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Happy People UG
Attn.: Mr. Ralf Steffan
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Toxicological evaluation of the TÜV analysis report on an e-cigarette liquid

Dear Mr. Steffan,

On 27 February 2013, you commissioned me to evaluate a TÜV report on the analysis of a liquid that is used as a filling for e-cigarettes and is inhaled as an aerosol after exposure to heat.

According to the analytical report prepared by TÜV NORD (112ARM091/8000641362), volatile organochemical compounds in the test liquid and in the gas phase generated after heating to 80°C were detected by means of GC/MS. The levels of toxicologically relevant substances in the test liquid and gas phase were also quantitatively analysed.

As a result of this screening, it was determined that the substances 1,2-propranediol (propylene glycol), glycerol, menthol and nicotine were present in the test liquid while propylene glycol, menthol and nicotine were present in the gas phase.

Nicotine: The effects of nicotine are attributable to stimulation of nicotinic acetylcholine receptors in the ganglia of the autonomous nervous system. This results in vegetative reactions, such as elevation of blood pressure and increased intestinal activity. The stimulation of nicotinic acetylcholine receptors in the adrenal medulla leads to the release of the stress hormone adrenalin that, in turn, potentiates the vegetative effects of nicotine. Nicotine is both a psychostimulant and a sedative. As nicotine consumption is associated with elevated levels of dopamine, its use can result in dependency (addiction). Although the dependency potential of nicotine is significantly increased by other constituents present in tobacco (smoke)¹, it can be assumed any addiction of the user will persist if they inhale nicotine alone. The test liquid is thus not suitable for use by those seeking to cure themselves of nicotine dependence.

According to the manufacturer, the nicotine content of the test liquid is 18 mg/ml. A user who consumes 3 ml of this liquid per day by way of inhalation will absorb a maximum of 54 mg nicotine. At present, however, there is no reliable data on the bioavailability of nicotine delivered by e-cigarettes. The results of a clinical study² indicate that, by means of careful selection of various hardware/liquid combinations and irrespective of the actual nicotine content of the liquids (4 – 24 mg/ml), users tend to consume until their nicotine plasma levels are in the approximate range 16 ng/ml – this is at the lower end of the range observed in smokers (15 – 24 mg/ml). The nicotine content of the test liquid can thus be seen as appropriate in this respect.

Propylene glycol (1,2-propanediol): Propylene glycol is a colourless liquid that is non-toxic if used as recommended. The substance is present as an additive in numerous foodstuffs, cosmetics, medicinal and tobacco products. Propylene glycol is absorbed by the body and converted to endogenous metabolites (mainly pyruvate and lactate) but can also be eliminated in unchanged form via the renal pathway. In common with many other substances, propylene glycol can trigger allergic reactions. These are exclusively dermal reactions and they are mild in terms of severity. In a clinical trial that included more than 45,000 subjects who were exposed to propylene glycol patches, fewer than 5% experienced skin irritation. The reactions were evaluated as significant in only 0.6% of cases. The authors conclude from their results that propylene glycol has an extremely low allergenic potential³.

As a propylene glycol solution is also inhaled when e-liquids are consumed, the possible risk of allergenic effects on the bronchial muscles (respiratory tract) and thus the prospect of the exacerbation of asthmatic reactions in appropriately predisposed individuals must be taken into account. The relevant literature contains no corresponding references. In fact, the results of a clinical study seem to point to the fact that propylene glycol may have a beneficial effect in subjects with bronchial asthma as the substance was observed to significantly attenuate the bronchoconstrictive potential of histamine and potentiate the antiasthmatic effects of the α_1 -antagonist prazosin⁴. It would thus seem that propylene glycol is unlikely to represent a risk to persons with bronchial asthma.

Glycerol: Glycerol is a constituent of all natural fatty acid esters (fats, oils) and it is an intermediate product of many mammalian metabolic processes. Glycerol is an authorised foodstuff additive and has the official code E 422. Glycerol is added to a range of different foodstuffs and tobacco products as a humectant. The toxic potential of glycerol is classified as very low in all relevant databases. Because of this non-toxicity, the EU has not specified an ADI value for glycerol. LD₅₀ in the mouse following oral intake is 4.09 g/kg bodyweight, equivalent to 306.7 g at a bodyweight of 75 kg. At the same time, however, glycerol can cause mild irritation of the skin and mucous membranes. The glycerol content of the test liquid can thus be seen as harmless from the toxicological perspective.

Menthol: In its pure form, menthol is a solid substance that occurs in four isomer forms that have melting points in the range 31 – 34°C. Menthol is added to cosmetics, confectionary and tobacco products as a flavouring and, because of its hyperemising effect, it is also used in salves and inhalants designed to mitigate the symptoms of head colds. At very high doses (species-dependent LD₅₀: 3 – 5 g/kg bodyweight), menthol can cause cardiac arrhythmia and respiratory distress. According to the manufacturer, the test liquid contains 1% menthol. Inhalative medicinal products contain up to 5% menthol. The menthol content of the test liquid can thus be evaluated as harmless from the toxicological perspective.

Nitrosamines: The concentrations of all nine detected nitrosamines classified as carcinogens were below the detection limit of 0.07 µg/ml (liquid) and 0.2 µg/m³ (gas phase). It can thus be concluded that the test liquid is 'nitrosamine-free'.

The test liquid was also investigated for its content of 20 different primary and secondary amines, of which two were detected in the liquid and the gas phase.

Methylamine: Methylamine was present in the gas phase of the heated test liquid at a concentration of 87.03 µg/m³. This is more than 100 times lower than the threshold limit value (10 ppm or 12 mg/m³). The content of methylamine is thus harmless from the toxicological perspective.

Di-n-butylamine: Present in the gas phase of the test liquid was 24.36 pg/m³ di-n-butylamine. This is more than 1000 times lower than the threshold limit value (5 ppm or 29 mg/m³). The content of di-n-butylamine is thus harmless from the toxicological perspective.

Formaldehyde: Detected in the gas phase was 20.7 µg/m³ (0.017 ppm) formaldehyde. This is approximately 30 times lower than the threshold limit value (0.5 ppm or 600 µg/m³), 6 times lower than the intervention level defined by the German Ministry of Health (0.1 ppm or 120 µg/m³) and 3 times lower than the concentration defined by the WHO as "representing little or no risk", i.e. 0.05 ppm (60 µg/m³). The content of formaldehyde is thus negligible and harmless from the toxicological perspective.

On the basis of the data supplied, it can be concluded that any pharmacotoxicological effect following the inhalation of the test liquid can be attributed solely to the effects of nicotine.

Yours sincerely



Dr. Bernhard-Michael Mayer

Professor of Pharmacology and Toxicology

References

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