**August 22nd 2014**

**To: The Danish Environmental Protection Agency**

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Dear Madame , dear Sir

**Re :Comments of SSC on the LOUS consultation draft for Styrene ( LOUS Group 3 , substance 28.1)**

On behalf of the Science Group of the Styrenics Steering Committee in Plastics Europe AISBL , 4/3 Avenue Van Nieuwenhuyse , B-1160 Brussels , Belgium , please find here below /enclosed some comments for your consideration on the LOUS styrene draft report.

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**Acknowledgement.**

SSC wants to take the opportunity to comment on the LOUS review of styrene (ST). First of all we acknowledge that in general this paper presents a well-balanced and profound compilation of data comprising regulations, manufacture and uses, waste management, environmental and human health effects including exposure. But there are some points that should be considered for revision especially by taking into account new studies.

**Major points for consideration**

On p. 9, 57/58 the **TDI derived by WHO (2003)** of 7.7 µg/kg bw/d is correctly mentioned that corresponds to a daily uptake of ~0.5 mg/person/d (body weight ~70 kg) or a concentration in food of 0.5 mg/kg food, based on a food consumption of 1 kg food/person/d. On the other hand, the EU migration limit from food contact materials is 60 mg/kg food (p.7) corresponding to an uptake of 60 mg/person/d. This large difference between EU and WHO warrants some critical interpretation.

First of all we want to draw attention to the recent publication of Gelbke et al. (2014) describing the derivation of health based exposure limits for consumers via food arriving basically at the same migration limit as that of the EU. This assessment is based on the most recent literature taking into account the UK Risk Assessment Report (RAR) of 2008 that is also one of the major data sources of the LOUS report. There are several scientific reasons why the migration limits of EU and Gelbke et al (2014) should be given preference to the TDI of WHO (2003). Just to mention a few:

- The database taken into consideration by WHO is quite outdated, the latest reference being from 1989, not reflecting the most important new studies some of which are already mentioned in the UK RAR.

- The total uncertainty factor of 1000 contains a factor of 10 for carcinogenicity and mutagenicity of styrene-7,8-oxide. This subfactor of 10 cannot be justified any longer taking into account the recent studies in this respect with ST and the conclusion at the EU level for no classification for both of these endpoints.

On the other hand, the derivation of Gelbke et al. (2014) is based on the assessment factors proposed by EFSA and ECHA.

- Also, the reduced body weight used by WHO to define the NOAEL warrants critical remarks (it is correctly assumed by LOUS that the study of Litton Bionetics (1980) corresponds to Beliles et al. (1985)):

    - The reduced body weight was observed in females only, the NOAEL for females being 12 mg/kg bw/d, but nevertheless the dose for males at this drinking water concentration was used (7.7 mg/kg bw/d). But the NOAEL for males was 14 mg/kg bw/d. This approach is inconsistent.

    - Decreased body weight was only observed in females at week 102 (not significant) and week 104 (significant) but not before up to week 78. In dosed males body weight rather was increased. This specific feature warrants a very cautious interpretation of the relevance of body weights as it may well be due to unspecific body weight loss in very old female animals as can be seen by the decreasing body weight in female controls from week 102 to week 104. Therefore the body weight effects noted in this investigation may well be a chance finding This is supported by the results of a long term rat inhalation study where no body weight effects were found in females up to 200 ppm (Cruzan et al., 1998). This dose would represent a total body burden of about 125 mg/kg bw/d according to calculations given by Gelbke et al. (2014).

Overall, we recommend that not much emphasis must be given to the TDI of WHO (2003).

As regards **hearing loss in exposed workers** it is mentioned that "*one study indicated that exposure to styrene at concentrations below 87 mg/m³ produced high-frequency hearing loss (Danish EPA, 2011)*" (p.52) and "*hearing effects in humans have been suggested to occur at considerably lower concentrations (below 87 mg/m³), but a NOAEC … has not been established*" (p. 56). Unfortunately, the Danish EPA report, although dated from 2011, did not take into account the most

recent study of Triebig et al. (2008). This study is highly relevant for the interpretation of hearing effects in humans as it is the only one considering present as well as past exposures. This is important because

- Hearing deficits may be caused by relatively short exposures (of a few weeks) at high concentrations
- Such hearing losses are irreversible
- The workforces generally investigated in such studies (laminators) have been exposed to much higher concentrations of ST in the past as compared to more recent times.

Therefore any study reporting only recent exposures at the time of hearing assessment cannot be used for risk characterisation for hearing effects. Under such considerations Triebig et al. (2008) could not confirm "*formerly published results on ototoxic effects below 20 ppm*". This study was used by Gelbke al (2013) to derive for hearing deficits a NOAEL of 40 ppm for risk assessment.

Overall, we propose that the study of Triebig et al. (2008) should be added to and assessed in the LOUS report.

A similar critique applies to **colour vision deficits described in workers**. It is stated that "*the most recent study (cited as Gong et al., 2006) showed that exposure to styrene would impair colour vision even if the exposure concentration was lower than 43 mg/m³*" (p. 52). Again we want to draw attention to a recent study of the same group of investigators (Seeber et al., 2009) that could not have been mentioned in the UK RAR of 2008 but unfortunately even later on was not referred to by the Danish EPA (2011). The authors conclude that "*both acute styrene exposure levels of 40 ppm (range of standard deviation up to 54 ppm) and long term exposures to 27 ppm (range of standard deviation up to 44 ppm with higher exposure levels in the past) for a period of about 15 years were not identified as causing elevated risks*". This study was used by Gelbke et al. (2013) to derive for colour vision deficits in humans a NOAEL of 50 ppm. This NOAEL also took account of the conclusion of the UK RAR (p. 181) that "*it is deemed that the slight changes in colour discrimination detected should not be considered as an adverse health outcome of styrene exposure.*

*It can be concluded that, since the effects observed at 50 ppm (216.5 mg/m³; 8h TWA) are not yet adverse, this exposure value can be considered a NOAEC*".

In this context also the statement concerning the study on amacrine cells may be put into perspective. On p. 52 the Danish EPA is referred to stating that "*there is one study showing effects on the number of the large amacrine cells as well as on the content of neuramines and glutathione of the retina of rats exposed repeatedly to 1300 mg/m3 styrene for 12 weeks. (Danish EPA, 2011)*". In interpretation of this investigation the UK RAR arrived at the conclusion that "*in the absence of any associated conventional histopathology and given the lack of information on what are the 'normal' levels of dopamine and glutathione in the retinal cells of rats, the rather minor morphometric and biochemical changes observed are unlikely to represent a toxic response*". This statement seems appropriate to put the results of this investigation into perspective.

As regards **prolactin and human growth hormone** there is an important misquotation of the UK RAR that needs to be corrected: on p. 55 of LOUS it is stated that "*the RAR reflected that, in the absence of confirmation of the results and explanation of the findings and their biological significance, these differences* ***could be*** *considered to be a reliable reflection of styrene toxicity*". In contrast, the assessment of the UK RAR reads: "*in the absence of confirmation of the results and explanation of the findings and their biological significance, these differences* ***cannot*** *be considered to be a reliable reflection of styrene toxicity"* (p. 154).

**Some minor comments**

On p. 52 of LOUS **the target organs** identified in animal studies are listed: "*the* ***nasal epithelium*** *(rat, mouse), the lung (mouse), the liver (mouse) and the central nervous system (rat, mouse)*". It is correctly mentioned that the effects on lung and liver of mice are of minor relevance for humans. But it is not mentioned that this also applies to nasal toxicity. After an in depth discussion the UK RAR concludes (e.g. p. 133) that "*rodent nasal epithelium damage induced by styrene is not of relevance in*

*relation to the potential repeated dose effects of styrene in humans at relevant levels of exposure"*. The interpretation of UK RAR may be added.

On p. 53 of LOUS the basic data on DNA binding are correctly mentioned: "*DNA binding studies indicate an interaction with DNA leading to various covalently bound DNA adducts in various organs from rats and mice exposed to styrene*". These findings have been discussed in detail in the UK RAR arriving at the conclusion (p. 218) that "*the binding of styrene metabolites to DNA was very low and did not indicate any specificity for the target tissue (mouse lung)*". This assessment of the UK RAR may be added.

**References**

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