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'The Industry Standard of Excellence'

ECITA response to proposal submitted for harmonised classification and labelling of nicotine, CAS 54-11-5, EC 200-193-3.

ECITA is a trade association with membership based mainly in the UK, although its members trade across the whole of the European Union, and indeed globally. Although ECITA has a significant focus on consumer protection, we have concerns about the nature of the changes contained in this CLH proposal, and the poor level of scientific justification for them. Changes to the harmonised classification have the potential to have significant effects on the transport and supply of these products, with the potential for significant increases in the costs to business. (The vast majority of the businesses operating in this sector are small to medium enterprises (SMEs).) This would inevitably have an effect on the price consumers pay for the products potentially damaging their value proposition as an alternative to cigarettes. Recent Eurobarometer survey data has identified price as a significant factor in selection of electronic cigarette products, making this a cause for significant concern[1].

The survey also highlighted that the number of people who consider electronic cigarettes harmful has increased, an aspect covered in more detail in the UK by Action on Smoking and Health, ASH. ASH data[2] indicate that the number of people who incorrectly believe that electronic cigarettes are as harmful as smoking has increased dramatically, leading ASH CEO Deborah Arnott to comment:

> "*The number of ex-smokers who are staying off tobacco by using electronic cigarettes is growing, showing just what value they can have. But the number of people who wrongly believe that vaping is as harmful as smoking is worrying. The growth of this false perception risks discouraging many smokers from using electronic cigarettes to quit and keep them smoking instead which would be bad for their health and the health of those around them*."

This is echoed by Dr Leonie Brose, who was involved in the statistical analysis of the data:

> "*We must clearly communicate the relative safety of electronic cigarettes to smokers. The proven harm of tobacco is currently getting less coverage than the much smaller and far less certain harm from electronic cigarettes. We owe it to smokers to provide them with accurate information*."

[1] http://ec.europa.eu/public_opinion/archives/ebs/ebs_429_en.pdf
[2] http://www.ash.org.uk/files/documents/ASH_891.pdf

An increase in the perceived danger of nicotine that is not justified, by robust scientific methodology and data, runs a very real risk of causing harm through unintended consequences.

At 4.2.2 RIVM cite that "[t]hey report 35 cases – 4 in 2010, 12 in 2011 and 19 in 2012. Age range 8 months to 60 years. Reported symptoms were mild and transient. Product concentrations ranged from 4 to 30 mg of nicotine per ml", Cantrell (2015).

The increase in the number of exposures can be expected to follow the increase in the availability of the products, something identified in the cited research. However, as the symptoms were categorised as "mild and transient" this does not seem to make a case for a change in classification. Indeed, the reference cited states that "[o]ur modest results suggest that adverse effects and accidental exposures to ECIG cartridges are unlikely to result in serious toxicity."

However, despite an increasing number of exposures to weak nicotine solutions, these have not resulted in serious toxicity. UK Poison Information Service data for 2013/14 indicated 204 reported exposures, of which 21 involved intentional overdose. Of these 204, 103 had no features of toxicity, and 94 had only mild toxicity. Only one case of severe toxicity was reported (although it is not clear if this was an accidental or deliberate exposure), and no deaths. No deaths have been reported as a result of either intentional inhalation of nicotine vapours via electronic cigarettes, or through accidental exposure to the concentrations found in the European market.

This would seem to indicate that there is not a pressing need to address the issue of reclassification.

Acute oral toxicity

The RIVM CLH report discusses in some detail the metabolism of nicotine in section 4.1.3 and the extent to which it varies between species. While this may question the applicability of the rat data for humans, it does not make a case for the mouse data being any more representative of human metabolism.

This is particularly concerning when the rat data (particularly van den Heuvel et al., 1990) is comparatively recent and of good methodology, whereas the mouse data is older and of more uncertain method. There is also considerable variation in the measured LD_{50} for mice, with the study identified as key by RIVM appearing to be uncharacteristically low compared with the remaining data. Examination of alternative sources also suggests that this LD_{50} may be unrepresentatively low, for example the United States Department of Health and Human Services National Toxicology Program data on Nicotine[3] reports an oral mouse LD_{50} of 24mg/kg (although the reference is to a book, and the exact origin of the data is unclear) and additionally refers to a study in which mice were administered i.v. triterated (3H) nicotine, causing only 5% deaths at a dose of 5mg/kg, although 'most' died at an i.v. dose of 10mg/kg. An LD_5 of 5mg/kg delivered intravenously is not supportive of a lower oral LD_{50} value.

[3] http://tools.niehs.nih.gov/cebs3/ntpviews/index.cfm?action=testarticle.toxicity&cas_number=54-11-5#Non-Human%20Toxicity%20Values

The choice of this study is also concerning in light of RIVM's expressed opposition to the applicability of the gavage method in rats, to human oral exposure, since this study also used a gavage method.

RIVM reported that they were unable to retrieve a more recent set of mouse data (Trochimowicz et al., 1994), but a fairly trivial search indicates the likely source of this as "Trochimowicz HJ, Kennedy Jr GL, Krivanek ND. Heterocyclic and miscellaneous nitrogen compounds. In: Clayton FE, ed. Patty's Industrial hygiene and toxicology. 4th ed. New York, John Wiley & Sons, Inc. 1994; IIE:3374-9, 3489-91.". It would seem that this reference would benefit from further evaluation.

Section 4.1.3 also cites Tutka, 2005 as identifying that "rabbits seem to be a good model for studying human NIC metabolism".

Taken as a whole, the RIVM proposal identifies that there are some issues with the current classification that it would be of benefit to address. However it does not make a robust case for the selection of mouse data over rat data for determining acute oral toxicity, nor for the selection of the specific mouse data selected. Before making such a sweeping change, a more thorough literature search should be conducted. A robust justification for the selection of the key species for classification should also be made, since section 4.1.3 contains nothing to suggest that the mouse data is more representative of human toxicology than other species, and as currently written actually proposes that rabbit data would be the most suitable.

Any decision-making would be much more robust if, after selection of a key species is justified, robust data using modern methodology could then be obtained for this exposure route (if it is not already available).

Acute inhalation toxicity

There seems very little justification for adopting the proposed LC_{50}, when the proposal itself identifies that "[t]he available acute inhalation data do not allow determination of an LC_{50} value". A comparison with criteria (4.2.4) that applies "can be estimated", "probably even lower" and "this is in the middle" to the calculation of an LC_{50}, following this statement, does not seem sufficiently robust.

While there may be some merit in the identification of an LC_{50} for nicotine as a pure substance, this is not a likely route of consumer exposure, and there have been no reports of serious acute toxicity involving inhalation of either nicotine-containing smoke from tobacco products or vapour/aerosol from electronic cigarettes. Since there are already extremely conservative workplace exposure limits in place to address occupational exposure to nicotine-containing mists or dusts (US NIOSH 0.5mg/m^3 8 hour TWA; UK HSE 0.5mg/m^3 8 hour TWA, 1.5mg/m^3 15 minute STEL) there does not seem any pressing need to address this issue.

It would not seem either appropriate or necessary to adopt an LC_{50} value unless better data on acute inhalation toxicity can be obtained on which to base a decision.

Conclusion

If a change to the current classification is to be justified, it should be supported by a robust justification for the choice of key species for any given exposure. Given the age of much of the available data, it should also ideally include new toxicological data for any given route and species. This would resolve the current ambiguity surrounding much of the literature data.

In the absence of robust data, a change to the classification would risk significant unintended consequences, particularly if such a change increased costs and/or reduced the availability of affected products, with the associated ramifications for SMEs and consumers.

[redacted]
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