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Dr. Ruth Lunn
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Division of the National Toxicology Program
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Re: Request for public comments on the nomination of coconut diethanolamide to the RoC

Dear Dr. Lunn

STEPAN Europe on behalf of The REACH Fatty Acid Alkanolamides (FAA) consortium greatly appreciates the opportunity to comment on the nomination of coconut diethanolamide as a candidate substance for the Report on Carcinogens (RoC).

During the registration of coconut diethanolamide under the EU REACH Regulation (EC) No 1907/2006 in 2010, all data pertinent to assessing the potential carcinogenicity of coconut diethanolamide have been thoroughly reviewed by the REACH FAA consortium. On the basis of all available information, it was concluded that coconut diethanolamide should not be considered as possibly carcinogenic to humans. A classification of coconut diethanolamide as carcinogen within the meaning and carcinogen definitions of existing EU Regulation (EC) No 1272/2008, the EU implementation law of the United Nations Globally Harmonized System (UN GHS) on the classification and labeling of chemicals was not deemed appropriate. Therefore, the REACH FAA consortium does not view the nomination of coconut diethanolamide as a candidate substance for the RoC as currently warranted.

In more detail, the outcome of the evaluation of the REACH FAA consortium included the following data and mechanistic considerations:

- Coconut diethanolamide containing residual levels of 18.2% diethanolamine (DEA) was considered to exhibited carcinogenic effects in a chronic dermal carcinogenicity study conducted by the NTP in mice based on the induction of liver and kidney tumours, but no evidence of carcinogenicity in male rats and equivocal evidence of carcinogenic effects in female rats[1];
- No evidence of *in vitro* and *in vivo* genotoxicity (including an *in vivo* mouse micronucleus assay[2]) in dedicated genotoxicity assays;

[1] http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr479.pdf#search=TR 479
[2] Kallesen Th (1985). Assessment of the mutagenic activity of UFANON K-80 in the mouse micronucleus test. Report no.: 10742. Report date: 1985-12-19.

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- Structurally similar lauric acid diethanolamine (CAS#120-40-1) containing residual levels of 0.8% DEA showed no evidence of carcinogenic activity in NTP dermal carcinogenicity studies in male/female rats and in male mice, but some evidence of carcinogenic activity was observed in female mice[3];
- Structurally similar oleic acid diethanolamine condensate (CAS# 93-83-4) containing residual levels of only 0.19% DEA showed no carcinogenic activity, neither in mice nor in rats;[4]
- Potential confounding effects of vehicle ethanol in NTP studies.

Importantly, the investigators of the NTP studies associated the observed carcinogenic activity of coconut diethanolamide and lauric acid diethanolamine in mice to free levels of DEA in the test substances. DEA has been shown to induce mouse liver and kidney tumours by a non-genotoxic mode of action that involves its ability to cause choline deficiency[5]. Choline is an essential nutrient in mammals and is therefore qualitatively applicable to humans. However, there are marked species differences in susceptibility to choline deficiency, with rats and mice being much more susceptible than other mammalian species including humans. These differences are due to the quantitative differences in the enzyme kinetics controlling choline metabolism. The fact that DEA is carcinogenic in mice and not in rats has therefore important implications for human health risk assessment. DEA has also been shown to be less readily absorbed across rat and human skin compared to mouse skin and a NOAEL for DEA-induced choline deficiency in mice has been, established to be 10 mg/kg/day, thus indicating there is a critical level of DEA that must be attained in order to affect choline homeostasis[6]. The lack of carcinogenic response in rats suggest that exposure to DEA did not reach the critical level and since rodents are more sensitive to choline deficiency than humans it can be concluded that the carcinogenic effects of DEA in mice are not predictive for humans.

In 2002, DEA was considered for possible listing in the RoC as "reasonably anticipated to be a human carcinogen". Diethanolamine was shown to be a non-genotoxic carcinogen in mice. However the proposed mode of action indicates a rodent-specific phenomenon which is not relevant for man. This evaluation was supported by a decision of the scientific board by NTP after a public hearing at which it was decided that DEA should not be listed as a carcinogen under the RoC[7]. Considering the similarity response pattern of DEA and coconut diethanolamide in rats and mice and the NTP investigators conclusions that the observed carcinogenic activity of coconut diethanolamide in mice is related to free DEA suggests that also coconut diethanolamide should not be considered for listing in RoC as "reasonably anticipated to be a human carcinogen".

[3] http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr480.pdf#search=TR 480
[4] http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr481.pdf#search=TR 481
[5] http://ntp-server.niehs.nih.gov/ntp/htdocs/Liaison/111902.pdf
[6] http://monographs.iarc.fr/ENG/Monographs/vol101/mono101-004.pdf
[7] http://ntp-server.niehs.nih.gov/ntp/htdocs/Liaison/111902.pdf

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Recently in 2012, due to a change in IARC's classification criteria basically allowing classification in cases where there is positive evidence of carcinogenicity only in both sexes of one species, the International Agency for Research on Cancer (IARC) published a monograph[8] which classified coconut diethanolamide as "possibly carcinogenic to humans" (Group 2B) on the basis of the same set of NTP studies.

While IARC acknowledged the association between the free levels of DEA in the test substance and the observed carcinogenic activity, it speculated on the basis of an observed increase in micronucleated erythrocytes in mice dermally exposed to coconut diethanolamide in a 90-day study, an effect not observed for DEA, that an additional genotoxic mode of action may be operational. Thus, considering the available data, the REACH FAA consortium is of the opinion that the observed increase in micronuclei may be secondary in nature due to general systemic toxicity (e.g. haematoxicity) revealed in the underlying repeated exposure regimen, because it is in contrast to the *in vivo* micronucleus data available to the REACH FAA consortium[9] as well as the absence of micronucleated erythrocytes in mice dermally exposed to structurally similar lauric acid diethanolamine[10].

Nevertheless, the REACH FAA consortium is currently undertaking further analysis of the data and research to elucidate whether the effects are secondary in nature or whether IARC's hypothesis of an additional genotoxic mode of action may be operational for coconut diethanolamide in mice. We therefore suggest delaying the consideration of coconut diethanolamide in the RoC process until the outcome of this analysis and research becomes available.

Please do not hesitate to contact STEPAN Europe on behalf of the REACH FAA consortium in case you require any further information or clarification.

Yours faithfully

[Redacted]

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[8] http://monographs.iarc.fr/ENG/Monographs/vol101/mono101-005.pdf
[9] Kallesen Th (1985). Assessment of the mutagenic activity of UFANON K-80 in the mouse micronucleus test. Report no.: 10742. Report date: 1985-12-19.
[10] http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr480.pdf#search=TR 480