The attached document represents CTP's then-current thinking on certain aspects of tobacco regulatory science. The information contained herein is subject to change based on advances in policy, the regulatory framework, and regulatory science, and, is not binding on FDA or the public. Moreover, this document is not a comprehensive manual for the purposes of preparing or reviewing tobacco product applications. FDA's review of tobacco product applications is based on the specific facts presented in each application, and is documented in a comprehensive body of reviews particular to each application.

Given the above, all interested persons should refer to the Federal Food, Drug, and Cosmetic Act, and its implementing regulations, as well as guidance documents and webinars prepared by FDA, for information on FDA's tobacco authorities and regulatory framework. This document does not bind FDA in its review of any tobacco product application and thus, you should not use this document as a tool, guide, or manual for the preparation of applications or submissions to FDA.

Date: October 27, 2017

From: Jonathan Fallica, PhD
                 Division of Nonclinical Science, Office of Science

> Digitally signed by Jonathan Fallica -S
> Date: 2017.11.17 10:43:02 -05'00'

> Digitally signed by Susan Chemerynski -S
> Date: 2017.11.17 10:50:38 -05'00'

Through: Susan Chemerynski, ScD, MPH
                 Team Lead, Toxicology Branch 4, Division of Nonclinical Science, Office of Science

                 Hans Rosenfeldt, PhD
                 Deputy Director, Division of Nonclinical Science, Office of Science

> Digitally signed by Hans M. Rosenfeldt -S
> Date: 2017.11.17 11:10:35 -05'00'

                 Kimberly Benson, PhD
                 Director, Division of Nonclinical Science, Office of Science

> Digitally signed by Kimberly A. Benson -S
> Date: 2017.11.17 11:39:59 -05'00'

To: File

Subject: SE Review: Evaluating carcinogenic HPHC increases and assumption of linearity for low-dose extrapolation

---

Purpose

The objective of this memorandum is to summarize the Division's current thinking regarding the evaluation of carcinogenic harmful and potentially harmful constituent (HPHC) increases in SE reviews, specifically their assessment using a linear low-dose extrapolation model. The cancer risks for most carcinogens, including HPHCs in tobacco products or tobacco smoke which have been identified by FDA as carcinogenic, are generally assumed to have a linear dose-response relationship below the lowest observable dose that causes cancer, and to be without a level below which adverse effects are unlikely to occur. The linear model assumption implies that there is an excess cancer risk[1] associated with exposure to the constituent at any level, and that cancer risk increases proportionally with exposure. This memorandum provides a summary of supporting scientific evidence and rationale for the use of a linear model to evaluate the potential excess cancer risks from exposure to carcinogenic HPHCs.

Background

The Federal Food, Drug, and Cosmetic Act (FD&C Act) provides a pathway for tobacco product manufacturers to introduce new tobacco products into interstate commerce by establishing that they are substantially equivalent (SE) to appropriate predicate products under section 905(j) of the FD&C Act. Section 910(a)(3)(A)(i-ii) of the FD&C Act provides that a substantially equivalent tobacco product "(i) has the same characteristics as the predicate tobacco product; or (ii) has different characteristics and

---

[1] Cancer risk is the likelihood, or chance, of getting cancer. It is generally expressed as "excess cancer risk" because individuals have a "background risk" of about one in four chances of getting cancer."(ATSDR, https://www.atsdr.cdc.gov/hac/PHA/CasmaliaResources/Appendix_A-B.pdf)

the information submitted demonstrates that the product does not raise different questions of public health."

In previously reviewed SE Reports, applicants have sometimes compared carcinogenic HPHC levels to established reference values for cancer as well as non-cancer effects, to support the assertion that HPHC increases in a specific new product do not raise different questions of public health in comparison to a predicate product. Comparisons solely to non-cancer reference values are not appropriate to assess carcinogenic risk of HPHCs. For noncancer endpoints, it is traditionally assumed that cellular defense mechanisms lead to a dose 'threshold' (i.e., low-dose nonlinearity) below which adverse effects are not likely to occur [1]. Accepted approaches for evaluating excess cancer risk typically assume a linear extrapolation from the lower end of observable cancer outcome range to zero. This assumption is applied in the absence of data to demonstrate otherwise. However, it is important to note instances where there is evidence to the contrary such as, the cancer risk assessment of certain drugs, which are immunosuppressive, or exhibit exaggerated pharmacology [2]. Consequently, if the level of a carcinogenic HPHC in a substantial equivalence comparison of tobacco products is greater in the new product as compared to the corresponding predicate product, the increase indicates a potential increase in the cancer risk (i.e., increase in the probability of cancer) from use and exposure to the new product as compared with the corresponding predicate product. CTP currently does not have regulatory standards based on a specific lifetime risk of cancer. In addition, a pre-specified "acceptable" ("permissible") or "negligible" increase in cancer risk has not been established for carcinogens in tobacco products or tobacco smoke.

Since the toxicological evaluation of SE Reports relies on a comparison of the product characteristics between the new and corresponding predicate products, the rationale for evaluating carcinogenic HPHCs using the principle of linear low-dose extrapolation is particularly important for public health, and therefore, is reviewed here. This memorandum will inform how carcinogenic HPHC increases in a new product relative to a specific predicate product should be evaluated to determine whether these HPHC increases cause the new product to raise different questions of public health.

Use of the linear model for carcinogen dose-response assessment and evaluation of cancer risk

In the dose-response assessment for carcinogens, experimental data from animal studies or epidemiological data (preferred, when available and of sufficient quality) provide the observed data to derive a point of departure (POD), or the estimated dose near the lower end of the observed range of cancer responses [3]. Since experimental studies are often performed at higher doses to achieve a measurable response within a given timeframe, extrapolation to the low-dose region, relevant to the average human level of exposure, is common practice. In approximating cancer risk at doses below an established observable effect, current accepted mathematical approaches conservatively assume a linear relationship between the dose of a carcinogen and risk at low doses, in a multistage cancer model characterized by initiation, promotion, and progression [3-7]. Consistent with this approach, the US EPA recommends using a POD supported by data as a default; lower bound POD estimation is commonly used because it is scientifically-based and accounts for the uncertainty in the true value of the POD [3]. In general, data below the POD lack statistical sensitivity to disprove the null hypothesis (i.e., the slope of the low-dose extrapolation is linear) [7-11]. Therefore, linear low-dose extrapolation of observable nonclinical or human data is supported across extrapolation parameters and even in instances where the observable dose-response data above the POD may be curvilinear [4, 8]; curvilinearity above the POD does not automatically rule out assumptions regarding low-dose linearity [3, 4, 8]. Any increase in

the dose of a carcinogen, below established PODs, is therefore assumed to increase the potential cancer risk in a linear fashion, in the absence of evidence to suggest otherwise [3, 12].

The use of a linear model for evaluating the cancer potency of most carcinogenic compounds has been a well-accepted and long-standing risk assessment practice [3]. This model assumes that there is a proportional relationship between cancer risk and the dose of a compound, specifically at low doses, and that any level of exposure to a carcinogen is associated with increased cancer risks. The concept of low-dose linear extrapolation is based on the linear non-threshold dose response model from the ionizing radiation literature [13]. While the application of this model to carcinogens is continuously evaluated and discussed in the literature, it is the current thinking, in the absence of data to suggest otherwise, that cancer potencies for most existing carcinogenic compounds should be calculated using the linear extrapolation model, which extends a straight line from a point at the lower end of the observed range of effects (cancer in this case) to zero. This assumption is made because it is thought that genotoxic carcinogens have effects that are irreversible, and can accumulate over a lifetime. For the regulatory purpose of protecting public health, DNA damage in a single cell can be assumed to ultimately be the point of origin for cancer; some HPHCs (e.g., ethylene oxide) have been shown in *in vitro* assays to have a linear relationship for induction of DNA alkylation [14], but current scientific methodology for other genotoxic substances is limited in resolving if such damage actually leads to cancer [15-17]. Nonetheless, there is supporting evidence derived from a standardized genetic toxicity assay, even when DNA damage in the tissues assessed in these assays does not directly correlate with the specific tissues where the tumor response is encountered [18]. Though clinical and nonclinical studies are limited to confidence about detection limits of observable outcomes, there is scientific evidence that even the smallest doses of a carcinogenic substance contributes to the totality of a response, and therefore, any increase in dose may increase the risk of a response [19]. EPA provides a framework and criteria for evaluating the mode-of-action for carcinogens and notes that carcinogens that are generally considered to be linear in this range include agents that are DNA-reactive and have direct mutagenic activity, or agents for which human exposures or body burdens are high and near doses associated with key precursor events in the carcinogenic process [1, 3]. Nonlinear approaches can also be used in cases where there is sufficient mode-of-action characterization of a carcinogenic HPHC, but ultimately, the analysis of available data for all combined cancer types for a given carcinogen informs the dose-response assessment process and characterization of risk [3, 9]. In the absence of scientific evidence to the contrary, the linear model approach is considered the default approach because it conservatively characterizes cancer risk, and is generally considered to be protective of public health [3].

Thus, when evaluating cancer risks from exposure to HPHCs, the use of a numerical estimate of risk derived with the application of the linear extrapolation method, such as EPA's inhalation unit risks, is appropriate. The slope of the line that extends from the POD down to zero, termed the slope factor or unit risk, quantitatively defines the relationship between dose and response and can be used to assess risk probabilities for different doses [3, 5, 7]. Thus, the slope factor of the linear approximation is useful as a tool to characterize risk per unit dose. Given that low-dose linear extrapolation to estimate the cancer slope factor is currently a commonly accepted approach for assessing carcinogenic risk, it is recommended that SE toxicology reviewers take this approach in their evaluation of HPHC increases, unless more compelling data are presented.

Evaluating Carcinogenic HPHC Increases in SE Reviews

As a substantial equivalence evaluation relies on a comparison between the new and corresponding predicate products, HPHC increases in a new product in comparison to the predicate product are evaluated to determine whether the HPHC increases cause the new product to raise different questions of public health. Any quantitative risk assessment voluntarily submitted by an applicant in SE Reports to evaluate HPHC increases should therefore be between the specific new and predicate products, including valid surrogate predicate products, that are the subject of the submitted SE Reports. This approach allows for the direct toxicological comparison of the new and predicate products. However, there are reoccurring examples in SE Reports where the provided information is insufficient for this approach to be applied. For carcinogenic HPHCs, SE Reports have provided comparisons of estimated carcinogenic HPHC exposure levels from the use of the new product to reference values developed based on non-cancer effects. Such comparisons may be appropriate to inform an evaluation of non-cancer hazards associated with the increase in HPHCs, however, it is not scientifically substantiated or meaningful for SE Review evaluations with respect to evaluating potential increases in cancer risks.

The magnitude of the increased cancer risk associated with increases in an HPHC can be quantified by using cancer risk-based reference values (e.g., inhalation unit risk), if available, which can be informative for evaluating whether HPHC increases in a new product in comparison to a corresponding predicate product cause the new product to raise different questions of public health. If not available, the evaluation for individual and specific carcinogenic HPHC increases will rely on the dose or exposure comparisons between the new and predicate products; given the linear low-dose extrapolation assumption for carcinogens, any increase in a specific carcinogenic HPHC would be proportional to an increase in cancer risk. If multiple carcinogenic HPHCs are increased or decreased in the specific new product in comparison to a specific predicate product, it may be appropriate to consider the totality of HPHC changes and calculate a total Incremental Lifetime Cancer Risk, which would allow for the evaluation of risk differences related to multiple changes in HPHC levels associated with the specific new and predicate products.

Summary

In the absence of compelling data supporting a dose threshold below which the carcinogenicity of a compound definitively does not occur, it is a standard assumption and toxicological practice to assume a linear relationship between the dose of a carcinogen and an increased risk of cancer. Thus, any analytically measurable increase in a carcinogen is assumed to result in a linear increase in cancer risk dependent on the slope estimated from the POD. Comparisons of carcinogenic HPHC levels to non-cancer reference values or their conversion to an "acceptable" or "permissible" dose or risk is not scientifically substantiated or meaningful. As such, any analytically confirmed increase in a carcinogenic HPHC in a new product could be assumed for regulatory toxicology review purposes of an SE Report to increase the cancer risk of the potential user of that product, indicating that carcinogenic HPHC increases in a specific new product in comparison to a specific predicate product may cause the new product to raise different questions of public health from a toxicology perspective. However, there may also be instances, depending on additional scientific information, that may alter this conclusion. In the evaluation of specific new and predicate products, where multiple changes in HPHCs are associated with a new product, it can be appropriate to consider the combined overall effects, especially since many HPHCs share a common mode of toxicological action (e.g., DNA reactive mutagenicity). The Division will continue to update this memorandum as scientific evidence becomes available.

References

[1] EPA CIRAAUUS, Toxicology BES, Studies DEL, Council NR. Science and Decisions: Advancing Risk Assessment: National Academies Press; 2009.

[2] Jacobs A, Jacobson-Kram D. Human Carcinogenic Risk Evaluation, Part III: Assessing Cancer Hazard and Risk in Human Drug Development. Toxicol Sci 2004;81:260-2.

[3] EPA US. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F. Washington , DC . Available on the Internet at https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment. 2005.

[4] Guess H, Crump K, Peto R. Uncertainty Estimates for Low-Dose-Rate Extrapolations of Animal Carcinogenicity Data. Cancer Res 1977;37:3475-83.

[5] Gaylor DW, Kodell RL, Chen JJ, Springer JA, Lorentzen RJ, Scheuplein RJ. Point Estimates of Cancer Risk at Low-Doses. Risk Analysis 1994;14:843-50.

[6] Lovell DP, Thomas C. Quantitative risk assessment and the limitations of the linearized multistage model. Hum Exp Toxicol 1996;15:87-104.

[7] Subramaniam RP, White P, Cogliano VJ. Comparison of cancer slope factors using different statistical approaches. Risk Anal 2006;26:825-30.

[8] Fygenson M. Risk assessment of low dose exposure to carcinogens. Trends Math 2001:65-75.

[9] Neumann HG. Risk assessment of chemical carcinogens and thresholds. Crit Rev Toxicol 2009;39:449-61.

[10] Ruden C. Evaluation of carcinogen risk assessments and the role of evidence-based toxicology in chemicals control. Toxicol Lett 2008;180:S17-S.

[11] Board SA. An SAB report: guidelines for cancer risk assessment. Washington DC: U.S. Environmental Protection Agency. EPA-SAB-EHC-97-010. Available from: http://www.epa.gov/sab/pdf/ehc9710.pdf. 1997.

[12] Crump K, Hoel D, Langley C, Peto R. Fundamental carcinogenic processes and their implications for low dose risk assessment. Cancer Research 1976;36:2973-9.

[13] The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. Ann ICRP 2007;37:1-332.

[14] WHO. Concise international chemical assessment document; CICAD 54: Ethylene Oxide. United Nations Environment Programme, International Labour Organization, and the World Health Organization. Geneva. 2003.

[15] López-Lázaro M. Stem cell division theory of cancer. Cell Cycle 2015;14:2547-8.

[16] Chaffer CL, Weinberg RA. How does multistep tumorigenesis really proceed? Cancer Discov 2015;5:22-4.

[17] Georgakilas AG, Redon CE, Ferguson NF, Kryston TB, Parekh P, Dickey JS, et al. Systemic DNA damage accumulation under in vivo tumor growth can be inhibited by the antioxidant Tempol. Cancer Lett 2014;353:248-57.

[18] Neumann HG. The role of DNA damage in chemical carcinogenesis of aromatic amines. J Cancer Res Clin Oncol 1986;112:100-6.

[19] Gaylor DW. The use of Haber's Law in standard setting and risk assessment. Toxicology 2000;149:17-9.