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Submitted via e-mail to EU TBT Enquiry Point

ACC Comments on G/TBT/EU/N/325

To whom it may Concern:

The American Chemistry Council (ACC)[1] appreciates the opportunity to provide the following comments on WTO TBT notification G/TBT/EU/N/325. These comments express concerns regarding the recent harmonized classification decision for dicyclohexyl phthalate (DCHP, CAS number: 84-61-7; EC number 201-545-9) communicated to the WTO by the European Commission as part of the draft proposal for a ninth adaptation to the technical progress of Regulation (EC) 1272/2008 on classification, labelling and packaging of substances and mixtures (the CLP Regulation). This communication aims to amend Annex VI to the CLP Regulation to include a new harmonized classification for DCHP as Reproductive Agent Category 1B, on the basis of developmental effects. DCHP is a phthalate ester with two cyclohexyl rings and is structurally distinct from those phthalate esters having linear or branched alkyl side chains with low or high molecular weight. It is used to make PVC plastisols, PVC and rubber compounds, used in sealant manufacture, and in the formulation of organic peroxide catalysts (phlegmatizer and dispersing agent).

The revised DCHP classification for developmental effects is not supported by the scientific data. As detailed below, clear and sufficiently convincing evidence of an adverse effect on sexual function and fertility or on development following exposure to DCHP has not been demonstrated, despite this being a clear requirement for ascribing a category 1B classification according to CLP Regulation. Therefore classification of DCHP as Category 1B according to CLP is not scientifically supportable. Considering the classification considerations for reproductive toxicity are consistent between CLP and the international UN Globally Harmonised System (GHS) for classification, classification of DCHP as Category 1B is also not scientifically supportable under GHS. No classification or at most classification as a Category 2 ("some evidence") reproductive agent would be consistent with the scientific data and balanced interpretation versus the CLP and UN GHS criteria.

[1]The American Chemistry Council (ACC) represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $804 billion enterprise and a key element of the U.S. economy. It is one of the nation's largest exporters, accounting for twelve cents out of every dollar in U.S. exports.

The significance of this proposed classification with regard to international trade is that, because it not based on a robust weight of evidence scientific evaluation, it could lead to inconsistent and very different regulatory conclusions in different regions leading to the disruption of trade of articles made with DCHP and thereby constitute a barrier to trade. For example there is a significant difference between the treatment of Category 1B reproductive agents and Category 2 under the EU REACH regulation, with Category 1B reproductive agents qualifying for the REACH Candidate List as "Substances of Very High Concern", with subsequent proposals for phase out subject to specific time limited approvals (the REACH Authorisation process). In addition it also means that articles made outside the EU containing DCHP and exported to the EU will be subject to notification requirements under REACH. EU regulations also ban the use of Category 1B substances in articles such as toys, electrical and electronic equipment and medical devices with the associated implications of unjustified restriction in the trade of such articles. So such articles containing DCHP will be subject to bans with the associated impact on trade. If this non-robust weight of evidence scientific evaluation approach is more broadly applied in the classification process, this could result in very broad impacts on trade. For example agricultural produce can also be impacted by such scientifically unjustified classifications, since crop protection agents which may be present as residues and which if classified as Category 1B reproductive agents are considered as endocrine disruptors under EU regulation, with the result that international trade of such produce could be impacted through restrictions and bans. In view of these potential trade impacts of a Category 1B classification under the CLP and/or GHS, it essential that robust scientific standards of evaluation are rigorously applied.

Detailed information on the lack of sufficient scientific evidence to support a Category 1B Classification for DCHP

- According to the RAC report (Feb 2015), the DCHP Category 1B classification for development is based on observations of reduced anogenital distance and mammae/nipple retention in males; and recorded effects on male reproductive organs (testicular atrophy, reduced testicular spermatid head count and decreased weight of the prostate and of the levator ani/bulbocavernosus). **When considered in the light of the entire database, the significance of these findings is low and therefore does not warrant classification.**
    - The CLP refers to this aspect as follows: "If, in some reproductive toxicity studies in experimental animals the only effects recorded are considered to be of low or minimal toxicological significance, classification may not necessarily be the outcome."
    - In principle, classification of Category 1B on the basis of reduced anogenital distance and mammae/nipple retention is not supportable as these are not evidence of adverse effects but rather biological markers which have been shown in many cases to be reversible. As defined by the WHO/IPCS (2004), an adverse effect includes a change that results in impairment of functional capacity.
    - A link between reduced anogenital distance and mammae/nipple retention with impairment in reproductive functional capacity has not been established in rodents or humans. Therefore, a reduction in male anogenital distance and retained mammae/nipples in the absence of observed impairment of reproductive function

cannot be considered "clear evidence of an adverse effect" and therefore cannot lead to Category 1B classification.

- While effects on reproductive organs were noted in some studies for DCHP, **the toxicological significance of these reported findings is questionable as they are not dose responsive, consistently observed, and/or reliably reported in the database.**
    - For example, it cannot be agreed that observations of testicular atrophy are reliable in a study (Ayodogan Ahbab, 2013) the dossier submitter described as 'not so well reported'.
        - This study failed to report several important parameters which are key for understanding if the observed effects are chemical specific (e.g. clinical signs, litter size, sex ratio, live birth index etc.).
        - The study also had gross errors in the reporting of organ weight outcomes where, for example, the testes are reported to weigh more than the entire animal; and questionable statistics (e.g. small standard errors were calculated for endpoints with large variation in reported values).
    - Deficiencies in study design impact the quality and reliability of the evidence and should not be overlooked in assessments. The CLP refers to this aspect of study quality consideration as follows: "if deficiencies in the study make the quality of the evidence less convincing, Category 2 classification could be the more appropriate classification."
    - The reported occurrence of reduced testicular spermatid head counts (Hoshino et al. 2005) is also of questionable significance.
        - This observation was found in only one of the two generations of animals examined; was not accompanied by a change in sperm motility morphology, or number; and did not lead to any deficit in the ability of these males to reproduce.
        - This finding was also not reported in other studies examining DCHP effects on sperm (Ahbab Ayodogan, 2013). The identified decreased weight of the prostate and levator ani/bulbocavernosus were also not dose dependent nor consistently reproduced in the database as they were only reported in one study (Yamasaki et al. 2009).

Consistency and toxicological significance of observations impacts the weight of the evidence and should be considered in a classification determination. For DCHP, the above observations are of low toxicological significance and therefore do not provide clear and sufficiently convincing evidence to warrant classification as category 1B.

- The RAC report aims to establish additional support for a Category 1B developmental classification for DCHP through discussion of the toxicological data for a group of substances termed 'transitional phthalates' which have a harmonised classification of developmental toxicants in Repro 1B. The CLP (and UN GHS) refers to and accepts consideration of data on chemically related substances in a classification decision, however if these considerations are to be important to classification both structural and biological similarity need to be supported.
    - The database for DCHP does not sufficiently support similarity in either of these categories. DCHP has a cyclical sidechain structure whereas the comparative

class of 'transitional phthalates' have linear and/or branched sidechains of varying length, making DCHP structurally distinct. This is of particular importance as the effects on the male reproductive tract caused by certain phthalates are hypothesized to be due to the carbon backbone lengths of the linear and/or branched monoester side chain (Fabjen et al. 2006).

- The 'transitional phthalates' referenced in the RAC opinion induce toxicological effects that are much more prevalent, consistent and severe compared to those effects observed for DCHP, making DCHP biologically distinct. For example, the Low Molecular Weight phthalate DBP (classified as Category 1B) displays areola mammae/nipple retention and decreased male anogenital distance in addition to a number of adverse developmental effects such as a high incidence of hypospadias, underdeveloped or absent epididymis and atrophy of seminiferous tubules.
- The structural and biological distinctions were recognised during the RAC discussion. However, despite this, both substances will now be classified as 1B. Having both substances classified as Category 1B is not in line with the scientific data or the principle of proportionate decision-making.

In conclusion, the reporting of the hazard data for DCHP in the RAC report is misrepresentative of what should be objectively and reasonably concluded from the database.

- Observations were considered significant without regard to their dose-responsiveness or reoccurrence in the larger dataset, both of which are key principles for evaluating the toxicological relevance of an outcome.
- Negative data were not given equal weight with more weight being given to positive unreliable outcomes than high quality negative outcomes.
- A lack of a structured and transparent approach to data assessment results in an appearance of greater certainty and weight in support of a hazard than the database scientifically warrants.
- A need for improved transparency and standardization to data assessment is exemplified best by the disparity in the basis for the decision captured in the final CLH report (dated February 4, 2015). In the opening scientific justification for the proposal, the basis for the classification decision is summarized as follows: "*Most pronounced signs seen were areole mammae/nipple retention and decreased anogenital distance, but also a malformation (hypospadias) was noted".* This is inconsistent with the conclusion section at the close of the document which reads: "*Effects on the anogenital distance as well as on the occurrence of mammae/nipple retention in male pups were recorded in multiple studies and the findings were considered to be specific and not secondary non-specific consequences. Effect on male reproductive organs was also recorded (testicular atrophy, reduced testicular spermatid head count and decreased weight of the prostate and of the levator ani/bulbocavernosus) and these findings are considered to be specific and not secondary non-specific consequences."* Based on these statements, the introduction of the document reflects a classification basis of AGD, nipple retention, and hypospadias whereas the concluding section reflects a classification basis of AGD, nipple retention, and histology effects on male reproductive organs. Therefore it is unclear what data

actually provide the basis for the decision and what level of evidence is considered by the RAC as necessary for a classification decision.

To conclude on a classification determination, there is a need to take into account the evidence for each substance in a robust weight of evidence approach and develop regulatory decisions that are commensurate and proportionate with the data (as stated in section 3.7.2.3 of the CLP regulation). Such an approach should result in the minimization of potential conflicts of interest, whether these are commercial, political, institutional or personal. This is particularly important when decisions such as a classification can trigger further regulatory measures, e.g. potential candidate listing, with clear socio-economic implications for industry and society. As detailed above, such a robust and transparent weight of evidence evaluation approach has not been carried out in the case of DCHP resulting in a scientifically unjustified classification.