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RE: SC Johnson comments on the CLH report on the harmonised classification and labelling of DEET

The CLH report on the harmonised classification and labelling of DEET proposes updates to the harmonised classification of DEET, a common insect repellent active ingredient. SC Johnson appreciates the opportunity to comment on the report, specifically in regard to the specific target organ toxicity and the skin irritation hazard endpoints.

Specific target organ toxicity – single exposure (STOT-SE) comments

KEMI investigated neurotoxicity following a single exposure to DEET, and the specific target organ – single exposure (STOT-SE) section in the CLH report captured the relevant studies to address this hazard and provides clear, concise summaries of the results. The result of the review is that there is enough available data to come to a conclusion, and the data do not meet the criteria/are not sufficient for classification. SC Johnson agrees with the conclusion that DEET does not warrant a classification as a specific target organ toxicant. The extensive history and volume of DEET use (i.e., billions of applications over 70 years) supports this conclusion. Focused monitoring of consumers has shown the absence of a significant number of consumer case reports, which helps demonstrate that the neurological effects noted in the dog studies are not indicative of a significant human health concern.

Many chemicals have been shown to cause at least one observed effect in at least one toxicological study in animals after the administration of a large dose. The neurological effects noted in the dog studies were only observed following a bolus oral dose that is not relevant to consumer exposure. No effects were observed in the animal studies involving dermally applied doses at levels that significantly exceed the typical amounts used on humans. Any chemical that has been used as long and as often as DEET is bound to be associated with some adverse effects in case reports (whether real and proven or by casual chance), but the data from the case reports of seizures in humans does not support a direct link between DEET exposure and seizures. Unlike many chemicals, DEET has a long history of deliberate human exposure. DEET has been extensively studied and has a lengthy history of significant human use with high levels of exposure (i.e., because DEET-containing products involve direct application to the skin). It is appropriate that this exposure and published reviews of human use are considered in the submission.

Although a specific target organ toxicant classification would not have significant consequences for many chemicals, such a classification would ban the marketing of insect repellents containing DEET at a level of 10% or greater. Products with less than 10% DEET only provide a short window of protection against mosquitoes, and especially in areas with high mosquito pressure or during outbreaks of insect-borne diseases (e.g., current Zika outbreaks), repellents are one method of mosquito protection recommended by government health agencies throughout the world, including within the EU.

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Comments on the existing skin irritation classification

Although the skin irritation classification was not addressed in the present CLH report, the existing classification regarding skin irritation is not based on the guideline study for defining skin irritation, and the classification is not consistent with the standard *in vivo* test to assess the skin irritation hazard. The regulations do mention that relevant data may be available from other dermal tests not specifically designed for skin irritation but that such studies must be evaluated on a case-by-case basis. The regulations also state that human evidence/experience can be used for classification. In the case of DEET, the result of the GLP primary skin irritation study conducted for DEET registration according to the regulatory testing guidelines did not meet the criteria for classification as a skin irritant. Although the guideline study for primary dermal irritation did not meet the classification criteria, a skin irritant classification was established based on repeated-dose studies in rats and micropigs®. Animals, rodents in particular, are known to be more sensitive to potential skin irritation effects compared with humans, and the classification does not appear to be representative of the extensive human data and experience from the use of DEET-based repellents.

As the skin irritation testing of products is based on the same guideline study that was negative for DEET, and DEET-based repellent products are not labelled as skin irritants, the utility of the skin irritation classification for DEET is unclear. For example, if the classification is to protect occupational users from an accidental exposure, then the classification does not appear to be warranted as this would be an acute exposure scenario for which the guideline skin irritation study, which provides an appropriate temporal comparison, did not meet the criteria for classification. If the classification is to inform consumers/users of repellent products, then the utility of this classification is also unclear as the products are tested and are not classified or labelled as skin irritants. Therefore, the benefit of this classification for informing or protecting human health is unclear. A possible negative impact of this classification, however, is that DEET-based repellents using more than 10% DEET will require testing to show that the formulations are not actually irritating to the skin. This may lead to unnecessary animal tests to address skin irritation (i.e., to obtain a non-irritating classification for a product in which producers inherently want, and design, to be nonirritating to the skin as repellents are intentionally applied to the skin). Although non-animal test methods exist, the utility and acceptance of *in vitro* tests for complex DEET-containing mixtures remains to be determined. The overall risk of clinically significant skin irritation events from the use of DEET-based repellents is extremely small, and DEET-based repellents have an extensive history of consumer use with billions of applications involving intentional dermal contact. Taken together, the skin irritation classification of DEET does not appear to be warranted.