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Given the above, you should not use this document as a tool, guide, or manual for the preparation of applications or submissions to FDA. Instead, all interested persons should refer to the Federal Food, Drug, and Cosmetic Act, and its implementing regulations, as well as guidance documents prepared by FDA, for information on FDA's tobacco authorities and regulatory framework. FDA also regularly posts additional resources for applicants, such as webinars and application tips, on CTP's website and social media.

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

Date: June 3, 2024

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Subject: Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications

Introduction

Premarket Tobacco Product Applications (PMTAs) are submitted for any new tobacco product seeking an FDA marketing order under section 910(b) of the Federal Food, Drug, and Cosmetic (FD&C) Act. A PMTA is required to provide sufficient scientific evidence to demonstrate that marketing of the new product is appropriate for the protection of the public health (APPH). Scientific data must address, among other things, any health risks and benefits of the new product to the US population as a whole. The final PMTA rule[1] and ENDS PMTA Guidance (FDA, 2023) both emphasize that an evaluation of genotoxicity and carcinogenicity is important in PMTAs. Under 21 CFR § 1114.7(k)(1)(i)(B), a PMTA must contain:

"The toxicological profile of the new tobacco product related to the route of administration, including the genotoxicity, carcinogenicity, reproductive toxicity, immunotoxicity, acute toxicity, and repeat dose (chronic) toxicity of the new tobacco product relative to other tobacco products. The toxicological profile also includes information on the toxicity of the ingredients, additives, and HPHCs, relative to the route of administration and the range of potential levels of exposure resulting from the use of, or exposure to, the new tobacco product, including studies which discuss the toxicological effects of any leachables and extractables that can appear from the container closure system and the ingredient mixture, such as additive or synergistic effects."

Additionally, under 21 CFR § 1114.27(b)(1)(ii)(B), FDA will only file for further review applications that contain information on "*the health risks of the new tobacco product compared to the health risks generally presented by products in the same product category as well as products in at least one different category that are used by the consumers an applicant expects will use its new tobacco product*."

The purpose of this memorandum is to describe and outline a standard and consistent toxicological approach for Division of Nonclinical Science (DNCS) reviewers to follow in evaluating cancer risk in ENDS PMTAs and provide a comparison framework to assess the estimated cancer risk of products under review in relation to combusted cigarettes and ENDS that have already received marketing granted orders (MGO).[2] This cancer risk evaluation framework is one aspect of toxicology PMTA review that, along with findings from other review disciplines, can be integrated by the technical project lead (TPL) in overall decision-making regarding whether the marketing of new products under review is APPH. The reviewer evaluation framework established herein is applicable only to ENDS. This is because the instructions to reviewers are with regard to assumptions specific to ENDS.

Background

Tobacco products are associated with many known human health risks including an increased incidence of cancer. As DNA damage and genetic instability play crucial roles in cancer development, reviewers should also consider the genotoxicity of tobacco products. Unrepaired or incorrectly repaired DNA lesions can result in cancer-initiating or driving mutations and genomic instability from different sources can enhance multistep tumor progression (Tubbs et al., 2017; Wang et al., 2008). Reviewers should recognize that while the cancer incidence associated with some tobacco products (e.g., cigarettes, smokeless tobacco) is well known due to

[1]Premarket Tobacco Product Applications and Recordkeeping Requirements October 2021. 86 Fed. Reg. at 55300 - https://www.federalregister.gov/documents/2021/10/05/2021-21011/premarket-tobacco-product-applications-and-recordkeeping-requirements

[2] The comparison of new products to the median of the authorized products is predicated upon the reviewer understanding that the applicant does not have access to all of the constituents in the comparison products that are included in their application. Thus, the median value represents the best comparison for the ELCR of comparison ENDS. In cases where the applicant has obtained an accurate ELCR value for specific comparison products, they may be used preferentially within the toxicology review; such an approach will be communicated to the TPL as part of the key findings of the toxicology discipline review.

decades of human health data, epidemiological data regarding the cancer risk from electronic nicotine delivery systems (ENDS) use will not be available for many years.

ENDS have been proposed to be a lower risk alternative to combusted cigarettes, primarily due to substantially lower levels of established harmful and potential harmful constituents (HPHCs) in these products. The 2018 National Academies of Science, Engineering, and Medicine (NASEM) report concluded there is "conclusive evidence that completely substituting e-cigarettes for combustible tobacco cigarettes reduces users' exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes" (NASEM, 2018). Indeed, a continuum of risk exists for all tobacco products (King et al., 2023), however deciding where an individual ENDS falls within this continuum in relationship to other tobacco products requires the accurate review and assessment of all hazards within the product. Comparisons of risks between combusted cigarettes and ENDS based on HPHCs[3] are useful in an initial review assessment, however, such comparisons generally do not take the toxicological concerns of other constituents into consideration.

HPHCs are chemicals or chemical compounds in tobacco products or tobacco smoke that cause or could cause harm to smokers or nonsmokers. As required by the FD&C Act [Section 904(e) of the FD&C Act (21 U.S.C. 387d(e)], FDA established a list of 93 HPHCs found in tobacco products and tobacco smoke, which focuses on chemicals that are linked to the five most serious health effects of tobacco: cancer, cardiovascular disease, respiratory effects, reproductive problems, and addiction. The established FDA HPHC list was defined based on the known risks of traditional tobacco products (e.g., cigarettes and smokeless tobacco products). In terms of cancer risk, the criteria for selecting the established carcinogenic hazard HPHCs depended on a chemical being both studied and identified as a carcinogenic hazard by agencies or programs such as the International Agency for Research on Cancer (IARC), the U.S. Environmental Protection Agency (EPA), the National Toxicology Program, and National Institute for Occupational Safety and Health. Specifically, known, probable, and possible carcinogens found within cigarette smoke and extracts from smokeless tobacco products were included. Reviewers should note, however, that it is possible that a constituent has not been classified according to carcinogenic hazard by EPA, IARC, or others because it has not been adequately studied or systematically reviewed by the relevant agencies (e.g., diacetyl, acetyl propionyl, bisphenol A) (Australian Government Department of Health, 2022; EFSA Panel on Food Contact Materials Enzymes Processing Aids, 2023). Therefore, FDA recognized that the established HPHC list may not include all constituents that are "harmful or potentially harmful" (FDA, 2012). Ultimately, reviewers should consider that the toxicological risk of tobacco products can come from many different constituent sources, depending on the tobacco product type.

In cigarettes, for example, the primary toxicological risk is derived from pyrolysis products due to combustion at high temperature. In contrast, ENDS generally operate at lower temperatures than cigarettes. Reviewers need to consider that while thermal degradation products, such as acetaldehyde or formaldehyde, still appear in ENDS, e-liquid constituents such as ingredients and leachables may also be transferred directly into the aerosol (Behar et al., 2018a; Farsalinos et al., 2015; Wagner et al., 2018). As such, the inherent toxicity of e-liquid constituents should be taken into consideration within the toxicology review as it is a toxicology concern. E-liquids typically contain nicotine (including ionized, freebase, or nicotine salts),[4] propylene glycol, vegetable glycerin, and flavoring ingredients. A survey of 16,839 e-liquids found that, on average, 10 (range of 3 - 18 across flavor categories) flavoring ingredients are added to a single e-liquid and that, on average, 63% of the total number of ingredients in e-liquids are flavoring ingredients (Krusemann et al., 2021). A study by Behar et al (Behar et al.,

[3] The established list of HPHCs is found at https://www.fda.gov/tobacco-products/products-ingredients-components/harmful-and-potentially-harmful-constituents-hphcs

[4] Nicotine salts are typically created in situ through the addition of ionized nicotine (primarily the base form of nicotine when the pH is less than 8.1) and a weak acid, like lactic acid or benzoic acid, into the e-liquid.

2018b), showed twelve of the most common e-liquid flavor ingredients, including cinnamaldehyde, menthol, benzyl alcohol, vanillin, eugenol, p-anisaldehyde, ethyl cinnamate, maltol, ethyl maltol, triacetin, benzaldehyde, and menthone, are often present in concentrations above 1 mg/mL in e-liquids. Furthermore, toxicology reviewers should consider that the organic and inorganic chemicals from container closure system components (e.g., coil, wicking material, glass or plastic vial container or cartridge) may leach into the e-liquid formulation. Published literature and ENDS PMTAs have shown that toxic chemicals such as cadmium, chromium, lead, nickel, chloroform, dichlorobenzene, bisphenol A, phthalates, parabens, and organophosphate flame retardants can leach into e-liquids of ENDS (Gray et al., 2022; Halstead et al., 2020; Wei et al., 2020). Overall, e-liquid ingredients and leachables, along with constituents on the established HPHC list, have the potential to be significant contributors to the cancer risk of ENDS and are to be considered within the toxicology review and evaluation of the PMTA data and information.

CTP toxicology reviewers have previously considered that the cancer risk of certain constituents associated with a new ENDS could be qualitatively discounted (or offset) if the product's HPHCs were lower than those generated by a representative cigarette. Through reviewing PMTAs, CTP found that HPHCs produced as a result of aerosolization were not the sole contributors of potential cancer risk in ENDS. CTP toxicology reviewers also realized, in the course of reviewing PMTAs, that comparisons are more complex than those in substantial equivalence (SE) reports where simple one-to-one weighing of the risks of individual constituents can be made. As opposed to SE, the comparison in PMTA is not only a one-to-one comparison of products within the same product category, but is also made across multiple product categories, making qualitative offsetting difficult. Differences in the potency of different genotoxicants or carcinogens also means that such offsetting realistically requires quantitative estimates and quantitative comparisons. For all of these reasons, offsetting the increased cancer risk presented by the potential genotoxicants and carcinogens in ENDS against reductions in other genotoxicants and carcinogens in cigarette smoke in a qualitative manner is not an adequate approach for toxicology review.

Based on current knowledge and the considerations discussed above, toxicology reviewers should quantitatively evaluate the cancer risk of ENDS by calculating an excess lifetime cancer risk (ELCR), which provides an extrapolated estimate for how many additional cases of cancer would be expected in a population exposed to a given toxicant concentration and intake level for an entire lifetime based on the toxicant's carcinogenic potency. It provides the reviewer a holistic approach to consistently estimate cancer risk in new products while also allowing a robust comparative analysis of a new tobacco product relative to other tobacco products. Reviewers can calculate the ELCR for each constituent that is associated with cancer health effects, and then sum them to determine a cumulative ELCR (US EPA, 1989, 2009). Reviewers should keep in mind that as the cumulative ELCR assumes additivity, it does not account for potential antagonism or synergism in the chemical mixture, (US EPA, 2018) but nonetheless provides an impartial and consistent starting point for the evaluation of all potential new products. Overall, calculating an ELCR for ENDS allows for a standardized assessment of cancer risk as part of the overall health risk assessment for new products under review.

Risk Assessment to Estimate Cancer Risk

In performing risk assessments reviewers use a multistep process which includes hazard identification, hazard assessment, exposure assessment, and risk characterization. Briefly, within the hazard identification step the review should determine whether a specific constituent is, or is not, causally linked to a particular adverse health outcome. Hazard assessment asks whether the identified hazards are of concern and what is the weight of evidence (WOE) for the hazard endpoint. After hazards are identified, reviewers should perform an exposure assessment to estimate the intensity, frequency, and duration of human exposures to a particular constituent. Finally, during risk characterization the reviewer should estimate the incidence of health effects under various

conditions of human exposure. Ultimately, the evaluation of the ELCR from the submitted information is one of the inputs from the toxicology review that goes into a risk-benefit framework that CTP will use to determine if marketing of a new product is APPH. Reviewers should keep in mind that ENDS also have non-cancer hazards, such as respiratory toxicity and cardiovascular risk, which will be the subject of a future memorandum.

In the absence of specific evidence, assumptions (e.g., "default options") may be utilized by the reviewer in ELCR analyses (US EPA, 2005). As ELCR is one of numerous inputs into a risk-benefit framework that OS will use to determine APPH, it is important as a reviewer that you are explicit about the assumptions and strength of evidence that contribute to ELCR calculations. Thus, for toxicology reviewers, default assumptions for the assessment of ELCR are described below.

Hazard Identification/Assessment

For toxicology reviewers, the primary step in any risk assessment is hazard identification. Many constituents in tobacco products are well studied and have data available to inform whether they are carcinogenic (e.g., EPA or IARC classifications). Data in the literature indicate that 80-90% of IARC carcinogens have a genotoxic mode of action (Bartsch et al., 1989). Therefore, genotoxicity is a critical mechanism of action for carcinogenesis. As described in ICH S2(R1) (ICH, 2012), compounds that have positive findings in genotoxicity tests have the potential to be human carcinogens and/or mutagens. While genotoxicity is not considered a definitive measure of carcinogenicity, it is important as a reviewer to include such hazards in cancer risk assessments to be protective of public health. For ENDS cancer risk analysis, toxicology reviewers should proceed with hazard identification according to a separate DNCS memorandum (see Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications, June 3, 2024). Briefly, DNCS intends for reviewers to use a similar tiered approach recommended and utilized by both EPA (US EPA, 2005) and IARC (IARC, 2019), for hazard identification with respect to carcinogenicity. ENDS constituents may be placed into one of five tiers (Tier 1-5) based on the expected carcinogenic risk of the constituent in ENDS. Importantly, Tier 1-3 classifications should be limited to constituents previously evaluated by either IARC or EPA and were found by those agencies to demonstrate carcinogenic potential. In considering the different constituent Tiers reviewers should keep in mind that Tier 1 constituents are "carcinogenic to humans" and have a weight of evidence (WOE) that demonstrates strong evidence of human carcinogenicity, whereas constituents included in Tier 2 are "likely to be carcinogenic to humans" and have a WOE that demonstrates carcinogenic potential to humans but does not reach the WOE for the descriptor "human carcinogen." Constituents included in Tier 3 have "suggestive evidence of carcinogenic potential" and have a WOE that demonstrates a concern for potential carcinogenic effects in humans, however the available data are judged to be not sufficient for a Tier 1 or Tier 2 classification. Tier 4 constituents are "potential carcinogenic hazards" and have a WOE from a broad range of data sources including human, animal, in vitro, or in silico data that indicates a concern for carcinogenicity or genotoxicity. Tier 5 constituents are "unlikely to contribute to the carcinogenic risk of ENDS" and have data, whether publicly available or submitted as part of an application, that are robust for deciding within your review that there is no basis for a human cancer hazard concern in the context of ENDS premarket application review. A discussion of what genotoxic or carcinogenic hazards should be moved forward for ELCR analysis is provided in a separate DNCS memorandum (see Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications, June 3, 2024). This memorandum is for toxicology reviewers and describes the process by which toxicology reviewers determine whether a particular potential carcinogen/genotoxin should be included in an ELCR calculation as described herein.

Exposure Assessment

In ENDS, the transfer of constituents to the aerosol depends heavily on the characteristics of each individual product and constituent (Behar et al., 2018a; Farsalinos et al., 2015; Wagner et al., 2018). Thus, where available, constituent aerosol yield data from an individual product should be considered within your review. Published

data indicate that the transfer efficacy of ingredients and leachables to aerosol is between 45-100%, depending on the specific constituent and characteristics of the specific product (Behar et al., 2018a; Farsalinos et al., 2015; Wagner et al., 2018). Thus, in the absence of product- and compound-specific data provided by the applicant showing the transfer efficacy of specific constituents of concern to the aerosol, reviewers should assume a conservative estimate of 100% aerosol transfer (Flora et al., 2016).

Reviewers should determine exposures of each genotoxic and carcinogenic constituent of concern in µg/day using applicant-provided heavy use scenarios (i.e., based on number of cartridges/puffs per day). Currently, there is no standard for how applicants estimate heavy use of their products. As recommended in the EPA's 1992 guidelines on chemical exposure and the NASEM report, the 90th and 99th percentiles of daily use are appropriate as default cutoff values that can be considered "health-protective" for chemical exposure evaluations (NASEM, 2009; US EPA, 1992). Heavy use for cigarettes has been routinely described as roughly a pack (20 cigarettes) per day, which approximates a 90th percentile of daily use (Health Canada, 2008; Pierce et al., 2011; US Department of Health and Human Services, 2014, 2020). If applicants do not provide heavy usage data for ENDS under review, reviewers may calculate constituent exposure using an assumption of similar nicotine exposure levels based on heavy use of combusted cigarettes (i.e., 40 mg/day nicotine, based on 20 cigarettes/day) (Jaccard et al., 2019). Additionally, in ENDS PMTAs, several non-intense and intense puffing regimens are utilized by applicants to report aerosol constituent yields. Currently, standardized puffing regimens for ENDS have not yet emerged, stemming, at least in part, from the highly variable modes of usage for the products (Wadkin et al., 2022). Aerosol yield data obtained under intense puffing regimens are generally appropriate for the ELCR calculations of a specific ENDS as they often reflect a worst-case scenario for constituent exposure; however, in certain circumstances, calculations performed using non-intense puffing regimens may also be appropriate for ELCR calculations if these data reflect the highest constituent exposure.

Use of a Threshold of Toxicological Concern

Once a daily exposure has been determined for an individual constituent (e.g., HPHC, ingredient, leachable) of potential cancer risk (Tier 1-4), it is necessary for reviewers to determine the extent that it contributes to the overall cancer risk of a product. In some cases, reference toxicity values are available (e.g., inhalation unit risks, discussed below). However, it is necessary to establish at what level a compound contributes meaningful cancer risk in tobacco products. In the absence of empirical data, reviewers should adopt a threshold of toxicological concern (TTC) value. TTC values are human exposure thresholds below which one would expect no appreciable risk to human health, despite the absence of chemical-specific toxicity data. Historically, the TTC approach was mainly born out of FDA's threshold of regulation (TOR) approach for food contact materials and oral exposures (Ball et al., 2007; Kroes et al., 2000). Broadly speaking, toxicologists needed—and continue to need—ways of evaluating chemicals that generally lack available and robust toxicity data. For reviewer reference, studies and reviews have been published on the application of a TTC approach based on various classes of chemical structures, including genotoxic alerts (Ball et al., 2007; Kroes et al., 2000; Talhout et al., 2011). In addition, tobacco product applications have included TTC approaches for constituents that are otherwise data-limited (i.e., experimental toxicity data is either lacking or inadequate to inform a toxicological evaluation). TTCs can be developed and implemented for various endpoints, but an initial step in evaluation of a chemical's toxicity is determining the potential for genotoxicity. As stated earlier, most known human carcinogens are genotoxic, and carcinogenic effects likely occur at lower intakes than those associated with noncarcinogenic toxicity (based on oral-derived data) (Ball et al., 2007; Kroes et al., 2000).

The following provides toxicology reviewers further background information regarding the development of cancer-specific TTCs. There is general consensus in the literature and among established regulatory documents that reviewers may refer to regarding the level at which genotoxicity is of likely concern for chemicals that are otherwise data-limited (Ball et al., 2007; European-Medicines-Agency, 2018; Kroes et al., 2004). This level is suggested to be 0.15 µg/day, a level that Kroes et al. determined was consistent with an excess lifetime cancer risk of 1 in 1,000,000. In addition, industry and regulatory documents alike have adjusted their decision-making criteria around a potential TTC for genotoxicity of 0.15 µg/day (ACC, 2020; More et al., 2019). The genotoxicity

TTC (0.15 µg/day) is derived from a combination of TD_{50} (median toxic dose) data, which is described as the daily dose of over 700 chemicals that individually induced a particular tumor type in half the animals (that otherwise would not develop the tumor over a lifetime) following oral dosage (Kroes et al., 2000; Kroes et al., 2004). From the TD_{50} data, simple linear extrapolation was used to obtain an exposure level consistent with an excess risk of 1 in 1,000,000, given plots of excess cancer risk versus exposure are often assumed to be linear (see Memorandum: Evaluating Carcinogenic HPHC Increases and Assumption of Linearity for Low Dose Extrapolation, October 27, 2017). Given potential route-to-route variability, Ball et al. assessed the availability of the 0.15 µg/day TTC to inform the evaluation of orally inhaled impurities in pharmaceuticals (Ball et al., 2007). Per the study authors, there were too few inhalation studies in an associated Carcinogen Potency Database (CPDB) to establish a threshold based solely on inhalation data. However, while the data were limited (27 chemicals out of >340 had inhalation data), per the authors' analysis the potencies of carcinogens tested by inhalation were consistent with those tested by all routes. Thus, the inhalation data in the CPDB, while limited, suggest that a TTC of 0.15 µg/day is acceptable for genotoxicity endpoints for the inhalation route given that the potency of the limited numbers of carcinogens tested by inhalation is similar to that of those tested by all routes (Ball et al., 2007).

While industry and regulatory documents have adjusted their decision-making around a potential TTC for genotoxic hazards of 0.15 µg/day related to a 1 in 1,000,000 risk level (ACC, 2020; More et al., 2019), other FDA centers have implemented this approach when considering genotoxic impurities in drugs and have established a TTC of 1.5 µg/day corresponding to a risk management level of 1 in 100,000 for pharmaceuticals that are in later stages of development or already marketed (ICH, 2023). A risk management level of 1 in 100,000 for impurities in pharmaceuticals that are in later stages of development or already marketed is justified based upon the established health benefit of the drug (ICH, 2023). Although there are no safe tobacco products, reviewers should consider that tobacco products do exist on a continuum of risk, and ENDS may offer a potential opportunity to reduce smoking-attributable risks when combusted cigarette users switch completely to ENDS (King et al., 2023). In their 2018 report, NASEM concluded there is "conclusive evidence that completely substituting e-cigarettes for combustible tobacco cigarettes reduces users' exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes" (NASEM, 2018). However, it is important for reviewers to recognize that CTP evaluates ENDS products not as an overall product class but makes authorization decisions on a product specific basis. While the NASEM conclusion was based on biomarkers of exposure to toxicants from combusted cigarettes and ENDS evaluated as separate tobacco product classes, this conclusion from the NASEM report did not consider all the potential hazards that could be present in an individual ENDS product (e.g., ingredients and leachables in addition to HPHCs). One of the purposes of this memorandum is to support reviewers in stratifying the cancer risk of ENDS, including lower concern ENDS that have lower amounts of toxic constituents, so that the Office of Science can determine whether these individual products under review provide a net health benefit to the U.S. population. Based on this information and to create consistency in review, toxicology reviewers should use the cancer-hazard TTC of 1.5 µg/day for individual ENDS constituents based on a risk management level of 1 in 100,000. It is important for reviewers to understand that this TTC is not a control threshold that would not allow the presence of any constituent above the TTC, but rather a threshold for constituents above which hazards and associated risks should be considered as part of the toxicological evaluation of the product.

Thus, in the absence of chemical-specific reference toxicity values for µg/day associated with 1 in 100,000 cancer risk, any genotoxic or carcinogenic constituent present at levels above 1.5 µg/day should be carried forward for the ELCR analysis as they contribute an appreciable cancer risk (i.e., > 1 in 100,000) at those levels. Notably, as suggested by Kroes et al., (Kroes et al., 2004) the TTC approach generally is not designed to and should not be used by reviewers to replace conventional risk characterization approaches for established and well-studied chemicals. As discussed in Kroes et al., and Serafimova et al., (Serafimova et al., 2021) a TTC approach would not normally be applied to inorganic chemicals, heavy metals, proteins, steroids, nanomaterials,

radioactive chemicals, organosilicon chemicals, chemicals with potential for bioaccumulation (e.g., polyhalogenated-dibenzodioxins, -dibenzofurans, and -biphenyls), and high-potency carcinogens (e.g., aflatoxin-like, N-nitroso, azoxy- compounds).

Cancer Potency Values

As mentioned earlier, where possible, a reviewer's ELCR assessment should rely on reference toxicity values, such as inhalation unit risk (IUR) values, to calculate ELCRs from individual constituents. IURs are an estimate of the increased cancer risk from inhalation exposure to a concentration of 1 µg/m^3 over a 70-year lifetime. IURs are derived from relatively high exposure concentrations for which the range of outcomes are distinct and quantifiable. Below the range of observation, the relationship (slope) between exposure and risk is assumed to be linear in the absence of data to the contrary (see Memorandum: Evaluating Carcinogenic HPHC Increases and Assumption of Linearity for Low-Dose Extrapolation, November 17, 2017). Because of the assumed linearity, reviewers can multiply the IUR by an estimate of lifetime exposure (in µg/m^3) to estimate the lifetime cancer risk for any level of a chemical submitted by an applicant. To correspond with the cancer-hazard TTC discussed above (i.e., 1 in 100,000) and ENDS specific exposure considerations, IURs may be adjusted to a level in µg/day that is associated with a 1 in 100,000 ELCR over a 52-year exposure duration. The IUR in µg/m^3 is converted to µg/day assuming an inhalation volume of 20 m^3 per day (US EPA, 2009) and adjusted for 52 years of exposure, which assumes initiation of tobacco product usage at 18 years of age and death at 70 years of age. To clarify further for reviewers, although general life expectancy has increased over time to 75-80 years of age (Arias, 2022; Kochanek, 2020), the average heavy lifetime tobacco users have an overall lower life expectancy of 67-74 years (Streppel et al., 2007). Additionally, U.S. EPA assumes 70 years lifetime exposure for the development of cancer reference toxicity values (e.g., IURs) and for the calculation of cancer risk from breathing air toxics (US EPA, 2024a, 2024b, 2024c). While the current legal age of tobacco purchase is 21 years of age under section 906(d)(5) of the Federal Food, Drug, and Cosmetic Act, the CDC MMWR still uses ≥18 years of age onset to estimate the commercial tobacco use among U.S. population (Cornelius, 2023). According to the 2023 National Youth Tobacco Survey (NYTS), 22.2% of U.S. middle and high school students reported ever using any tobacco product, corresponding to 6.21 million persons, and 10.0% of students reported current use of any tobacco product, corresponding to 2.80 million persons (Birdsey, 2023). ENDS were the most used tobacco product in 2023 (7.7%; 2.13 million) among those middle and high school students (Birdsey, 2023). Together this information supports the use of an age younger than 21 years, such as that used by CDC MMWR. Thus, 52 years approximates a lifetime of tobacco product use. These adjusted IURs are then used by the toxicology reviewer to calculate the ELCR resulting from constituents that are identified as carcinogenic hazards.

Reviewers should identify and select IUR values for constituents for use according to a three-tier hierarchy described in a separate DNCS memorandum (see Memorandum: Use of Reference Values in the Toxicological Evaluation of Inhaled Tobacco Products, March 14, 2019). Tier 1 includes reference toxicity values from EPA's Integrated Risk Information System (IRIS) that should be used preferentially over other reference toxicity values. Tier 2 includes EPA's Provisional Peer Reviewed Toxicity Values (PPRTVs) that should be used if toxicity values are not available in IRIS. Tier 3 includes additional EPA and non-EPA toxicity values, where priority is given to sources that are the most current, peer-reviewed, transparent, and publicly available. Oral Slope Factor (OSF) is the estimate of the increased cancer risk from oral exposure to a dose of 1 mg/kg-day for a lifetime. OSF may be used for inhalation route with appropriate scientific justification, adjustments, and uncertainty factors for route-to-route extrapolation (US EPA, 1994, 2009). After reviewers select appropriate IURs where available, reviewers should adjust IURs by calculating a level in µg/day that is associated with a 1 in 100,000 ELCR according to Equation 1:[5]

[5] In Equation 1, 24 hours is not reflective of anticipated vaping times per day. It is reflective of standard or default adjustment factors used in inhalation toxicity reference value development and derivation. Because DNCS is adjusting carcinogenicity reference information for the purposes of screening ingredient quantities per day, 20 m^3 (over 24 hours) is intended to be used as a default adjustment factor by toxicology reviewers. Of note, in Equation 1, time adjustments are intermediary, as they are captured in both the numerator and

$$\text{Adjusted IUR } \left(\frac{\mu g}{day}\right) = \frac{AT \times \text{Target Risk}}{IUR \times ET \times EF \times ED} \times \text{Daily Inhalation Rate} \qquad \text{(Equation 1)}$$

where

AT = Averaging Time (EL x 365 days/year x 24 hours/day)
EL = Lifetime over which exposure occurs (70 years)
Target Risk = 1×10^{-5} (1 in 100,000 ELCR)
IUR = Inhalation unit risk in $(\mu g/m^3)^{-1}$
ET = Exposure time (24 hours/day)
EF = Exposure frequency (365 days/year)
ED = Exposure duration (52 years)
Daily Inhalation Rate = 20 m^3/day

Equation 1 above considers initiation of tobacco product usage at 18 years of age and death at 70 years of age, which results in a tobacco product specific exposure duration of 52 years. Table 1 includes selected example IUR levels adjusted using Equation 1 that are associated with 1 in 100,000 ELCR.

Table 1. Examples of adjusted inhalation unit risk values to levels in µg/day associated with 1 in 100,000 ELCR[6]

Constituent	IUR $(\mu g/m^3)^{-1}$	Source	Adjusted IUR (µg/day) associated with 1 in 100,000 ELCR
Acetaldehyde	2.20E-06	EPA (1988)	122.38
Acrylonitrile	6.80E-05	EPA (1987)	3.96
4-Aminobiphenyl	6.00E-03	Cal EPA (1992)	0.04
2-Aminonaphthalene	5.14E-04	Cal EPA (1992)*	0.52
Arsenic	4.30E-03	EPA (1995)	0.063
Benzene	7.80E-06	EPA (2000)	34.52
Benzo[a]pyrene	6.00E-04	EPA (2017)	0.45
1,3-Butadiene	3.00E-05	EPA (2002)	8.97
Cadmium	1.80E-03	EPA (1987)	0.15
Chloroform	2.30E-05	EPA (2001)	11.71
Chromium	1.20E-02	EPA (1998)^	0.022
Crotonaldehyde	3.27E-05	TCEQ (2015)	8.23
Formaldehyde	1.30E-05	EPA (1989)	20.71
Isoprene	2.20E-08	TCEQ (2015)	12237.76
Lead	1.20E-05	Cal EPA (2009)	22.44
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	1.40E-02	Cal EPA (2001)	0.019
N-Nitrosonornicotine (NNN)	4.00E-04	Cal EPA (1992)	0.67

denominator for which the units cancel out. In addition, because of the association of 20 m^3 being over 24 hours, if adjusting the exposure time down to a shorter period (smoking and ENDS use are less than 24 hours/day), the associated volume/day (e.g., daily inhalation rate) must also be adjusted to the same time period (e.g., 5 m^3 over 6 hours). The proportional adjustments of a smaller ET in the denominator as well as a smaller inhalation rate multiplier, results in the same adjusted IUR.

[6] *IUR is calculated from a cancer potency value (e.g. mg/kg-day)-1 assuming 70 kg body weight and daily inhalation rate of 20 m3/day; ^IUR is based on chromium (IV); #IUR is based on nickel refinery dust

Nickel	2.40E-04	EPA (1987)[#]	1.12
Propylene oxide	3.70E-06	EPA (1990)	72.77

Toxicology reviewers should recognize that many constituents found in tobacco products, including established HPHCs, will not have reference toxicity values available for cancer risk assessment. This especially applies to data-limited constituents often added to or identified in ENDS. In the absence of chemical-specific reference toxicity values, a TTC has been used as a default potency factor value for risk analysis (Meek et al., 2011; OECD, 2018; Patlewicz et al., 2018). CTP has a regulatory need to assess the overall cancer risk of tobacco products, even in the absence of reference toxicity values for all constituents with identified cancer hazards. At this time, using a TTC to estimate the cancer risk posed by cancer hazards for which there is no IUR available is the best available option for estimating cancer risk from such constituents. Therefore, due to the assumption of linearity, where chemical-specific potency information is not available (e.g., no IUR available), reviewers should use the above adopted TTC of 1.5 µg/day, corresponding with a cancer risk of 1 in 100,000 (Ball et al., 2007; FDA, 2018), for Tier 1-4 constituents as a default cancer slope factor to calculate ELCR from individual constituents. Reviewers should consider additional information for specific constituents which may increase the accuracy of the cancer slope factor, and therefore the ELCR analysis, if applicants provide such information in their PMTA.

Excess Lifetime Cancer Risk Calculations

Risk assessment using risk or response addition may be used to assess the cumulative risk of toxicity of a mixture made up of constituents having similar adverse health outcomes (e.g., cancer). Risk or response addition is a process in which the individual mixture constituents are scaled by their relative potencies and then added together to estimate an overall cumulative ELCR (Beronius et al., 2020; USEPA, 2000). In line with the assumptions described above, reviewers can calculate the cumulative ELCR per product resulting from genotoxic and carcinogenic constituents as follows. Importantly, reviewers should calculate a cumulative ELCR for each new ENDS in a PMTA review, including a separate cumulative ELCR for each e-liquid formulation under review, as applicable.

A reviewer should first calculate the ELCR per 100,000 for each individual constituent according to Equation 2:

$$\text{ELCR} = \frac{\text{Daily exposure}}{\text{Potency value}} \qquad \text{(Equation 2)}$$

where

ELCR	=	Constituent specific ELCR
Daily exposure	=	Daily exposure (µg/day) under heavy use scenarios
Potency value	=	Adjusted IUR in µg/day or default value of 1.5 µg/day, corresponding to a 1 in 100,000 risk level

Next, the cumulative ELCR ($ELCR_C$) per product may be calculated by summing the constituent specific ELCRs from all constituents with cancer hazards as indicated in a separate DNCS memorandum (see Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications, June 3, 2024) according to Equation 3:

$$\text{ELCR}_c = \sum \text{ELCR} \qquad \text{(Equation 3)}$$

Importantly, the additive nature of Equation 3 does not account for potential antagonism or synergism in the chemical mixture, as such relationships are presently unknown. If scientific evidence is or becomes available to indicate potential antagonism or synergy within the mixture, reviewers should consider the applicability of such data to the $ELCR_c$ analysis and how such information can be adequately conveyed to the TPL.

When calculating the cumulative ELCR, reviewers should include all constituents that have an individual risk level above 1 in 100,000 (i.e., an ELCR over 1) and that are determined to go into the ELCR per the companion memorandum "Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications, June 3, 2024" in the ELCR assessment. Notably, applicants may provide justification or additional evidence that may allay your review concerns for genotoxicity or carcinogenicity and support reclassification of a constituent to a different Tier. Detailed decision trees regarding additional evidence reviewers can consider that may outweigh evidence that identified carcinogenic or genotoxic hazards are provided in a separate DNCS memorandum (see Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications, June 3, 2024). If such information is provided by the applicant, toxicology reviewers should evaluate this information to determine whether constituents can be classified into a different Tier and calculate the ELCR using constituents that are determined to go into the ELCR per the companion memorandum "Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications, June 3, 2024."

It is important for a reviewer to know that if the applicant does not provide adequate constituent information for calculation of the ELCR, such as not providing leachable information or providing incomplete ingredient information, toxicology reviewers should not perform an ELCR analysis until the missing constituent information is received from the applicant.

ENDS Risk Characterization

For reviewer awareness, under § 1114.27(b)(1)(ii)(B), FDA may refuse to file those applications that do not contain information on "the health risks of the new tobacco product compared to the health risks generally presented by products in the same product category as well as products in at least one different category that are used by the consumers an applicant expects will use its new tobacco product." Information regarding the potential health risks in comparison to other tobacco products is required for review under 1114.7(k)(1)(i). Thus, when determining if the ENDS under review is of toxicological concern, it is important for a reviewer to compare it to other tobacco products on the market, including products within the same category and subcategory (e.g., the ENDS marketplace), as well as products from other categories (e.g., combusted cigarettes) as appropriate. Therefore, toxicology reviewers should compare the cumulative ELCR of products under review to the ENDS MGO marketplace[7] and combusted cigarettes.

To make these comparisons, the $ELCR_c$ of the new product under review should be evaluated along with the $ELCR_c$ range of the ENDS MGO marketplace and the 1R6F reference cigarette. Toxicology reviewers should report the new product $ELCR_c$ as a percent above or below the median of the ENDS MGO marketplace. The current ENDS MGO marketplace $ELCR_c$ median is 118 excess cancer cases per 100,000 users.[8] The new Kentucky reference cigarette, or 1R6F, was designed in a collaboration between the FDA and the University of Kentucky to replace the depleting stock of 3R4F reference cigarettes. The 1R6F reference cigarette has been rigorously

[7] While an applicant may provide comparison products from the ENDS category for comparison to the new product, typically, these comparisons do not contain a complete accounting for all the constituents in the comparison products, resulting in the inability to effectively calculate an ELCR for the comparison products. Thus, the median value of the authorized ENDS represents the best comparison for the ELCR of calculation of the new product. In cases where the applicant has obtained an accurate ELCR value for specific comparison products, they may be used preferentially within the toxicology review, with appropriate signal to the TPL.

[8] The marketplace median will change over time and reflects only those products authorized at this point in time.

tested for HPHC yields (Jaccard et al., 2019) and is considered an appropriate representative of combusted cigarettes because associated HPHC yields are reflective of the average marketed U.S. cigarette's HPHC yields. Based on the measured HPHC yields from Jaccard et al. (Jaccard et al., 2019), as well as assuming 20 cigarettes per day exposure and that all cancer hazards were included, the calculated $ELCR_c$ of a 1R6F is approximately 10,000 per 100,000. This translates to an $ELCR_c$ probability of 1 in 10. This estimate is within an order of magnitude of epidemiological findings that demonstrate a 1 in 5 cancer incidence for smokers (Fowles et al., 2003). The lower projected risk as compared to the observed epidemiological findings may also indicate that the proposed $ELCR_c$ process is not overly conservative.

There is a need for reviewers to clearly convey the findings from the cancer risk assessment so they can be incorporated into the regulatory decision-making process, which may employ risk-management . Risk management is the process by which policy actions are selected to regulate hazards identified in risk assessment. Specifically, risk management is a process "in which risk and non risk information is integrated to inform choices among options" (NRC, 2009). Importantly, risk assessment is independent from the risk management process, however, it is an essential component of the scientific underpinning for making a risk management decision (NRC, 1983, 2009). To date, no formalized risk management framework has been created for the comparative evaluation of the toxicological risks associated with tobacco products. Furthermore, there is no current framework for the comparison of ENDS to combusted cigarettes. To maintain consistency and limit subjectivity between toxicology reviewers, while also allowing for robust risk-based decision making, we identified the need for a range of qualitative risk management descriptors (Table 2) that reviewers can use to communicate the cancer risk of ENDS under review relative to 1R6F cigarettes. To develop these risk management descriptors, we calculated the $ELCR_c$ for each product from the ENDS MGO marketplace and compared these values to the 1R6F combusted cigarette. We identified that the relative risk of the lower range of the ENDS MGO marketplace in comparison to cigarettes was ~1% of 1R6F. Conversely, the higher range of the ENDS MGO marketplace reached >50% of the 1R6F $ELCR_c$.[9] The current ENDS MGO marketplace dataset is limited, however it provides the most comprehensive constituent data available at this time and is therefore a useful foundation for establishing risk-based decision making for ENDS in relation to combusted cigarettes. When considering the continuum of calculated cancer risk that exists within the ENDS MGO marketplace, percent reductions from the calculated 1R6F $ELCR_c$ were selected to create cutoffs for separate risk management descriptors to describe "lower concern," "moderate concern," "increased concern," "elevated concern," and "serious concern" levels for ENDS cancer risk relative to cigarettes. It is critical to note that these risk management cutoffs are based on toxicant exposure levels only and that the relationship between reduced toxicant exposure and cancer risk may not be proportional. For example, a 50% reduction in cigarette consumption was associated with only a 28% reduction in lung cancer risk (Chang et al., 2021).

Table 2. Qualitative Risk Management Descriptors

Percentage of 1R6F $ELCR_c$	Descriptor	Calculated Cancer Risk
< 1.0%	Lower Concern	≤ 1:1000
1-10%	Moderate Concern	1:999-1:100
10-25%	Increased Concern	1:99-1:44
25-50%	Elevated Concern	1:43-1:20
> 50%	Serious Concern	>1:20

[9] Importantly, previous ENDS MGO marketplace authorizations were based on a multidisciplinary analysis that considered the overall population health benefit and risks identified by other disciplines.

In general, ENDS that are in the "lower concern" categories compared to 1R6F cigarettes may be a lower risk alternative to cigarettes. Therefore, such products are unlikely to raise toxicological concerns regarding cancer risk in the context of PMTA review, given the potential opportunity for ENDS to reduce smoking-attributable health risks when combusted cigarette users switch completely (King et al., 2023). If complete constituent information is available in a PMTA and the ELCR assessment places an ENDS into the "lower concern" category compared to 1R6F cigarettes and below the median of the ENDS MGO marketplace, the new product is unlikely to raise toxicological concerns regarding cancer risk even if the applicant does not initially submit all potentially relevant information. In this scenario, information from the applicant such as data to reclassify Tier 4 constituents into Tier 5 (see Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications, June 3, 2024) is unlikely to change the conclusions of the cancer risk evaluation.

For ENDS in the moderate, increased, elevated, or serious concern category compared to 1R6F cigarettes, increasing exposure levels may result in a higher cancer risk compared to lower concern ENDS, although there is uncertainty as to whether the relationship between increasing exposure and risk is proportional. Importantly, reviewers need to be aware and consider in their assessment that as the calculated risks due to the use of an ENDS approaches the calculated risks due to the use of combusted cigarettes (1R6F), there is increasingly more uncertainty as to whether a reduction in exposures truly results in decreased cancer risk relative to combusted cigarette exposure (1R6F). Furthermore, if an ELCR assessment places a new product above the median of the ENDS MGO marketplace, the new product may have a greater cancer risk than products from the same category. Such products may raise toxicological concerns for cancer risk, in the context of PMTA review, considering nonusers who initiate ENDS use with these products, users of other ENDS that switch to these products, and that lower concern ENDS may provide a greater public health benefit for combusted cigarette users who are able to switch completely. For moderate, increased, elevated, and serious concern level products, communication to the applicant regarding the cancer risk of the ENDS under review is recommended in the toxicology review. Additional information provided by the applicant, such as additional data regarding potential carcinogenic or genotoxic hazards, may lower the estimated cancer risk of the ENDS under review and alter the overall conclusions of the cancer risk evaluation in the toxicology review. PMTAs with incomplete constituent information (e.g., missing leachable study, incomplete ingredient information) lack sufficient information for a complete cancer risk evaluation, which raises toxicological concerns. Such concerns should be communicated to the applicant accordingly. Ultimately, toxicological concerns (or the lack thereof) regarding ENDS cancer risk must be weighed along with and against additional toxicological concerns (e.g., respiratory toxicity, cardiovascular toxicity), as well as the concerns of other disciplines by the TPL.

Risk Characterization in Toxicology ENDS PMTA Reviews

The toxicology reviewer should provide a full account of the hazards present in each product including the identity, toxicity, hazard tier (if applicable), exposure, and resulting risk evaluation within the narrative section of their PMTA review. For ELCR analysis specifically, reviewers may include tables to indicate the genotoxic or carcinogenic hazards present, the data available supporting said hazards, the tier that the constituent falls into, the exposure estimate on a µg/day basis, and the resulting ELCR for the individual constituent (Example Table 3 and 4).

Table 3. Sample ELCR calculation

Product	Constituent	CAS Number	Tier	Measurement (e-liquid or aerosol)	Daily Use (µg/day)	IUR/TTC (µg/day)	ELCR
PM0000XXXX	Chemical A	XXXX	X	X	X	X	X
	Chemical B	XXXX	X	X	X	X	X
	Chemical C	XXXX	X	X	X	X	X

Table 4. Example Constituents of concern from ELCR analysis

Application type	Constituent	CAS Number	Tier	Toxicity	Reference
PM0000XXXX	Chemical A	XXXX	X	X	X
PM0000XXXX	Chemical B	XXXX	X	X	X
PM0000XXXX	Chemical C	XXXX	X	X	X

Additionally, the narrative of the toxicology review should indicate any case where an assumption was made. For example, if the applicant did not measure a constituent in aerosol, a default assumption of 100% transfer to the aerosol should be used and appropriately indicated. Another example assumption is the use of the default slope factor of 1.5 µg/day for a 1 in 100,000 risk level for constituents that lack specific inhalation unit risk values.

If additional information is provided beyond what was available in the original application (e.g., in a subsequent amendment submitted by an applicant), toxicology reviewers should evaluate such information to determine if changes to the ELCR assessment are necessary. For example, as discussed above, applicants may provide additional information that allays reviewer concerns regarding a constituent's genotoxicity or carcinogenicity and supports reclassification of a constituent into Tier 5. In this instance, such a constituent would no longer be included in the ELCR analysis. Alternatively, applicants may provide additional data to address and replace default assumptions used in the original reviewer ELCR evaluation, such as proposing a constituent specific cancer slope factor that could be used in lieu of the default slope factor of 1.5 µg/day. Overall, toxicology reviewers should make adjustments to their ELCR assessments if scientifically justified based upon additional data.

To aid in the synthesis of the toxicological findings, the $ELCR_c$ and risk characterization summary should be conveyed in the key findings of the toxicology discipline review. For that summary, the toxicology reviewer should indicate the constituents that contribute to the $ELCR_c$, which Tier those constituents fall into, and specify any assumptions used in the analysis. Toxicology reviewers should build upon the following example language to convey the risk within the key findings section of their review to the TPL:

> *The $ELCR_c$ of the new product is X which is Y percent above/below the median of the ENDS MGO ENDS marketplace. The new product $ELCR_c$ equates to Z percent of the risk of the 1R6F cigarette, which is a [Insert Risk Management level here] concern. The contributor(s) of this risk, as calculated, is a tier 1/2/3/4 constituent (Z per 100,000). [Insert description of available data for the primary constituents that contribute to the $ELCR_c$ and their predictive value as described elsewhere in relevant DNCS memoranda (see Memorandum: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications, June 3, 2024)]. [If applicable] This $ELCR_c$*

calculation relied on the following assumptions: [List default assumptions (e.g., constituent X was measured in the e-liquid and 100% transfer was therefore assumed)].

Assumptions and Considerations

There are assumptions in the described ELCR analysis. However, there are current approaches that can be taken to mitigate these assumptions, which are listed below along with the assumptions.

First, there may be inconsistencies in how applicants report information within their PMTAs. For example, some applicants may provide targeted aerosol measurements of ingredients or leachables for their products whereas other applicants may not, and this may create the need for some exposure assumptions. In the absence of product-specific data provided by the applicant showing the transfer efficacy of specific constituents to the aerosol, a conservative estimate of 100% aerosol transfer is assumed. Therefore, without the aerosol data, reviewers may find that the ELCR calculations for these products may ultimately be overestimates due to the lack of data available on the aerosol content of constituents of concern. However, given that the transfer efficiency of ingredients and leachables to aerosols has been measured between 45-100% (Behar et al., 2018a; Farsalinos et al., 2015; Wagner et al., 2018), the overestimates are unlikely to be more than 2-fold. An applicant can overcome this assumption by providing requested aerosol data to indicate the transfer efficacy of constituents of concern for their individual product.

Additionally, the identification or evaluation of leachables depends on the methodology the applicant utilizes to obtain these data. Presently, there is variability in how applicants measure and address extractables and leachables; this is considered a limitation for the comparative analyses of ELCRs calculated from identified leachables. Applicants may also use different justifications and estimates to support heavy use of their products as there is no standard for how applicants report this information. However, this assumption can be mitigated by evaluating constituent exposure using "health protective" cutoff values that represent the 90th and 99th percentiles of daily use. In addition, future application review processes can include standardized or "boilerplate" language alerting applicants to best practices for reporting constituents of concern.

Second, use of the default value of 1.5 µg/day as a potency value for chemicals that lack reference toxicity data may ultimately be an over or underestimate of the potency of those chemicals. However, this assumption is mitigated by the fact that the same default potency value for constituents that lack reference toxicity values are applied for the ELCR analysis of a specific product under regulatory review and the ENDS marketplace. Moreover, as mentioned above, CTP has a regulatory need to evaluate the overall cancer risk of tobacco products under review and this assumption is necessary to meet this need for products that have cancer hazards but lack reference toxicity values.

Third, this analysis assumes a linear dose extrapolation although some chemicals may not have a linear dose-response. Notably, within the preamble of the final PMTA rule,[10] FDA in Response 66 indicates an assumption of linearity should be made for low-dose extrapolation of carcinogenic constituents. Consistent with EPA Guidelines for Carcinogen Risk Assessment (US EPA, 2005), a linear extrapolation is appropriate when the evidence supports the mode of action of gene mutation due to direct DNA reactivity or another mode of action that is thought to be linear in the low dose region and when available evidence is not sufficient to support a nonlinear extrapolation procedure. Nonlinear methods are only used when sufficient evidence supports a nonlinear mode of action.

[10]Premarket Tobacco Product Applications and Recordkeeping Requirements October 2021. 86 Fed. Reg. at 55300 - https://www.federalregister.gov/documents/2021/10/05/2021-21011/premarket-tobacco-product-applications-and-recordkeeping-requirements

Fourth, as part of the review we are assuming additivity of individual carcinogenic hazards in the ELCR calculations. While this approach is standard practice (NRC, 1994; US EPA, 2005, 2009), synergism, potentiation, and antagonism are potential mechanisms that could affect the overall carcinogenicity of both conventional cigarette smoke and ENDS aerosol. Notably, there are important differences between the composition of cigarette smoke and ENDS aerosol. Both have overlapping constituents, such as aldehydes, but also constituents that may be unique to either. Additionally, reviewers should consider overlapping constituents between cigarette smoke and ENDS aerosol as these could be present in different ratios in each mixture. Therefore, the potential for synergy, potentiation, and antagonism to deviate from the additive ELCR estimates may not be the same for cigarette smoke and ENDS aerosol and the exposure/carcinogenic risk relationship may differ between ENDS and combusted cigarettes. Nonetheless, reviewers should consider within their review all submitted or referenced information that indicates whether two or more constituents in the aerosol of a new product have a combined risk that is more or less than additive. Indeed, mixture effects have been cited as one reason why the uncertainty factors that are commonly used in the development of reference values, such as IURs and the TTC used in this memorandum, may be less conservative than anticipated (Martin et al., 2013).

Finally, the risk management descriptors in this document are established based upon reduced toxicant exposures relative to 1R6F, under the assumption that lower toxicant exposure results in an actual lower cancer risk. However, there is uncertainty regarding the relationship between toxicant exposure and actual cancer risk. Differences in composition between ENDS aerosol and cigarette smoke, and the differential potential for non-additive response relationships such as synergy, add to this uncertainty. Moreover, relevant to the risk management descriptors and framework outlined herein to evaluate ENDS under review in relation to 1R6F cigarettes, there is an assumption that combusted cigarettes are the most commonly consumed tobacco product. These risk management descriptors are associated with very high levels of carcinogen exposure and only make sense in the context of a comparison to combusted cigarettes. Eventually these risk management descriptors may become irrelevant as nicotine users transition to tobacco products that are less risky than combusted cigarettes.

Summary

This memorandum describes how ELCR is used by toxicology reviewers to estimate the additional lifetime risk of cancer posed by use of a new ENDS and how to compare that to products within the same category (i.e., the MGO ENDS marketplace) and to other categories (i.e., 1R6F cigarettes). This ELCR analysis uses methods consistent with the general risk assessment framework used by EPA for Air Toxics Assessment (US EPA, 2018). Reviewers are to calculate the ELCR for each constituent of concern by dividing the exposure concentration (µg/day) by the potency value (preferably an adjusted IUR in µg/day or the default TTC value of 1.5 µg/day, corresponding to a 1 in 100,000 risk level). If multiple carcinogenic or genotoxic hazards are present in a new ENDS, reviewers should calculate their ELCRs separately and sum them for a cumulative product ELCR. To convey these findings to the TPL, toxicology reviewers should specify the $ELCR_c$ value, a risk management qualitative descriptor, the constituents that contribute to the $ELCR_c$, associated tiers of those constituents, and the constituent's contribution to the cumulative ELCR. Further, the toxicology reviewer should convey any assumptions that were made during the calculation of the $ELCR_c$ value to the TPL as part of the toxicology review. If an applicant does not initially submit all potentially relevant information and submits additional information by amendment, such information should be evaluated and adjustments to ELCR calculations should be made, if scientifically supported. DNCS will update this memorandum as needed to incorporate ongoing scientific developments in the assessment and evaluation of ENDS cancer risk and to ensure alignment with CTP and FDA mission requirements and priorities.

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