International Pharmaceutical Excipients Council of the Americas

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Chair

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Carbohydrate Editor-in-Chief
International Journal of Biological Macromolecules

RE: *Is sodium carboxymethyl cellulose (CMC) really completely innocent? It may be triggering obesity*, Reference https://doi.org/10.1016/j.ijbiomac.2020.09.169

Dear Sir or Madam,

Members of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) have reviewed the above referenced article. IPEC-Americas appreciates the opportunity to provide comments.

IPEC-Americas Background

IPEC-Americas represents more than 50 excipient manufacturers, distributors and pharmaceutical/biopharma companies to support the safe production and use of excipients. IPEC-Americas is dedicated to working closely with regulatory authorities, industry organizations and scientific bodies (globally) to advance public health on matters relating to the quality, safety, manufacture, distribution, use and functionality of excipients. IPEC is the sole association representing excipients.

IPEC-Americas Concerns

Members of the International Pharmaceutical Excipients Council of the Americas (IPEC-Americas) have reviewed the research article entitled “Is sodium carboxymethyl cellulose (CMC) really completely innocent? It may be triggering obesity” published in the *International Journal of Biological Macromolecules* 2020 163:2465-2473. IPEC-Americas has a major concern related to the peer review process for this article and are taking this opportunity to bring this to your attention.

Baran et al. presented a study implicating CMC as a potential cause of obesity through in situ prenatal exposure of the developing embryo/fetus. The authors used the Zebrafish model for assessing developmental toxicity and to identify perturbations in other biologically meaningful endpoints including behavioral and gene expression. While the authors concluded that CMC was neither teratogenic nor neurotoxic, injection of CMC into the yolk sac did increase lipid accumulation in a dose dependent manner and altered lipid regulating gene expression (e.g., Peroxisome proliferator-activated receptors).

In reviewing this publication, IPEC toxicologists concluded that the title of the article was scientifically misleading and alarmist. Further, the data provided in this publication, was scientifically inconsistent with previously reported toxicological safety information for CMC, and provided questionable new data to support revisiting potential safety concerns for CMC. In the

interest of publishing accurate scientific data to advance human risk assessment, IPEC-Americas is providing to the Editors a summary of our major concerns:

1. The route of exposure was inappropriate for this type of study with CMC. It is well-known that CMC (and other modified celluloses) is not absorbed by the human intestinal tract,[1,2,3,4,5] and that this lack of absorption prevents systemic exposure. Since there is no systemic exposure, there cannot be exposure to the human embryo/fetus via either the yolk sac (through first trimester) or the placenta and maternal circulation (second and third trimesters). Directly injecting CMC into the Zebra fish yolk sac does not mimic any realistic human embryo/fetal exposure.

2. There is no evidence from numerous laboratory animal studies that CMC exposure results in increased body weights. CMC (and other modified celluloses) has been shown to decrease body weights in long term dietary studies.[6,7] Shelanski and Clark[8] conducted a 3-generation study feeding study that produced no effects on body weights in any generation. Further, sub-chronic general toxicity studies have shown no effects on body weight except at high dose levels where body weights were decreased.[1,7]

   There is a general concern by the IPEC toxicologists for the misinterpretation of data supporting the contention of CMC's systemic toxicity. Specifically, the authors reference to their data and to the EFSA "*Call for technical and toxicological data on sodium carboxymethylcellulose (E466) for uses as a food additive in foods for all population groups including infants below 16 weeks of age*" are misinterpreted. The EFSA data call-in was not based on increasing safety concerns related to the studies of Viennois et al. and Sökmen et al., but because of EU regulations and the new guidance document on infants under 16 weeks of age:[9]

   > *"The reason was that the risk assessment approach followed until now by the EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS Panel) in the re-evaluation of food additives does not apply to this age group[4]. The ANS Panel has, therefore, specified in its opinion that the re-evaluation of uses for this particular age group will be performed separately.*
   >
   > *On 31 May 2017, EFSA's Scientific Committee (SC) published a guidance document[5] on the risk assessment of substances present in food intended for infants below 16 weeks of age, enabling the ANS Panel to assess the safe use of sodium carboxymethylcellulose (E466) and of other food additives for the population group below that age"*

3. Additionally, Baran *et al*. claim both that "*the side effects and toxic properties have not been fully elucidated*" and "…*it has been reported in most studies that CMC is not toxic*." In fact, the *potential toxic* properties of CMC have been fully investigated by ADME, acute, sub-chronic, chronic, genetic, development and reproductive toxicology studies, which have been thoroughly reviewed by JECFA,[1] the Cosmetic Ingredient Review Panel,[7] and EFSA.[10,11]

4. Baran *et al*. also used intraperitoneal CMC exposure to justify oral exposure as a potential hazard (Klugman et al.[12]). In applying route-to-route extrapolation, such as going from yolk sac to oral administration, there are important pharmacokinetic and pharmacodynamic considerations that must be considered for bridging to potential systemic toxicity, such as that

intraperitoneal exposure is not interchangeable with oral exposure for a non-absorbable polymer.

5. Baran *et al.* mis-quoted another study (Bär et al.) by stating CMC "*has some negative effects in mice and rats*" when Bär *et al*. actually concluded "*the results of the present study do not conflict with the general recognition of the human safety of CMC…*"[13]

Summary

Consequently, IPEC-Americas is calling attention to the Editorial Board of IJBM, the authors misinterpretation of scientific data to support a sensationalist title and erroneously inflate the importance of the reported findings. This article is not in line with the Journals publication policy to maintain the highest scientific standards.

Respectfully yours,

Janeen Skutnik-Wilkinson
Chair, IPEC-Americas

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1 International Programme on Chemical Safety World Health Organization (1989) **Modified Celluloses** Tox Monograph: FAS 26-JECFA 35/81 http://www.inchem.org/documents/jecfa/jecmono/v26je08.htm

2 Joint FAO/WHO Expert Committee on Food Additives (JECFA) (1999**)** WHO FOOD ADDITIVES SERIES: 42 SODIUM CARBOXYMETHYL CELLULOSE, ENZYMATICALLY HYDROLYSED. http://www.inchem.org/documents/jecfa/jecmono/v042je10.htm

3 Adiotomre, J, Eastwood, MA, Edwards, CA and Brydon WG. (1990) Dietary fiber: in vitro methods that anticipate nutrition and metabolic activity in humans. Am J Clin Nutr 52:128-34.

4 Frawley, JP, Wiebe, AK and Klug, ED (1964) Studies on the Gastro-intestinal Absorption of Purified Sodium Carboxymethyleellulose. Fd Cosmet Toxicol 2:539-543

5 Bergfeld, W., Liebler, D., & Slaga, T. (2009). Final Report of the Cosmetic Ingredient Review Expert Panel Amended Safety Assessment of Cellulose and Related Polymers as used in Cosmetics March 23, 2009. http://www.beauty-review.nl/wp-content/uploads/2014/08/Amended-Safety-Assessment-of-Cellulose-and-Related-Polymers-as-used-in-Cosmetics.pdf

6 T.F. McElligott, E.W. Hurst. (1968) Long-term feeding studies of methyl ethyl cellulose ('Edifas' A) and sodium carboxymethyl cellulose ('Edifas' B) in rats and mice. Food and Cosmetics Toxicology 6(4): 449-460 https://doi.org/10.1016/0015-6264(68)90135-1

7 Cosmetic Ingredient Review Panel (1986) Final Report on the Safety Assessment of Hydroxyethylcellulose, Hydroxypropylcellulose, Methylcellulose, Hydroxypropyl Methylcellulose, and Cellulose Gum. Journal if the American College of Toxicology 5(3):1-59.

8 Shelanski, HA, and CLARK, A.M. (1948) Physiological action of sodium carboxymethylcellulose on laboratory animals and humans. *Food Res.* 13:29-35.

9 European Food Safety Authority (2017) Call for technical and toxicological data on sodium carboxymethylcellulose (E 466) for uses as a food additive in foods for all population groups including infants below 16 weeks of age. https://www.efsa.europa.eu/sites/default/files/consultation/callsfordata/180718_sodium.pdf

10 European Food Safety Authority (2017) Re-evaluation of celluloses E 460(i), E 460(ii), E 461, E 462, E 463, E 464, E 465, E 466, E 468 and E 469 as food additives. EFSA Journal 16(1):5047. DOI:10.2903/j.efsa.2018.5047

[11] European Food Safety Authority (2020) Safety and efficacy of sodium carboxymethyl cellulose for all animal species. EFSA Journal 18(7):6211 https://doi.org/10.2903/j.efsa.2020.6211

[12] F.B. Klugmann, G. Decorti, F. Mallardi, L. Baldini, Enhancement of paracetamol induced hepatotoxicity by prior treatment with carboxymethylcellulose, Pharmacol. Res. Commun. 16 (3) (1984) 313–318.

[13] Bär, A, Til, HP and Timonen, M. (1995) Sl:tbchronic Oral Toxicity Study with Regular and Enzymatically Depolymerized Sodium Carboxymethylcellulose in Rats. *Fd Chem. Toxic.* 33(11): 909-917