The American Conference of Governmental Industrial Hygienists (ACGIH) draft scientific opinion on formaldehyde

Formacare input to the public consultation

Formacare is the formaldehyde sector group of the European Chemical Industry Council (Cefic) representing key European producers of formaldehyde, aminoplast glues and polyols. Made up of representatives from large and small chemical manufacturing companies across Europe, Formacare promotes the safe use and manufacturing of formaldehyde in accordance with the strictest health, safety and environment regulations.

Executive Summary

Formacare would like to take the opportunity to comment on the recent ACGIH (2016) draft proposing for Formaldehyde (FA) a TLV-TWA of 0.1 ppm and a STEL of 0.3 ppm. We ask ACGIH to take into consideration the most recent assessments of FA by European scientific and regulatory committees, specifically

- The TWA (0.3 ppm) and STEL (0.6 ppm) proposed by the Scientific Committee on Occupational Exposure Limits (SCOEL)
- The classification for carcinogenicity proposed by the Risk Assessment Committee (RAC) of ECHA, i.e. cat 1B, meaning that the weight of evidence is not sufficient for cat 1A (human carcinogen)
- The assessment for respiratory sensitization of the German MAK commission (a designation as an asthma inducing agent would not be justified).

With regard of the derivation of an occupational exposure limit, we propose that the following points should be elaborated and discussed in more detail under consideration of the assessment of SCOEL:

- Threshold for nasal tumor formation
- Species sensitivity for formation of DNA adducts and protein cross links
- Interpretation of sensory irritation in humans
- Justification for the TLV based on respiratory tract irritation
- Potential key studies for sensory irritation

In addition, some minor points are listed that may be corrected or supplemented.

Introduction

We recently became aware of the ACGIH (2016) draft proposing for Formaldehyde (FA) a TLV-TWA of 0.1 ppm and a STEL of 0.3 ppm. We would like to make ACGIH aware of a draft assessment of SCOEL (Scientific Committee on Occupational Exposure Limits) (2015) arriving at a proposal of 0.3 ppm (8-hour TWA) and 0.6 ppm (STEL). SCOEL is an independent scientific committee charged by the European Commission to give advice on the development of occupational exposure limits in the European Union. The draft of SCOEL was published for public consultation (deadline 2016-Feb.-17). Admittedly, this draft may be modified according to the comments received. Nevertheless, to our opinion, it is pertinent for the international harmonization of chemical's regulations and we invite the ACGIH to consider the most recent SCOEL arguments. ACGIH only referenced the former SCOEL (2008) documentation that will be superseded by a new SCOEL assessment most probably in 2016.

In addition, ACGIH categorized FA as an A1-Confirmed Human Carcinogen. Here we would like to draw the attention of ACGIH to the assessment of the Risk Assessment Committee (RAC) of the European Chemicals Agency (ECHA). RAC is a European independent scientific committee responsible for providing scientific opinions to the European Commission on the risks of substances to human health and the environment. After detailed review of the epidemiological data, RAC concluded 30 Nov. 2012 that FA should be classified as a cat. 1B carcinogen (may cause cancer) and that the epidemiological evidence was not sufficient to assign cat 1A. Cat. 1A is used for substances "known to have carcinogenic potential for humans largely based on human evidence" while cat. 1B is "largely based on animal evidence". The rationale of RAC is available under at the following link.

Finally, ACGIH proposed the assignment of RSEN for respiratory sensitization. We want to make ACGIH aware of a detailed assessment of dermal and respiratory sensitization by the German MAK commission (Hartwig, 2014) concluding "that FA is responsible for allergic asthmatic conditions only in very rare cases in spite of the wide range of possibilities of exposure" and that a designation as an asthma inducing agent would not be justified.

In summary, we ask ACGIH to reconsider:

1. their TWA and STEL and to take note of the arguments of SCOEL
2. the A1-carcinogen assignment and to take note of the considerations of RAC
3. the designation of RSEN and to take note of the German MAK commission.

In this document, our comments will focus and briefly outline the basic reasoning of SCOEL for derivation of numerical occupational exposure limits. Important references that have not been mentioned by ACGIH will be given. For details, the ACGIH may consult the SCOEL (2015) document.

The most important points

Threshold for nasal tumor formation: An important consideration for derivation of a TLV is the question whether the nasal tumors in experimental animals can be considered a threshold effect for which a NOAEL may be established. In this respect the publication of McGregor et al. (2006) should be taken into consideration showing that nasal carcinogenicity is driven by sustained cytotoxic irritation and cell proliferation with a clear threshold. The same conclusion was reached by WHO (2010) when developing their guideline for Indoor Air Quality and by Nielsen et al. (2010). Based on these consideration SCOEL (2015) considered FA as a group C carcinogen (genotoxic carcinogens for which a practical threshold is supported) according to the SCOEL (2013) guideline. This corresponds to the German MAK commission (DFG, 2015) assigning FA into their carcinogen group 4 with a very similar definition. We propose that these considerations should also be reflected in the ACGIH documentation.

Species sensitivity for formation of DNA adducts and protein cross links: A more detailed discussion of species differences in the formation of DNA adducts and protein cross links would be appropriate. Based on the study of Moeller et al. (2011) and the interpretation of Swenberg et al. (2011), SCOEL

(2015) arrived at the following conclusion: “There are clear indications that the monkey is less sensitive than the rat if FA-DNA adducts (Moeller et al., 2011, Swenberg et al., 2011) or DPC formation (Casanova et al., 1991) are taken as indicator for target tissue exposure and probably humans are also less sensitive than monkeys (Casanova et al., 1991).”

***Interpretation of sensory irritation in humans**:* On p. 12 ff a long list of studies in humans at the workplace or with volunteers under controlled exposure conditions is given including the tables 1 and 2 compiled 1981 and 1989. But as sensory irritation in humans is a pivotal effect, a critical review of these studies is missing to allow a clear conclusion on the relevance of the studies for setting a TLV. In this respect we would like to refer to the discussion of SCOEL (2015) (p. 22 ff). Here the studies most relevant for assigning an occupational exposure limit are clearly defined. It was concluded by Paustenbach et al. (1997) and Arts (2006) (and by SCOEL) that studies on residents or at the workplace (because of several important confounders, among those mixed exposures or recall bias) are much less suited for setting an occupational exposure limit than controlled chamber studies. For the latter, preference should be given to those measuring objective parameters for sensory irritation because subjective parameters again are subject to many confounders, e.g. expectations or personality traits. Therefore we call the ACGIH to evaluate and categorize all the studies listed by these criteria. In addition, many figures given in the tables and the text are not helpful because they cover large spans of exposure not allowing to define a level without effects. Finally, we would like to stress that the most recent controlled chamber study is not included by ACGIH, namely the study of Mueller et al. (2013). This study grouped the volunteers into hypo- and hypersensitive persons to nasal irritation of CO2. As regards objective signs of sensory irritation a NOAEL of 0.7 ppm (4 h) and of 0.4 ppm for 4 h with peaks of 0.8 ppm for 15 min was established without differences between hypo- and hypersensitive subjects. The results of the Lang et al. (2008) and Mueller et al. (2012) studies should be interpreted in conjunction by ACGIH to arrive at a level without effects on sensory irritation.

***Justification for the TLV based on respiratory tract irritation**:* In the ACGIH documentation, a justification is missing how the TLV was developed based on sensory irritation. SCOEL (2015) followed the guidance of Brüning et al. (2014). This publication describes how local toxicity/irritation at the eyes and the upper respiratory tract in experimental animals and humans can be integrated as a basis for setting occupational exposure limits. It is advised that ACGIH should also take into account the concept of Brüning et al. (2014).

***Potential key studies for sensory irritation of ACGIH**:* Apart from Lang et al. (2008) 4 studies in humans are specifically mentioned in the chapter on TLV Recommendation, namely Andersen and Molhave (1983), Alexandersson and Hedenstierna (1988), Horvath et al. (1988) and Edling et al. (1988). As these studies are placed in a prominent place, it is assumed that ACGIH gives special weight to them and we will briefly discuss these studies. In the latter 3 publications exposed workers are assessed. Such studies are less suited for derivation of an occupational exposure limit because they may be compromised by the presence of other contaminants as pointed out by Paustenbach et al. (1997) and Arts et al. (2006). Also the broad exposure ranges have to be taken into account as well as high peak exposures of generally unknown frequency and duration. An important factor also is recall bias of the workers when subjective irritation is the endpoint of interest, like in the studies of Alexandersson and Hedenstierna (1988) and

Horvath et al. (1988). Both of these studies have been assessed in detail by Paustenbach et al. (1997) and they were found not to be of variance with their proposed TLV of 0.3 ppm and a ceiling of 1 ppm.

The study of Edling et al. (1988) basically suffers from the same shortcomings, i.e. a large range of exposure concentrations and high peaks of 4 ppm of unknown frequency and duration. Furthermore an unspecified part of the workers were not only exposed to FA but also to wood dust. Although it is noted that was no difference in histological findings between FA+wood dust- and FA-only exposed workers, this is not substantiated by statistical analyses and therefore this statement cannot be assessed.

The study of Andersen and Molhave (1983) has an important weakness in design because it did not include an unexposed control group. In this respect, SCOEL noted that this "was a controlled study in volunteers in which 3 out of 16 subjects reported eye irritation at a FA concentration of 0.24 ppm. This study has the fundamental weakness that no control group with sham exposure was included while Arts et al. (2006) and Paustenbach et al. (1997) observed that in control groups exposed to 0 ppm 15-22% of the participants will report slight eye irritation. … Recently, Arts et al. (2006) applied a benchmark approach to the study of Andersen and Mølhave (1983) and arrived at the conclusion that a concentration of 0.24 ppm FA, based on slight subjective discomfort, a 95% confidence interval, and assuming a background response of 1/16 (6.25%), would be acceptable." Thus, based only on a background response in 6.25% of the volunteers (instead of 15-22%), a concentration of 0.24 ppm FA is to be assumed not to lead to sensory effects.

In conclusion, a decision for the TLV proposed by ACGIH cannot be based on these 4 studies.

Some additional points to be corrected/supplemented

p.2, left, point (4): It is said that the Chang et al. (1983) study found a significant increase in cell proliferation in the olfactory epithelium at 15 ppm. This is not correct; the cell proliferation was increased in the respiratory epithelium. Also in the study of Speit et al. (2011) cell proliferation was increased in the respiratory epithelium, and in monkeys (Monticello et al., 1989) cell proliferation was by far more increased in the respiratory as compared to the olfactory epithelium.

p. 2, right, 1st paragraph and p.11, left: Here the computer modellings predominantly of the CIIT group are mentioned including Swenberg et al. (2011). We propose that the 2 most recent "bottom up modellings" of Starr and Swenberg (2013; 2016) should be added that took into account the relation of endogenous and exogenous DNA adducts.

p. 7, right, Morgan et al. (1986b): It is said, that "Nasal **carcinomas** considered by Morgan et al. (1986b) to represent a malignant manifestation of the benign polypoid adenomas, **were** found in 1 rat inhaling 14.3 ppm." This should be modified as there was only **one** nasal carcinoma of this type in this rat.

p. 10, right, bottom: The study of Heck et al. (1985) is mentioned showing the FA at 1.9 ppm does not lead to an increase in blood concentrations in humans. In the same study a concentration of 14.4 ppm in rats and in a study with monkeys at 6 ppm (Casanova et al., 1988) no increased blood levels were observed. This is strengthened by Kleinnijenhuis et al. (2013) in rats with labelled FA at 10 ppm without an effect above approximately 1.5 % endogenous FA blood concentration. These findings are important showing that even high FA concentrations after inhalation do not affect systemic blood levels.

p. 11, left, bottom: The figures given for exogenous and endogenous adducts according to Swenberg et al. (2011) are partly incorrect, for example: exogenous adducts at 0.7 ppm are $0.039x10^{-7}$ and endogenous adducts do not increase with FA concentrations. Perhaps the original papers of Lu et al. and Moeller at al. should also be cited.

In addition, the important interpretation of Swenberg et al. (2011) is worthwhile to be mentioned, namely that the relationship of exogenous/endogenous adducts is smaller in primates than in rats indicative of a difference in susceptibility (p S133, right/S134, left).

p. 11 right, top, referring to Swenberg et al (2013): The mentioned "higher sensitivity" of humans compared to rats does not refer to data of the authors, but rather to an assessment of USEPA (2010). This USEPA (2010) assessment is critically reviewed in this publication. By their own data when comparing exogenous and endogenous DPC and adducts in the nose, Swenberg et al conclude that the relationship at 6 ppm is very similar for rats and primates, but at 2 ppm it is lower in primates. This indicates to a lower sensitivity of primates at low exposures corresponding to the assessment of Swenberg et al. (2011) mentioned above.

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