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Pure nicotine reclassification by RIVM

Background

The Dutch National Institute for Public Health and the Environment, RIVM has proposed a reclassification of nicotine toxicity for the purpose of nicotine labelling (CLH report).

They propose to reclassify pure (i.e. 99.9%) nicotine as follows:
• From oral acute toxicity category 3 (Toxic if swallowed) into oral acute toxicity category 1 (i.e. Fatal if swallowed),
• To add inhalation acute toxicity category 2 (i.e. Fatal if inhaled)
• Retain the dermal acute toxicity category 1 (i.e. Fatal in contact with skin).

Implications for vaping industry

• Potential effects on manufacturing practices where pure nicotine is handled
• Adverse publicity for e-liquids, i.e. an inhalation from e-products "fatal if inhaled"
• Additional labelling requirements.

Grounds for challenge
1. Community need

CLH Report's justification for why action is needed is summarised below:

1. "…the current policy discussions on the use of the e-cigarette, the increase in accidents with e-cigarette refills and its increasing popularity"
2. Current acute oral toxicity classification for nicotine is a "minimum classification". That means manufacturers and importers should investigate if a more severe classification applies.

Grounds for challenge:
Although incidence is increasing with increased use with millions consumers worldwide, the absence of symptoms or minimal toxicity experienced as a result of the accidental nicotine exposures indicates the current labelling of both nicotine and the 'mixtures of nicotine' (i.e. e-liquids) is effective enough and no reclassification is required.

Grounds for challenge
2a. Toxicological classification details – Acute Oral Tox

CLH Report in brief

• Metabolism differences between rats and humans means the rat is not the appropriate species to base oral tox classification on.
• Lowest available LD50 is from mice: 3.34 mg/kg hence warranting category 1 classification (most restrictive).

Grounds for challenge:
CLP guidelines are to use rat as preferred species, not the most sensitive species.
Based on total nicotine hepatocyte metabolism, the metabolism differences are bigger between mice and humans than between rats and humans. Therefore, the default ECHA CLP guidance that rat is the preferred species, still stands. Last but not least, all rat oral acute toxicity studies indicate category 3 oral toxicity (less restrictive).

Grounds for challenge
2b. Toxicological classification details – Acute Inhalation Tox

CLH Report in brief:

No standard LC50 study with nicotine inhalation exposure exists in the public domain. The proposed classification is based on a single 20 minute acute toxicity study with conventional tobacco cigarettes, where the most conservative value was used and a factor of 4 was applied to account for the accumulation of dose that might have taken place had the exposure been over the required 4 hours.

Grounds for challenge:

In the absence of appropriate animal LC50 data (as in this case), ECHA recommends a weight of evidence approach that includes human experience. Decades of occupational, smoking and NRT experience, as well as the more recent vaping, does not indicate lethality concerns via inhalation. Recommended NRT dosages equate up to 0.027 mg/L and it is recognised as a safe and well tolerated treatment. Similar nicotine levels are measured with current e-vapour products. Moreover, peak arterial nicotine levels from tobacco smoking are typically around five times higher than those from NRT and current e-vapour products. Hence, ECHA recommendation cannot be extended from human experience with the vastly more efficient tobacco cigarette to other less efficient nicotine containing products.

Grounds for challenge
2c. Toxicological classification details – Acute Dermal Tox

CLH Report in brief

• Nine acute dermal exposure studies in rats, rabbits and one is cats, are referenced. Dermal LD50's reported are 50 - >360 mg/kg bw.
• Classification is effectively based on the most sensitive rabbit study (50 mg/kg bw)

Grounds for challenge

First, the most sensitive rabbit study only reported an estimated LD50, which is not accurate. Therefore, the other studies should be considered as well. The only two the CLH report indicates as

acceptable are LD50 = 285 mg/kg in rats (nicotine sulfate) and 66-100 mg/kg in cats (40% dilution). The range of all the reported LD50's is 50 - >360 mg/kg bw.

Second, the cat dermal study used a 40% aqueous solution, whereas classification is based on the toxicity of the pure compound. Nicotine dermal penetration shows a parabolic dependence on nicotine concentration where 100% nicotine had similar flux as 1% w/w nicotine aqueous solution. It is thus likely the pure nicotine is less dermally toxic than what was tested on the cats. Category 2 rather than category 1 would be more appropriate.