, EFSA reduced the TDI for BPA from 50 to 4 µg/kg bw/day. The TDI was made temporary and EFSA committed to re-evaluate BPA again when a two-year study by the U.S. National Toxicology Program is expected to become available in 2017.

Work is underway at EFSA on a “scientific protocol” to define upfront how to search, review and integrate all the new scientific evidence not included in EFSA’s previous assessment. EFSA will consult publicly on this preparatory work in 2017 so stakeholders can have their say before the re-evaluation begins.