Submission challenging nicotine CLP reclassification proposal

Background

RIVM have submitted a CLH report proposing changes to the harmonised nicotine classifications (1). RIVM propose that oral acute toxicity Category 3* (Toxic if swallowed) is insufficient and that a Category 1 (Fatal if swallowed) is suggested. In addition to this, a new inhalation classification; Category 2 (Fatal if inhaled) has been put forward. The current dermal classification; Category 1 (Fatal in contact with skin) has been maintained.

Fontem Ventures disagrees with the proposal to change the oral acute toxicity and the proposed inhalation classification. In Fontem Ventures' scientific opinion, the current oral toxicity classification is still valid and the inhalation classification should be Category 3.

General comments

Fontem Ventures strongly disagrees with the comment in the proposal that there is a need for action at the community level.

The CLH report claims action is needed due to the increase in accidents with e-cigarette refills and its increasing popularity. Fontem believe the current oral classification is still valid as recent incidences of accidental nicotine exposure have resulted in minimal adverse findings (2, 3). Also, the misconceptions underlying the toxicological risk posed by nicotine to the human population, by the oral route, has recently been reviewed by Mayer (2014)(4).

Specific comments – Oral Toxicity

Fontem Ventures considers that current knowledge of human exposure to nicotine, and the limited reported incidences of a severe nature, should be the primary factor for assessing the classification of nicotine. Ascertaining values from animal studies performed under non-GLP conditions, or those considered of an unacceptable level, should subsequently be discarded.

However, should animal studies be considered, Table 11 of the CLH report by Van den Heuvel *et al* (1990) (5) established an LD50 of 70 mg/kg. This study was a comprehensive collaborative study using 31 laboratories and complied with OECD guidelines.

Fontem Ventures deems that the rat LD50 data are more relevant than the mouse data when considering the metabolic pathways in the detoxification of nicotine. The toxicity of nicotine is receptor-specific and driven by the parent compound rather than its metabolites. Therefore the retention of nicotine would be the presiding toxicity factor and this should be considered when determining an LD50 of the parent compound. As the metabolism of nicotine is much slower in humans than the mouse it would therefore be considered that the rat is in fact the more relevant model (6).

We therefore conclude that the current oral acute classification should remain as Category 3 based on the consideration that the rat data previously used is still valid and metabolic differences in the mouse preclude the use of this species.

Specific comments – Inhalation Toxicity

Fontem Ventures would question the need for a Category 2 classification of nicotine via the inhalation route. Although it is accepted pharmaceutical products are exempt from CLP regulations, some regulators (eg. Medicines and Healthcare Products Regulatory Agency (MHRA)) are recommending licensing of e-cigarettes, also known as electronic vapour products (EVPs), as nicotine containing pharmaceutical products. A classification of Category 2 would therefore disseminate alarming messages to the general public by indicating possible fatal classification via inhalation of e-liquid mixtures when labelled on similar consumer products.

Surprisingly, there is a distinct lack of appropriate animal LC50 data for nicotine. Therefore, in the absence of reliable data, human exposures, as per the ECHA guidance need to be considered. Exposures via occupational exposures, smoking, medicinal nicotine replacement therapies and also the recent increase in vaping, of which there has been no evident increase in adverse events related to acute inhalation, should therefore be considered.

The only study RIVM are basing the Category 2 classification with, is on the study by Shao *et al* (2013) (7) which reports an LC50 (20 minutes) of 2.3 mg/L. A factor of four has been used to convert to a 1 hour exposure resulting in an LC50 of 0.58 mg/L with an additional factor assumed to give an overall LC50 of 0.25 mg/L. We consider a default factor of four to be overly conservative for compounds such as nicotine that have a short half-life as shown in human studies with nicotine inhalers (8). Nevertheless, in the absence of any other animal data and taking into account the ECHA guidance of a factor of four should be appropriate for conversion to a 4 hour exposure.

Caldwell *et al* (2012) (9) performed a review of clinical trials performed with nicotine inhalers, where 5 minute exposures were reported to be as high as 130 mg/mL (130’000 mg/L) with repeated use. Data demonstrated that even with such high concentrations, adverse effects were essentially limited to cough and burning throat.

Due to a combination of the limited animal data and the available human evidence we conclude that Category 3 (ie. LC50 of 0.58 mg/L) would be sufficiently conservative for classification and labelling purposes of nicotine via acute inhalation.

Final remarks

We want to work with regulatory bodies to create appropriate and effective regulations to encourage even greater consumer confidence with nicotine containing products such as EVPs.

As ECHA correctly states, proper classification based on validated and experienced danger levels provides consumers with crucial information. This directly implies that classification of substances in categories not reflecting their experienced (and texted) toxicity endangers the long-term usefulness of such a system (Mayer, 2014).

We want to lead the market in promoting safe packaging and discouraging the sale of e-liquids which do not have safe, tamper-free refill systems. At the same time, we must avoid over-regulating; we do not want to possibly limit the potential public health benefit that experts now forecast.

A growing consensus of experts in the field of public health – such as Professor Robert West at University College London (10) and the pressure group Action on Smoking and Health (ASH) (11) – believe that EVPs could make a significant contribution to public health. Some EVP users report that the products are a more effective smoking cessation tool than

traditional NRT offers. They argue that by offering a real alternative to smoking tobacco, use of EVPs could reduce tobacco-related deaths by thousands per year. Therefore we do not want to detract consumer confidence with excessive labelling.

We agree that it will take many years, even decades, before we have clarity over the long-term health impact of EVPs. However, what is clear is that the growing consensus of scientific opinion has now concluded that the potential public health benefits of EVPs outweigh the risks. Even the World Health Organisation (WHO) accepts that "average [EVP] use produces lower exposure to toxicants than combustible products" (12).

We, like many others, believe that the effect is positive - and want to work with regulatory bodies to create an appropriate and effective set of rules to encourage even greater consumer confidence in these products.

To conclude, Fontem Ventures considers that with regards to nicotine containing mixtures, we must create an environment where we send positive signals about EVPs in the way they are regulated.

References

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