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To: "Shane, Barbara (NIH/NIEHS) [E]" <shane@niehs.nih.gov>
Conversation: N.Olea
Subject: N.Olea

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Dear Dr. Shane,

Please find below my comments on the DRAFT NTP BRIEF ON BISPHENOL A [CAS NO. 80-05-7] of April 14, 2008. Thank you for giving us the opportunity to take part in this fruitful discussion from the other side of the Atlantic.

1. Comments on the question: What is Bisphenol A?

BPA is one among dozens of bisphenols. This fact should be considered in the presentation of any paper on BPA. Technical grade BPA (used in most of the labs making BPA experiments) and industrial BPA are not the same, and people are exposed to manufactured products made of industrial BPA. Therefore, caution should be taken when extrapolating BPA results to the real world of exposure to bisphenols. Moreover, it is necessary to investigate the presence of many other biologically active monomers, which can be more active than BPA.
(An example: It would be naïve for risk assessment professionals to limit their risk assessment work on PCBs to

one of their isomers or their work on phthalates to one of their congeners, so why ignore other bisphenols?)

See our peer-review publications -not included in the NTP BRIEF- for additional information.

Pérez, P., Pulgar, R., Olea-Serrano, M.F., Villalobos M., Rivas, A., Metzler, M., Pedraza V., Olea, N.: The estrogenicity of bisphenol-A related diphenylalkanes with various substituents at the central carbon and the hydroxyl groups. Environ. Health Perspect 106:167-174, 1998.

Rivas A, Lacroix M, Olea-Serrano F, Laios I, Leclercq G, Olea N. Estrogenic effect of a series of bisphenol analogues on gene and protein expression in MCF-7 breast cancer cells. J Steroid Biochem Mol Biol. 82: 45-53, 2002.

2. Comments on the question: Are people exposed to BPA?

2.1 It is surprising that the document makes no mention of the BPA found in recycled paper and cardboard used for food packaging. This may be one of the most important sources of BPA exposure in humans, especially in children. Unfortunately, studies that address this issue are surprisingly scarce. Nevertheless, I believe that a report that does not take into consideration the published information on this issue is shockingly incomplete.

See our peer-review publications -not included in the NTP BRIEF- for additional information

Lopez-Espinosa MJ, Granada A, Araque P, Molina JM, Puertollano MC, Rivas A, Fernández MF, Cerrillo I, Olea-Serrano MF, López C, Olea N. Estrogenicity of paper and cardboard extracts used as food containers. Food Additives

and Contaminants, 24(1):95-102. 2007

2.2. I have two concerns about the statement that “short-term exposure can occur following application of certain dental sealants or composites made with bisphenol A-derived material such as bisphenol A-dimethyl acrylate (bis-DMA)”. First, because sealants that are placed in children’s months to prevent caries will not disappear until a long time (several years) after their application and the long-term release of monomers from sealant polymer has not been studied in children. Therefore, the expression “short-term” seems too restrictive. Second, because BPA has been shown to leach from Bisphenol-A dyglyciylether dimethacrylate (Bis-GMA) based sealants, which are used to treat children and are much more frequent and widespread than bis-DMA. In fact, bis-GMA itself is estrogenic.

See our peer-review publications -not included in the NTP BRIEF- for additional information

Olea, N., Pulgar, R., Pérez, P., Olea-Serrano, F., Rivas, A., Novillo-Fertrell, A., Pedraza V., Soto, A., Sonnenschein C. Estrogenicity of resin-based composites and sealants used in dentistry. Environ. Health Perspect., 104:298-305, 1996

Olea, N. Olea’s response. Environ Health Perspect, 107:290-291, 1999

Pulgar R, Olea-Serrano MF, Novillo-Fertrell A, Rivas A, Pazos P, Pedraza V, Navajas JM, Olea N. Determination of bisphenol-A and related aromatic compounds released from Bis-GMA-based composites and sealants by high performance liquid chromatography. Environ. Health Perspect 108:21-7, 2000

2.3 The draft report states that "….free bisphenol A and its major metabolites (bisphenol A-glucuronide and bisphenol A-sulfate) can all be measured in humans, only free bisphenol A is considered to be biologically active". However, some bisphenol-A congeners and metabolites are of major concern and should be included in the data on BPA. I base this assertion on our experience with chlorinated BPA: i) Mono-, di- and tri-chloro-BPA are spontaneously formed in chlorinated drinking water, and there appears to be no information on their synthesis; ii) As in the case of BPA, these BPA derivatives were shown to be estrogenic in several *in vitro* bioassays; and iii) chlorinated BPA bioaccumulates in adipose tissue. Therefore, the statement that only BPA is considered to be biologically active is misleading.

See our peer-review publications -not included in the NTP BRIEF- for additional information:

Fernandez M, Rivas A, Olea-Serrano F, Cerrillo I, Molina-Molina JM, Araque P, Martínez-Vidal JL, Olea N. Assessment of total effective xenoestrogen burden in adipose tissue and identification of chemicals responsible for the combined estrogenic effect. Anal Bioanal Chem 2004: 379: 163-170

Fernandez MF, Arrebola JP, Taoufiki J, Navalon A, Ballesteros O, Pulgar R., Vilchez JL, Olea N. Bisphenol-A and chlorinated derivatives in adipose tissue of women. Reproductive Toxicology 2007, 24(2):259-64

Finally, as a physician with personal responsibility for the people and patients I treat, my main concern about the BPA issue is that scientists and policy makers of the 21st Century, experts in the management of sophisticated tools, still consider that humans (children) are exposed to single chemicals, which appears to be very disingenuous. Hence, the whole process of risk assessment is flawed. How can I explain to my students at the School of Medicine that the information you and I provide, after years (!) of in-depth analysis, is limited to the effects of BPA because of our continued failure to acknowledge that children are exposed to more than one chemical at the same time?

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