European Journal of Nutrition & Food Safety

13(4): 67-69, 2021; Article no.EJNFS.70516
ISSN: 2347-5641

Assessment of Four Studies on Developmental Neurotoxicity of Bisphenol A

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Authors' contributions

This work was carried out in collaboration among all authors. The opinion has been assessed and approved by the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of VKM. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/EJNFS/2021/v13i430409

Grey Literature

Received 05 May 2021
Accepted 10 July 2021
Published 30 July 2021

ABSTRACT

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has on the request from the Norwegian Food Safety Authority (Mattilsynet) assessed four studies on developmental neurotoxicity following low dose exposure to bisphenol A (BPA) (Adriani et al., 2003; Carr et al., 2003; Negishi et al., 2004; Ryan and Vandenbergh, 2006). The background for the request is uncertainties related to developmental neurotoxcity of BPA raised by the Nordic environmental agencies in Norway, Sweden and Denmark. VKM was asked to consider if these studies provide sufficient evidence to set a lower no observed adverse effect level (NOAEL) in the hazard characterisation of BPA. Further, a Norwegian exposure scenario based on available exposure data should be performed. The task has been assessed by the Scientific Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics (Panel 4).

Bisphenol A (CAS number 80-05-7) is primarily used as a monomer in the production of polycarbonate, which is used to make food containers, such as beverage bottles, baby bottles, tableware and storage containers. It is also used as a precursor of certain epoxy resins used for protective coatings for food and beverage cans. BPA is permitted for use in food contact materials

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in the European Union (EU) with a specific migration limit (SML) of 0.6 mg/kg food. The migration limit in the EU regulations has yet to be modified according to an opinion from the European Food Safety Authority (EFSA) from 2006 where a new established tolerable daily intake (TDI) of 0.05 mg BPA/kg body weight (bw) was derived from a NOAEL of 5 mg/kg bw/day.

A European Union Risk Assessment Report (RAR) of BPA produced in accordance with Council Regulation (EEC) 793/93 has recently been updated (April 2008) reviewing a previously requested 2-generation study in mice (Tyl et al., 2007) and new data on human exposure and effects of BPA. A NOAEL of 50 mg/kg bw/day was suggested in this report. The Nordic environmental agencies (Norway, Sweden and Denmark) have participated in the discussions on this updated EU RAR of BPA and they strongly disagreed that this NOAEL also covers developmental neurotoxicity. According to the Nordic environmental agencies, the four above mentioned studies indicate a possible risk for developmental neurotoxicity of BPA at very low exposure levels (0.1-0.25 mg/kg bw/day). The position of the Nordic environmental agencies has been included as a footnote in the revised EU RAR.

Recently, in April 2008, the U.S. National Toxicology Program (NTP), Health Canada and Environment Canada have published draft reports on effects of BPA, including developmental effects (neural and behavioural effects) and expressed some concern for neural and behavioural effects in fetuses, infants and children at current human exposures. The European Commission has therefore asked EFSA to further assess possible age dependent toxicokinetics of BPA in animals and humans and their implications for hazard and risk assessment of BPA taken into account the most recent information and data available.

The present opinion from VKM Panel 4 is based on an evaluation of the design, conduct (or accomplishment) and the results in the four above mentioned studies. The study design has been evaluated in light of international recommendations given in relevant guidelines dealing with developmental neurotoxicity testing in animals. The recent international developments on BPA in the U.S. and Canada are not addressed in this opinion.

The report by Tyl and co-workers was central in the EFSA opinion from 2006 and the updated EU RAR from 2008. The Tyl study is a GLP compliant 2-generation reproductive toxicity evaluation in mice performed according to a modified OECD 416 guideline. However, the study did not include functional tests for developmental neurotoxicity.

VKM has reviewed the four above mentioned studies on neurodevelopmental toxicity of BPA as requested by the Norwegian Food Safety Authority. Although the design and reporting of these studies suffer from major and serious shortcomings, the overall findings may raise some concern.
It is the opinion of the VKM Panel 4 that the four studies do not provide sufficient evidence for setting a robust lower NOAEL for BPA than the current EFSA NOAEL of 5 mg/kg bw/day. The Panel is aware that the EU Commission recently has requested EFSA to re-evaluate the information available on BPA.

In order to eliminate any uncertainty regarding potential developmental effects of BPA at low doses, it is recommended that a GLP compliant study is carried out according to OECD guideline 426. Such a study should utilize a broad concentration range from the very low doses up to those with known maternal effects.

A Norwegian exposure scenario based on available data on exposure to BPA from food and beverages and via the environment was performed. In general, exposure levels of BPA in Norway are low. The estimated exposure of infants and children is in the range of 3.5 – 13.2 µg/kg bw/day, whereas the estimated aggregated exposure of adults is 1.5 µg/kg bw/day. As a result of the current use of BPA in food contact materials and other consumer products, infants and children are exposed to higher levels of BPA per kg body weight than the rest of the population.

Keywords: The Norwegian Scientific Committee for Food Safety; the VKM; bisphenol A.

Available: https://vkm.no/download/18.d44969415d027c43cf16e27/1500392500562/55ac9fb6ae.pdf

ISBN: 978-82-8082-256-7

NOTE:

This work was carried out in collaboration between all authors. The opinion has been assessed and approved by the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of VKM. All authors read and approved the final manuscript.

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Suggested citation: VKM. (2008) Assessment of four studies on developmental neurotoxicity of bisphenol A. Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety, ISBN: 978-82-8082-256-7. Oslo, Norway.

COMPETING INTERESTS

Authors have declared that no competing interests exist.