Toxicological Risk Assessment Approach – Filtration Materials for Tobacco Products

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1 General Assessment Principles

The ingredients used as Filtration materials (see section 2) in tobacco products (in this document, tobacco products include both combustible cigarettes and heated tobacco products), are assessed according to the company quality standard and subjected to rigorous toxicological risk assessment with the objective of assessing that product modifications do not result in new hazard for human health or an increase of the inherent toxicity of the products.

The toxicological risk assessment generally follows the four-step analytic process for human-health risk assessment (National Research Council Committee on Risk Assessment of Hazardous Air Pollutants, 1994), which includes hazard identification; dose-response assessment; exposure assessment; and risk characterization.

1.1 Hazard Identification and Dose-Response Assessment

The hazard properties of chemicals are determined based on the available data reported in public and commercial databases to identify and characterize the potential hazards on humans. When available, data from internal studies are included in this assessment. Data obtained from the relevant route of exposure are prioritized (e.g., inhalation route for inhaled products and oral route for snus, nicotine pouches, and other oral products).

When data are limited, a read-across approach and Threshold of Toxicological Concern (TTC) may be used. Regardless of the availability of the chemical-specific toxicity data, an exposure below TTC is deemed to be of no appreciable risk to human health (Kroes et *al*., 2005). The TTC principle is used by the European Medicines Evaluation Agency to assess genotoxic impurities in pharmaceutical preparations and has been endorsed by both the World Health Organization International Program on Chemical Safety for the risk assessment of chemicals and the European Union Scientific Toxicology, Ecotoxicology and the Environment (Kroes et *al*., 2005).

When appropriate, individual flavoring ingredient is subjected to a thermal fate analysis, specifically when the ingredient has a boiling point >290°C (and is used at >0.1%, in the case of e-vapor products) or if a specific concern is highlighted. Such analysis is done to assess the potential generation of toxic properties during heating and/or aerosolization.

Materials used in the devices determined to be in direct contact with the consumable or aerosol (airflow) are also subject to hazard identification and dose-response assessment according to their intended use. In the case of e-vapor products, materials in contact with the e-liquid are subjected to extractable and leachable analyses.

In addition, further analysis on materials may be included (e.g., chemistry analysis of the heated/burnt materials coupled by literature and in silico analysis). For example, Volatile Organic Compounds (VOC) analysis (e.g., at 100°C) and pyrolysis analysis (e.g., at 500°C or 1000°C) are conducted to evaluate the thermal degradation profile following heating or burning of the materials.

Finally, in addition to the assessment at the level of ingredients and non-tobacco/substrate materials described here, hazard identification and dose-response assessment are also conducted on the final products when appropriate; for example, aerosol chemistry, in vitro studies (such as laboratory cytotoxicity, genotoxicity, and mutagenicity tests), and/or in vivo studies. Such studies are used not only to assess the hazard related to the emitted aerosols but also the potential interactions among ingredients in the mixture and other components, as well as the potential hazard related to the cumulative effects of specific ingredient(s).

1.2 Exposure Assessment

Exposure assessment evaluates and/or estimates the mouth-level exposure—i.e., exposure to the mouth exclusively and not to the other organs, such as hands—to the ingredients and non-tobacco/substrate materials originated from smoke-free products according to their intended use and design specifications. Various assumptions are used to estimate the level of exposure to the consumers based on the available knowledge. When applicable, such assumptions are complemented by the available real-world evidence (e.g., behavioral studies, real-world data). In addition, when possible, the ingredient’s transfer efficiency (from substrate to emission) is taken into consideration to complement the exposure estimation.

1.3 Risk Characterization

This step is conducted to ensure that the ingredients and non-tobacco/substrate materials, as well as the chemicals detected in the emissions/aerosols are acceptable (i.e., deemed unlikely to exert safety concerns) for their intended use. The assessment mainly involves setting a certain use level of ingredient, internally referred to as the Maximum Recommended Level (MRL), which is analogous to the Derived No Effect Level (DNEL) under REACH (Kreider & Spencer Williams, 2010) or Reference Dose (RfD) (Barnes et al., 1988). When appropriate, modifying factors accounting for differences in species, route of exposure, duration of exposure, and pharmacokinetics are incorporated into the risk assessment. Such an approach is aligned with the risk assessment approaches used by others (EPA, 1993, Schenk et al., 2014). Moreover, an assumption of 100% absorption is taken for inhalation products, which is the worst-case scenario for the absorption, distribution, metabolism, and excretion (ADME) that may occur in the body following exposure to the ingredient of interest. Such assumption is taken to minimize any risk to consumers exposed to inhaled products.

2 Filtration Materials used to manufacture tobacco products

Presently, most cigarette filters are made from cellulose acetate, with charcoal occasionally used in specialized filter products intended to remove vapor phase smoke constituents. The primary purpose of the cigarette filter is to act as a trap for the particulate or gas vapor material generated by the burned tobacco. In addition to the filtration function, the filter may also serve as a mouthpiece to prevent direct contact between the tobacco rod and the mouth.

3 References

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