

Our Reference P-I180/ICL/20180710  
Date 10 July 2018  
**Subject** Targeted Public Consultation CLH MEKO (CAS: 96-29-7, EC: 202-496-6) as STOT RE

To whom it concerns,

The Reconsile REACH Consortium manages around 190 REACH registration dossiers of silanes and siloxanes on behalf of its members (Dow Silicones Belgium SPRL, Momentive Performance Materials GmbH, Elkem Silicones France SAS, Evonik Resource Efficiency GmbH, Shin-Etsu Silicones Europe BV and Wacker Chemie AG, who are manufacturers, importers or only representatives as defined in REACH (Regulation (EC) No 1907/2006)).

Reconsile members have an interest in MEKO (CAS: 96-29-7, EC: 202-496-6) because it is formed when using oximosilanes in silicone sealants.

On behalf of the members of the Reconsile REACH Consortium, ReachCentrum is submitting the feedback in Annex to this letter under the "Targeted Public Consultation on the proposal for the harmonised classification and labelling (CLH) of butanone oxime; ethyl methyl ketoxime; ethyl methyl ketone oxime; EC 202-496-6; CAS 96-29-7".

It is the opinion of the members of the Reconsile REACH Consortium that MEKO does not meet the classification criteria for STOT-RE. Please find the detailed argumentation to support this in the Annex.

We remain at your disposal for further information.

Kind regards,

Signed

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Annex: Feedback on the targeted consultation regarding the proposal for the harmonised classification for Butanone Oxime (MEKO, CAS No. 96-29-7, EC No. 202-496-6) as STOT-RE

**Annex: Feedback on the targeted consultation regarding the proposals for harmonised classification for Butanone Oxime (MEKO, CAS No. 96-29-7, EC No. 202-496-6) as STOT-RE**

The non-classification of Butanone Oxime (MEKO, CAS No. 96-29-7, EC No. 202-496-6) according to the BAuA document (*CLH Report: Proposal for Harmonised Classification and Labelling, Based on Regulation (EC) no.1272/2008 (CLP Regulation) Annex VI, Part 2, substance Name: Butanone oxime, Version 2.0, May 2017*) for the haematotoxicity animal findings is based on the severity of the haematology findings at the dose levels within the category assignments. It is not that the effects are not seen at these levels or that the effects do not occur at higher doses, rather that the effects within the category dose range are not considered severe/adverse to health. We include some excerpts from the BAuA document that support this:

*STOT-RE is assigned on the basis of findings of 'significant' or 'severe' toxicity. In this context 'significant' means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. 'Severe' effects are generally more pronounced or serious than 'significant' effects and are of a considerably adverse nature which significantly impact on health.*

*However, no significant/severe toxic effects from both the oral and inhalation toxicity studies were observed at dose levels approximately equal to the STOT-RE 1 cut-offs according to CLP (guidance values in Annex I, Part 3, Table 3.9.2).*

*Classification in Category 2 is applicable, **when significant toxic effects** observed in a 90-day repeated dose study conducted in experimental animals are seen to occur within the guidance values.*

*Repeated dose toxicity studies with butanone oxime in rats, mice and rabbits showed haematotoxicity such as anaemia after exposure by oral application or inhalation. The observations of haemotoxic effects caused by butanone oxime are considered represent a borderline case regarding classification for target organ toxicity arising from a repeated exposure. There is no doubt that butanone oxime produced significant health effects after repeated exposure. The effects of butanone oxime on the blood observed after repeated exposure by both the oral and the inhalation routes are considered as 'adverse' and at the high dose levels they can equally be considered as 'severe'. Anaemic findings and secondary effects observed in rats after repeated oral administration of 100 mg/kg bw/d and higher in a two-generation toxicity study and at the highest concentration tested of 374 ppm (1346 mg/m<sup>3</sup>) in a 2-year inhalation combined chronic toxicity and carcinogenicity study were not severe enough to justify classification. There was a tendency of reversibility of most of the disturbed erythrocyte parameters in male and female rats at termination of the combined chronic toxicity and carcinogenicity study. The observed increase in haemosiderosis in the spleen, liver or kidney was not combined with severe morphological changes like necrosis, fibrosis or cirrhosis. In conclusion, the effects observed from both the oral and inhalation toxicity studies at dose levels approximately equal to the STOT-RE 2 cut-offs according to CLP (Annex I, Part 3, guidance values: oral (rat): 10 < C ≤ 100 mg/kg bw/d; inhalation (vapour, rat): 0.2 < C ≤ 1.0 mg/L/6h/d) are not considered as significant toxic effects according to the CLP criteria (CLP Guidance, 3.9.2.5.2)*

According to the guidance on the application of the CLP criteria (*Guidance on the Application of the CLP Criteria*, Version 4.1, ECHA July 2017: section 3.9.2.5.2 are fulfilled within the critical range of doses:

**Annex I: 3.9.2.7.3.**

- (a) morbidity or death resulting from repeated or long-term exposure. Morbidity or death may result from repeated exposure, even to relatively low doses/concentrations, due to bioaccumulation of the substance or its metabolites, and/or due to the overwhelming of the de-toxification process by repeated exposure to the substance or its metabolites;**

*Examples:*

- *Premature deaths in anaemic animals that are not limited to the first three days of treatment in the repeated dose study. (Mortality during days 0–3 may be relevant for acute toxicity.)*
- *Clinical signs of hypoxia, e.g. cyanosis, dyspnoea, pallor, in anaemic animals that are not limited to the first three days of treatment in the repeated dose study.*

- (b) significant functional changes in the central or peripheral nervous systems or other organ systems, including signs of central nervous system depression and effects on special senses (e.g. sight, hearing and sense of smell);**

- (c) any consistent and significant adverse effect in clinical biochemistry, haematology, urinalysis parameters;**

*Examples:*

- *Reduction in Hb at  $\geq 20\%$ .*
- *Reduction in functional Hb at  $\geq 20\%$  due to a combination of Hb reduction and MetHb increase.*
- *Haemoglobinuria that is not limited to the first three days of treatment in the repeated dose study in combination with other changes indicating significant haemolytic anaemia (e.g. a reduction in Hb at  $\geq 10\%$ ).*
- *Haemosiderinuria supported by relevant histopathological findings in the kidney in combination with other changes indicating significant haemolytic anaemia (e.g. a reduction in Hb at  $\geq 10\%$ ).*

- (d) significant organ damage noted at necropsy and/or subsequently seen or confirmed at microscopic examination;**

- (e) multifocal or diffuse necrosis, fibrosis or granuloma formation in vital organs with regenerative capacity;**

*Example:*

- *Multifocal or diffuse fibrosis in the spleen, liver or kidney.*

- (f) morphological changes that are potentially reversible but are clear evidence of marked organ dysfunction (e.g. severe fatty change in the liver)**

Example:

- *Tubular nephrosis.*

- (g) evidence of appreciable cell death (including cell degeneration and reduced cell number) in vital organs incapable of regeneration.**

*In the case where multiple less severe effects with regenerative capacity were observed, the classification should apply as “Assessment shall take into consideration not only significant changes in a single organ or biological system but also generalised changes of a less severe nature involving several organs.”*

Example:

- *Marked increase of haemosiderosis in the spleen, liver or kidney in combination with other changes indicating significant haemolytic anaemia (e.g. a reduction in Hb at  $\geq 10\%$ ) in a 28 day study.*
- *Significant increase in haemosiderosis in the spleen, liver or kidney in combination with microscopic effects like necrosis, fibrosis or cirrhosis.*

**Annex I: 3.9.2.8.1.** It is recognised that effects may be seen in humans and/or animals that do not justify classification. Such effects include, but are not limited to:

- (a) clinical observations or small changes in bodyweight gain, food consumption or water intake that have toxicological importance but that do not, by themselves, indicate ‘significant’ toxicity;**
- (b) small changes in clinical biochemistry, haematology or urinalysis parameters and/or transient effects, when such changes or effects are of doubtful or minimal toxicological importance;**

Example:

- *Significant decrease in Hb without any other significant indicators of haemolytic anaemia.*
- *Minimal to slight increase in MetHb formation without any other indications of significant haemolytic anaemia.*

- (c) changes in organ weights with no evidence of organ dysfunction;**  
**(d) adaptive responses that are not considered toxicologically relevant.**

Example:

- *Only adaptive or compensating effects without significant signs of haemolytic anaemia.*

- (e) substance-induced species-specific mechanisms of toxicity, i.e. demonstrated with reasonable certainty to be not relevant for human health, shall not justify classification.**

According to the CLP criteria, a substance is classified for Category 2 STOT-RE blood effects via oral exposure if the dose at **which the effect is considered adverse occurs is  $\leq 100$  mg/kg/day**.

### Conclusion

In conclusion, the effects observed from both the oral and inhalation toxicity studies at dose levels approximately equal to the STOT-RE 2 guidance values according to CLP (Annex I, Part 3, guidance values: oral (rat):  $10 < C \leq 100$  mg/kg bw/d; inhalation (vapour, rat):  $0.2 < C \leq 1.0$  mg/L/6h/d) do not fulfil any of the criteria to trigger a classification. Therefore, from our point of view MEKO does not meet the classification criteria for STOT-RE.