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## Big Tobacco lights up e-cigarettes

### E-cigarette regulation needs: production, sale and use

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“We desperately need clinical trials and observational studies”, but, while it is claimed that e-cigarettes are less toxic than regular cigarettes [1], there are still safety and health issues that need to be clarified before they can be said to be “safe” and “clean”.

The growing success of electronic cigarettes seems to have bridged the gap between regular tobacco and nicotine replacement but this attractive new device is a completely novel tool for intake of chemicals so this implies some risks. However, it should enable smokers to downgrade their sword of Damocles to a less serious addiction.

Production of e-liquids involves large amounts of pure nicotine. A 500 L production tank of 24 mg/mL nicotine e-liquid needs 12 kg of nicotine. It is very probable that producers, as there is no regulation now, will stock hundreds of kilograms of nicotine. This seriously dangerous amount of alkaloid will have to be shipped, stored, and handled in the production site. How?

The juice will be prepared with aromas ranging from tobacco to fruit, liquorice, chocolate and many other attractive flavours that might encourage “non-vapers” to taste them. A 10 mL, 24 mg/mL nicotine e-liquid bottle will contain 240 mg of nicotine, available for purchase in shops and could cause acute poisoning. When the juice is ready, shipped and sold, users will keep it in bottles designed with no specific safety rules, and suicide attempts by ingestion of the liquid have been reported [2]. Nicotine is readily absorbed by the skin and anybody can touch a leaky bottle, exposing themselves to the alkaloid.

Regulation must also take into consideration poor manufacturing and the possibilities of contaminants. Low-quality nicotine, glycerol, propylene glycol or flavours could greatly increase the toxicity. For example, NOR-nicotine contamination can give rise to the formation of carcinogenic nitroso-NOR-nicotine in the stomach; ethylene glycol is hugely more toxic than its three-carbon analogue. The e-cigarette itself can also release metals and nanoparticles in the aerosol [3].

E-cigarette exposure routes are not completely clear. Are the chemicals in vapours inhaled or ingested? In what ratios? Acute effects of e-cigarettes have been reported in healthy subjects [4]. The liquids contain a number of chemicals beside nicotine [5], that have not been tested sufficiently for this exposure route. This is a critical point. In toxicology quite different parameters are used and compounds that are “safe” when ingested may even be carcinogenic if inhaled, like acetaldehyde, for example, which is commonly found [5] in e-liquids.

The nicotine concentration in samples analyzed is not constant. We found differences between declared and actual concentrations ranging from -70% to +20% [6]. This has been observed by other authors too [7], indicating that it is a common problem in the e-cigarette market. A nicotine-releasing patch or a chewing gum releases a defined amount of drug but the doses released and absorbed by different e-cigarettes are unknown. Indications for use are needed and research has still to accurately define e-cigarette nicotine release and absorption.

Finally, we recently observed the formation of new products, like acrolein, during the vaporization [6]. These degradations have been discussed even among “vapers” and in Internet sites [8]. They have not been published yet but have been observed and were presented to the scientific community at a recent meeting [9]. Chemicals in the e-juice undergo pyrolysis during vaporization, and this process is probably specific for liquids with different composition and for different vaporizer designs, and needs to be characterized.

This brings us to the observation that inhaled “vapours” are not just vaporized e-liquids, but mixtures of new compounds that will necessarily have to be investigated and defined. For instance, acetaldehyde and the more chemically reactive acrolein are well-known thermal decomposition products of glycerol.

There is no single opinion [10 11] about making e-cigarettes available like tobacco. Within the EU Member States, regulatory approaches differ [12]. Malta regulates e-cigarettes like tobacco products, nine Member States as consumer products and 14 as medicinal products. Others have no specific rules. Public health agencies [12] demand more research on the safety and long-term effects of these products and do not recommend the use of electronic cigarettes.

Production needs urgently to be regulated similarly to medicines, especially as regards the accuracy of dosing and for occupational safety. A research effort is essential to understand the effects of degradation products on consumers' health, as well as the toxicity of trace components and the kinetics of nicotine absorption.

The fact that regulators in different countries have felt obliged to consider e-cigarettes as drugs is not just a question of zeal [10] but simple risk management which is crying out for data from accepted assessment procedures.

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