

## Whistleblower Response to FDA Report

CTP<sup>1</sup> did not argue implementation of the memo as written, it argued implementation of the memo as intended. While this OS Report addressed the static position of the concerned toxicologists, CTP did not; instead, they changed their position in an ongoing process, went to the commissioner's office to get feedback, and responded to feedback given where the toxicologists who expressed concerns were not afforded this same opportunity. Thus, CTP dynamically and iteratively addressed the memo through an evolving process with OSC and the FDA Office of the Commissioner<sup>2</sup> and ultimately dismissed the issues raised by the concerned toxicologists and the expert panel without giving these disagreeing constituencies the ability to provide context, feedback, or rebuttal.<sup>3</sup>

The investigation gathered a significant amount of information, and the resulting report is so expansive that this response should not be considered exhaustive,<sup>4</sup> but examples are provided to highlight inconsistencies (e.g., the report distinguishes best available science and sound regulatory science but is unclear what the standard is for either of these criteria,<sup>5</sup> CTP inconsistently rejects or applies different frameworks without evidence,<sup>6</sup> CTP inconsistently states how many risk assessments CTP manages).<sup>7</sup>

Overall, it appears CTP has loosened the standard of risk assessment review in SE applications and the tiering standard recited by the CTP is not more protective. CTP does not appear to resolve uncertainty in favor of an NSE determination.<sup>8</sup> CTP implemented the use of an unclear memo that is inherently flawed, and now proposes edits that still leave a vague, hazy standard of review as acknowledged in the review of the original memo by both concerned toxicologists and the expert panel. CTP starts from a poorly drafted memo that lacks support and does not improve on the basic flaws noted via the edits proposed.

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<sup>1</sup> This report discusses reports from different levels of the FDA: Division of Nonclinical Science (DNCS) at the division level, Office of Science (OS) at the Office level, Center for Tobacco Products (CTP) at the Center level, and the FDA. While citing the source of an assertion, this report uses CTP as the attributable source for statements from these different levels within the FDA to simplify the discussion, with a few broader references to the FDA.

<sup>2</sup> OSC Report pages 21-28 [Note: This response uses "OSC Report" to refer to FDA's response to OSC referral in case number DI-20-0372].

<sup>3</sup> Dismissed them as an issue in the OSC Report then noted such issues would be addressed in the future.

<sup>4</sup> The concerned toxicologist memo and the expert panel report addressed several issues (CTP's synergy and mixture arguments are conclusory while the concerned toxicologist memo provides references to address these such as assumptions of independent action methods of mixtures risk assessment; exposure assessment allows extrapolation for different periods of time including estimates of deliberate consumption) some would take more time to address so only some key issues are noted below; in addition this response is not well served by recapitulating the concerned toxicologist's memo which includes many supportive scientific references and all were dismissed by CTP. Note that OSC Report Page 30 has the whistleblower assert a QRA would suggest a definitive determination, but QRA would provide a more scientifically supportable determination than the approach used in the HPHC memo.

<sup>5</sup> OSC Report page 23 distinguishes best available science from best regulatory science (citing OS appeal decision) but it is unclear how to distinguish the two.

<sup>6</sup> While CTP asserts approaches developed by EPA and ATSDR were not developed for risk evaluation of tobacco products (CTP Director's decision page 5), it disregards the fact that FDA and other government agencies, have applied quantitative risk assessment methods developed by EPA and NAS to a broad variety of products. See also the concerned toxicologists May 31, 2019 memo. Compare OSC Report CTP page 12-13 (citing OS Appeal Decision and HPHC memo) where CTP dismisses the risk assessment approaches used at other agencies, CTP, and recommended by the concerned toxicologist with OSC Report 21 where CTP asserts that a tiered approach is appropriate because it is used by "FDA and other organizations (e.g., EPA)" such as EPA (emphasis added). But see OSC Report page 38 ("[M]anagers were not comfortable adopting [QRA] used by [the EPA].")

<sup>7</sup> The OSC Report notes CTP asserts QRAs are both relatively rare (page 34) and many applicants submit them (page 10 note 17).

<sup>8</sup> OSC Report page 45 (asserting "CTP resolves uncertainty in favor of an NSE determination."). The concerned toxicologists made CTP aware in several reviews that the error could cause an SE product to be NSE and an NSE product to be SE. This was written in the appendices to several draft toxicology reviews performed by one of the concerned toxicology reviewers (which CTP prevented from being signed).

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In fact, CTP's own examples demonstrate this failure. Particularly, example 4 notes an analytically non-equivalent increase in formaldehyde and acrolein with a decrease in TSNA; the FDA asserts this would require an evaluation of submitted QRA,<sup>9</sup> but it is unclear if this falls into tier 1 ("application for a tobacco product that has more than one or two increases should usually result in an NSE determination . . .")<sup>10</sup> or falls into tier 2 ("where . . . one or two relative HPHC increases . . . can be reasonably by offset relative HPHC decreases . . .")<sup>11</sup>. Either way the tiering approach fails. Tier 1 does not apply because it is defined as *only* all HPHC increases or decreases, and example 4 includes both. If it is tier 2, it is unclear how only these three HPHCs can be used in any risk assessments as the carcinogenic effect of TSNA may be used to offset the carcinogenic effects of formaldehyde, but it is unclear how the non-cancer respiratory toxicant effects can be offset by TSNA's carcinogenic effect.<sup>12</sup> Technically, example 4 could also fall in the tier 3 as there are two HPHC increases, and thus the tiering indicates CTP decision would likely be NSE.<sup>13</sup> Effectively, in using the FDA rationale as proposed, the increase in respiratory toxicity cannot be offset by an increase in TSNAs (not a respiratory toxicant). In addition, this does not address how to account for differences in potency semi-quantitatively (as potency is evaluated using a quantitative approach); thus, it is unclear how decreases will offset increases.<sup>14</sup> Instead, CTP argues "Within these categories [carcinogenic or non-carcinogenic] CTP does not see a scientific basis to rank toxicants as more or less 'problematic'"<sup>15</sup> which is at odds with toxicology's foundational, scientific concept of potency (further, CTP asserts the science regarding toxicity magnitude "is not here"<sup>16</sup> which is misleading and scientifically unsound). If CTP makes such an assertion, then to provide a broad example there would be no difference between water and formaldehyde. While clearly there are better demarcations between toxic and non-toxic chemicals, a dismissal that no chemical is more or less problematic than a more toxic chemical is a concern, especially when the discussion has to do with human exposure to these chemicals.

CTP asserts "the risk of allowing a more dangerous product is low" because of the processes in place (e.g., reviewer's guides, quality control review, routine review, defined processes, and a training program).<sup>17</sup> None of these processes can assess the quality and validity of a quantitative or semi-quantitative risk assessment. Reviewer's guides and training are cited, but even the OS Report notes that the "addendum declines to provide specific examples and points

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<sup>9</sup> Application of proposed tiering criteria in OSC Report at 36-38 to example 4 on pages 2-3 of Addendum to CTP Response.

<sup>10</sup> OSC Report at 38. This may be considered "fatally-flawed" by FDA as "no [decrease] that could be possibly offsetting" as noted on OSC Report at 10 because there is no offset for the respiratory toxicant. This is partly because CTP disregards analytically non-equivalent HPHCs.

<sup>11</sup> *Id.*

<sup>12</sup> US FDA, HPHCs in Tobacco Product and Tobacco Smoke (April 2012) <https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-established-list> (categorizing formaldehyde and TNAs as carcinogens and formaldehyde and acrolein as respiratory toxicants). Notably this does not address the full scope of differences in the non-cancer effects of HPHCs on target organ endpoints (may include hepatotoxicity, immunotoxicity, and other effects)

<sup>13</sup> OSC Report at 36 noting a product has "more than one or two HPHC increases" and two is more than one placing it in tier 3. Moreover, as noted in OSC Report at 39, CTP has nearly predetermined that a tier 3 difference is unlikely to be SE (asserting "the rare compelling QRA that can resolve the uncertainty regarding the relative risks"). Moreover, the description of tiering on page 36 (more than one or two) does not match the description on page 39 (more than two).

<sup>14</sup> See also example 3 in the Addendum to CTP Response at 2 which lacks clarity of how an increase in formaldehyde is offset by a decrease in TSNAs and a decrease in acrolein (does CTP consider potency?).

<sup>15</sup> OSC Report page 27, citing CTP Addendum.

<sup>16</sup> OSC Report page 40.

<sup>17</sup> CTP Director's Decision pages 8-9.

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in general” to training and organizational structure.<sup>18</sup> Nowhere else in the OSC Report or the appendix does CTP provide specific direction on how to perform risk assessment (either as described in the memo or otherwise). Quality control review is described vaguely as OS staff review with an undefined scope, and possibly OCC review which is legal review. Technical Project Lead review is an overall review that relies on discipline-specific review, so this is very unlikely to catch scientific errors in toxicology or risk assessment.

In conflating all review as sufficient review, CTP conflates risk assessment with risk management. For example, a toxicology reviewer performs a technical risk assessment or risk evaluation, whereas the Technical Project Lead makes a risk management decision to determine whether the new tobacco product raises different questions of public health when compared to the predicate tobacco product. CTP errs by asserting the TPL risk management evaluation is a check on the primary toxicology reviewer’s toxicological risk assessment evaluation and toxicology review. The TPL often lacks the expertise to check the scientific validity of the toxicological risk assessment. Current OS-wide SE training does not provide risk assessment specific training on the memo process or broader risk assessment concepts. None of these non-toxicological review processes are adequate to determine the validity of toxicological risk assessment. The processes are set up to have multiple checks, but only the discipline-specific reviewer process has the capacity to adequately identify scientific risks so most of the checks do not adequately guard against the problems noted by concerned toxicologists and the expert panel. Trainings set up by CTP also have been insufficient in this regard (e.g., an email from around April 22, 2021 directs reviewers to view risk assessment slides from an external training from about 4 years ago at CTP; otherwise the whistleblower was unaware of such training specifically for risk assessment over the last few years).

Notably, this “process for reviewer agreement” has also been a venue for management suppression of the scientific opinion of reviewers. CTP’s process of resolving disputes of scientific opinion is unclear and has been a major contributing factor to (and in some cases the cause of) the departure of concerned toxicologists. At present, none of the originally cited concerned toxicologists remain at CTP.<sup>19</sup> CTP not only prevented these scientists from performing risk assessment review, but prevented them from presenting their opinions on risk assessment in division meetings when others were allowed to present on the same topic.

DNCS managers state that they intended the memo as a “global resolution to the critical scientific disagreement that cropped up . . . and would continue to arise.”<sup>20</sup> This is problematic for several reasons. First, this purported resolution is not appropriate to a scientific dispute, as it does not account for and address scientific objections; instead, it merely dictates a process that reviewers are expected to follow regardless of whether they find it to be scientifically sound or appropriate.<sup>21</sup> Second, the memo appears to be developed and implemented

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<sup>18</sup> OSC Report page 28, referencing the OS response to the report.

<sup>19</sup> OSC Report page 4 notes confusion and ambiguity in the process.

<sup>20</sup> OSC Report page 52.

<sup>21</sup> OSC Report page 61 (“well-considered and appropriate *management directive* that DNCS staff are expected to follow.”) (citing OS Appeal Decision at 4) (emphasis added).

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unilaterally by management without input or feedback from the concerned toxicologists. In fact, no changes were made despite the serious concerns raised by the concerned toxicologists until this OSC complaint was raised. This suggests a lack of concern with scientific input on management's part, and a general resistance to changing the memo in question.<sup>22</sup> Third, DNS management noted that application-specific discussions would continue to arise.<sup>23</sup> The memo, as presented, appears to be an attempt to quash scientific disagreement and promote efficient review at the cost of scientific rigor.

Even the purported objective of the memo changes throughout the report. In the OSC Report CTP told the FDA Office of the Commissioner the purpose of the memo is to "resolve uncertainty with respect to the risks" presented by a new tobacco product in the SE pathway.<sup>24</sup> The original purpose of the memo as it was written was to record the current approach to set key criteria comparing HPHCs in an SE application and possibly other application review pathways.<sup>25</sup> In other places the purpose or intent is cited as a "rapid assessment tool,"<sup>26</sup> as intended to "answer questions [of uncertainty] through a tiered process,"<sup>27</sup> and intended as a "global resolution to the critical scientific disagreement."<sup>28</sup> It is unclear why CTP would be unable or unwilling to clarify its position, despite multiple concerned toxicologists coming forward, for an extended period of time and would only resolve what has been suggested as a misperception after this OSC complaint was raised and an investigation well underway.

The HPHC Memo notes it "takes into account previous approaches to risk assessment," but other than generic reference to an EPA document and an ATSDR document, the memo does not provide what information was used to develop CTP's new thinking nor does it adequately describe how these previous approaches would be used to inform the risk assessment review process. It is insufficient to take something into account if it is then applied incorrectly or excluded without cause. CTP disregards both scientific evidence on risk assessment and foundational concepts of toxicology. It is true that each of the steps provided in this CTP HPHC memo have been performed in a very similar manner and with more scientific support by EPA, ATSDR, FDA, NIOSH, and other government agencies in the context of a QRA (considering which chemicals have been increased in a given exposure context and consider the health effects of those chemicals, even in mixtures). The comparison is not without problems, however. CTP says that their process is different from other agencies because the risks with tobacco use are unique, but asserts that it is consistent with review in other FDA Centers.<sup>29</sup> CTP has to rely on far less information than is usually received and reviewed at these other Centers, however, and that is a significant and impactful difference. For example, CDER, CBER, and CDRH receive non-clinical and clinical toxicology studies often submitted by applicants in support of their product application. CTP typically receives far less information from applicants, usually relying primarily

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<sup>22</sup> In fact, the Jones memo completely dismissed these concerns.

<sup>23</sup> OSC Report page 52.

<sup>24</sup> OSC Report page 39.

<sup>25</sup> HPHC memo page 2

<sup>26</sup> OSC Report page 13 and 24.

<sup>27</sup> OSC Report page 44.

<sup>28</sup> OSC Report page 52.

<sup>29</sup> OSC Report page 42.

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on HPHC data. Some of the richest information provided to CTP is data on HPHCs, and yet CTP chooses to disregard much of the available health-related information on these HPHCs.<sup>30</sup> Moreover, while CTP claims that its approach is analogous to that used in other FDA centers,<sup>31</sup> it disregarded the concerned toxicologists when they suggested risk assessment methods used in other FDA Centers.<sup>32</sup> Similarly, CTP dismisses EPA risk assessment approaches as inappropriate<sup>33</sup> but cites EPA as appropriate support for tiering without support for either decision.<sup>34</sup>

While explaining differences in what it considers best available science<sup>35</sup>, CTP asserts it gained a “better understanding of HPHC data in SE Reports”<sup>36</sup> but has not conveyed exactly what this new understanding might be. While CTP properly acknowledges the FDA and other regulatory organizations use tiered approaches, CTP does not provide references or scientific evidence for applying these approaches to the HPHC memo decision-making process. Instead, CTP seems to merely advocate its use because it works elsewhere within the FDA and at other agencies regardless of differences in scientific context, while at the same time dismissing other potentially more scientifically appropriate forms of review found at these same agencies because they supposedly would not work with the unique context of CTP.<sup>37</sup> CTP says the Expert Panel lacks the vast years of tobacco experience that resides with CTP’s experts.<sup>38</sup> If that becomes the standard, external review of CTP’s processes becomes all but impossible. CTP further impedes transparency by failing to disclose what specific expertise or science CTP has applied or how it does so. CTP points to reviewer guides, memos, review processes, and training generally,<sup>39</sup> but advances no scientific evidence to bolster these unsupported assertions.

CTP’s responses to this investigation appears to map ongoing efforts at avoiding scientific transparency, as CTP: (1) cites procedural limitations;<sup>40</sup> (2) makes general assertions of experience without provided scientific references or evidentiary support (data or references),<sup>41</sup>

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<sup>30</sup> See Expert Panel particularly recommendations 1 and 3.

<sup>31</sup> OSC Report page 42 (“CTP’s overall approach . . . aligns . . . with how other FDA Centers handle uncertainty.” *Contra* OS Report page 12 (“The fact that QRA has been successfully used for other scientific purposes and even in some prior SE application reviews does not mean it is . . . the most appropriate method for the use of SE [R]eports.” (citing OS Appeal decision pages 2-3).

<sup>32</sup> Concerned toxicologist’s May 31, 2019 memo page 3, notes 34-35 (“QRA . . . has been widely adopted [by] federal regulatory agencies, including the FDA.” (citing 2001 GAO Report and Gaylor et al, 1997) which was dismissed in the OS Appeal memo (see *supra*, note 31).

<sup>33</sup> OSC Report page 38 (asserting why EPA methods are not appropriate); OSC Report page 32, note 98 (dismissing quantitative methods from other agencies) (citing the HPHC Memo).

<sup>34</sup> OSC Report page 21 and note 58 (explaining the tiered approach is appropriate because it is used by other agencies such as the EPA).

<sup>35</sup> Referred to as best regulatory science by CTP.

<sup>36</sup> OSC Report page 21, citing CTP Director’s Decision.

<sup>37</sup> On page 12-13 of the OSC Report CTP inconsistently dismisses the risk assessment approaches used at other agencies (citing OS Appeal Decision and HPHC memo) and even at CTP (citing the OS Appeal decision) but then on page 21 of the OSC Report CTP states it that a tiered approach is appropriate because it is used by FDA and used by other agencies such as EPA (which also disregards that not all tiered approaches are the same). In essence, CTP dismisses other agency approaches as inappropriate for CTP (HPHC Memo page 2) but then asserts the tiering approach is appropriate because it is used at the FDA and other regulatory agencies (OSC Report page 21 citing OS Response to Scientific Report). See also *supra* notes 30-34 and accompanying text.

<sup>38</sup> OSC Report page 23, citing CTP Director’s Decision.

<sup>39</sup> OSC Report page 23, citing CTP Director’s Decision.

<sup>40</sup> OSC Report page 12 citing OS Appeal Decision (“Agency’s need to manage programs and resources to best benefit our public health mission . . . and the efficient use of resources”); OSC Report page 14 citing OS Appeal Decision (“[to] meet FDA performance goals,”); OSC Report page 24, citing CTP Director’s Decision (“resources are used efficiently”)

<sup>41</sup> OSC Report page 21, citing CTP Director’s Decision (“OS staff must consider practicality and public health impact in the context of a rigorous scientific standard”); OSC Report page 22, citing CTP Director’s Decision (“informed by eight years of experience with the tobacco SE program,

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and (3) makes conclusory statements.<sup>42</sup> CTP management agreed QRA is a peer-reviewed approach to comparing harmful substances in a complex mixture,<sup>43</sup> and CTP (both the Director and OS) acknowledges a full QRA is ideal to evaluate quantitative differences between products.<sup>44</sup> Still, in departing from this ideal, the OSC report notes CTP “declines to provide any specific examples and points in general to training”.<sup>45</sup>

In contrast, the concerned toxicologist memo provides multiple relevant scientific references. CTP dismissed the Toxicology Expert Panel’s review as not informed by CTP OS’s years of experience, but omits the crucial fact that the CTP concerned toxicologists (including one concerned toxicologist who was one of the first toxicologists hired in the newly formed Center and who has as many years of CTP experience as anyone in this scientific dispute) raised the same and substantially similar concerns noted by the expert panel. The CTP concerned toxicologists had extensive experience with the SE review and training program and included one member at CTP since 2010. So, CTP dismissed concerns by its own concerned toxicologists, then dismissed the same or substantially similar concerns by an expert panel using the excuse that the panel did not have CTP-specific knowledge to be able to adequately raise concerns.

CTP asserts that the concerned toxicologists do “not demonstrate the new approach is inappropriate for the intended use,”<sup>46</sup> but there is a critical difference between showing that an approach is inappropriate for a given use and showing that an approach is not scientifically supported or valid. The first will yield results that can be expected to be incorrect as it simply the misapplication of an otherwise potentially valid tool; a hammer is not a screwdriver. The second will yield results that likely are not correct, valid, or useful in any given application; a stick can be used as a hammer or a screwdriver but does a poor job as either. It is one thing to use an accepted and legitimate tool but applied in a new context, and another to use something that is not recognized as a legitimate or valid tool at all and hope for the best. This arguably less ‘wrong’ but still misguided application is inappropriate in reviewing products that impact public health without further development and evidentiary support (and preferably some degree of validation). Any risk assessment model is a tool that should be fit-for-purpose.<sup>47</sup> The CTP toxicologists unequivocally objected to the use of unsupported and potentially invalid procedures, and provided scientific references showing that the HPHC memo is not supported by scientific evidence, available data, or current toxicological principles. As such it should not be the basis of CTP decisions.<sup>48</sup> In response, CTP has provided only process-

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including reviewing over 7000 SE Submissions . . . makes best use of limited resources while maintaining focus on protecting public health”); OSC Report page 26 citing CTP (“Addendum experience completing thousands of SE reviews and with input from staff.”).

<sup>42</sup> OSC Report page 21, citing CTP Director’s Decision (“fully quantitative approach was unnecessarily burdensome”); OSC Report page 21, citing CTP Director’s Decision (“[CTP] believes the approach in the memo is scientifically sound”).

<sup>43</sup> OSC report page 7.

<sup>44</sup> CTP Director’s Decision page 7(citing OS Response to Scientific Panel Report page 1).

<sup>45</sup> OSC Report page 28, referring to CTP Addendum.

<sup>46</sup> CTP Response to OSC Page 2.

<sup>47</sup> NATIONAL RESEARCH COUNCIL, *SCIENCE AND DECISIONS*, 6 (National Academies Press 2009) (explaining, inter alia, that more attention has to be focused on designing, planning, and scoping a risk assessment); Lauterstein, et al. *Nonanimal toxicology testing approaches for traditional and deemed tobacco products in a complex regulatory environment: Limitations, possibilities, and future directions*, 62 *TOXICOLOGY IN VITRO* 1, 10 (2020).

<sup>48</sup> See CTP Toxicologist Memo (May 31, 2019)

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related justifications that falsely imply scientific appropriateness and validity that simply is not present.

CTP managers appear to hint that CTP distrusts applicant QRAs because they are complicated and can be used to skew analysis and to mislead.<sup>49</sup> Any scientific tool can be misused; that cannot be a basis for allowing or disallowing use. When a company applies for some type of FDA product approval in an application process, FDA's role is to evaluate the scientific evidence submitted in applications and determine whether it provides scientific support for its claims under the statutory framework. Concern about improper or incomplete data is not new in FDA's regulatory review process. FDA must use a science-based approach to evaluate the science submitted by an applicant.

CTP indicates that in conditions where one or more HPHCs are increased, it expects a QRA could not establish that the new product is SE.<sup>50</sup> This suggests that CTP has effectively predetermined application outcomes irrespective of what evidence an applicant might provide for review.<sup>51</sup> CTP has made the policy decision that an applicant essentially cannot submit any sufficient information if the new product contains one or two HPHC increases (asserting that a QRA would fail to resolve),<sup>52</sup> but has not provided scientific support for the policy decision leaving the CTP review process open to challenge on lack of sufficient evidence. CTP notes an appeal process for applicants<sup>53</sup> as a check on an error, but it is unclear why an applicant would appeal a decision allowing their product to go to market even though it is more harmful.<sup>54</sup> As CTP has appeared to argued a lack of trust in applicants' disclosures as a necessary factor in its policy choices, it seems unconvincing and inconsistent for CTP to also expect applicants to call attention to errors in their favor.

While an administrative agency has significant discretion in making decisions, the agency needs to make these decisions from a position of statutory authority within its mission and provide sufficient evidentiary support for these decisions. A court will look to the administrative record to determine if it contains sufficient evidence to support factual determinations, but substantial evidence must contain more than a mere scintilla.<sup>55</sup> Given its mission and statutory authority, the FDA is expected to have relevant data and scientific principles to satisfactorily explain its

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<sup>49</sup> OSC Report page 34-37.

<sup>50</sup> OSC Report page 36 (QRAs seldom, if ever, resolve any remaining uncertainty with respect to the relative risks posed by the new product after either using the qualitative or semi-quantitative approach for one or two HPHC increases (Tier Two), or concluding that the qualitative or semi-quantitative approach is inapplicable (i.e., Tier Three).")

<sup>51</sup> Implying CTP will not review such scientific information, data, references, or other evidence submitted; *see also infra* note 56 and accompanying text.

<sup>52</sup> OSC Report page 38, 40 ("in many cases, [QRAs to resolve increases in Tiers 1 to 3] should fail.").

<sup>53</sup> OSC Report page 24, citing CTP Director's Decision.

<sup>54</sup> Applicant's need to sell products to make money which would be a disincentive to challenging a successful application.

<sup>55</sup> *Biestik v. Berryhill*, 139 S. Ct. 1149, 1154 (2019) (holding, in the context of the Social Security Administration's disability finding, substantial evidence is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." (Citing *Consolidated Edison*, 305 U. S. 197, 229 (1938)).

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decisions;<sup>56</sup> it cannot advance conclusory opinions or opinions unsupported by evidence.<sup>57</sup> While CTP has provided procedural limits, general assertions, and conclusory statements, it has not advance any scientific support for its positions on risk assessment or uncertainty analysis. In contrast, its critics have based their argument soundly on scientific references and on current and accepted scientific practice.

CTP needs to improve the clarity and validity of the risk assessment process by addressing the concerns of the concerned toxicologists<sup>58</sup> and the expert panel. CTP has not addressed how it can dismiss analytically equivalent HPHCs using only chemistry data without addressing health effects. Currently, however, CTP disregards the health effect impacts of equivalent HPHCs by claiming that any difference between two analytically equivalent substances is negligible.<sup>59</sup> Toxicologically, however, this is not necessarily the case; analytically equivalent substances fall within a similar range, but even slight differences between a potent substance could make a meaningful difference in risk assessment. CTP disregards scope of analytical equivalence as too small and acceptable to dismiss without considering the potency of effects of these increase toxicants.<sup>60</sup> CTP could provide an analysis on the chemical limits to determine the significance of health effects in this range and then make scientifically based and policy informed decisions.

Additionally, the proposed tiering approach for review is still unclear.<sup>61</sup> This unclear standard can allow a tobacco product that should be NSE to be SE, thus allowing a more dangerous product on the market. While CTP asserts that it errs on the side of being protective, it uses only uncommon examples such as where only one or two HPHCS are increased without addressing the full scope of possibilities. It is rare that a tobacco application comparing a new tobacco product to a predicate tobacco product will only encompass one analytically non-equivalent an increase or a decrease. If such an extreme is possible, then so too is an extreme where a tobacco product application has only increases of analytically equivalent HPHCs which could be an increase in risk raising different questions of public health. As most tobacco product SE comparisons will likely have two or more increases, tier 1 and 2 will not likely be relevant to many applications. As most applications will be tier 3, it seems likely CTP will summarily dismiss these applications as NSE. This appears to predetermine the decision and

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<sup>56</sup> Administrative Procedure Act 5 U.S.C. § 706; see also *Motor Vehicle Mfrs. Ass'n v State Farm Mutual Auto. Ins. Co.* 463 U.S. 29, 43 (1983) (holding an "agency must examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made.'" (citing *Burlington Truck Lines, Inc. v. United States*, 371 U.S. 156, 168 (1962)).

<sup>57</sup> *Rutherford v. United States*, 542 F.2d 1137, 1140, 1143 (10th Cir. 1976) (holding the FDA must support its decisions with substantial evidence, and FDA conclusory statements are inadequate to support an agency decision).

<sup>58</sup> While the OS Director notes a toxicologist's evaluation rarely affected his decisions (OSC Report page 35) (1) CTP reported submitted QRAs are already relatively rarely present in a submission; (2) the OS Director managed the chemical-based development of the analytically equivalent or non-equivalent evaluation of HPHCs in the Division of Product Science, and (3) the OS Director and DNCS management did not respond to the concerned toxicology reviewer's evaluation where differences were noted in the different approaches (previously the concerned toxicologists had several reviews with an appendix explaining the difference and the impact).

<sup>59</sup> OSC Report page 41.

<sup>60</sup> OSC Report page 41-42; CTP argues giving any weight to analytically non-equivalent difference would "introduce error into the evaluation" (OSC Report page 35). This disregards the fact error already exists in the evaluation, and CTP chooses to dismiss this error. There is variability and uncertainty in analytical measurement, in considering potency, and in estimating the health effects. Thus, this conclusory statement dismisses but does not scientifically address error. The HPHC memo completely disregards this error, and the QRA provides a method to account for such error. The agricultural variability due to analytical limitations cited as not sufficiently reliable (OSC Report page 35) has been accounted for in QRAs performed by other government agencies on a variety of products, including variable environmental or agricultural products.

<sup>61</sup> See notes 3-8 *supra* and accompanying text.



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preclude review of applicants' submitted materials; to render a decision without reviewing what the applicant provided would be arbitrary and capricious, especially if it is scientifically valid.

CTP asserts a full quantitative risk assessment is not the proper way to evaluate a tobacco product SE application, so why has it spent hundreds of thousands to likely millions of dollars on a Risk Modeling Simulation Tool (RMST) software program to help reviewers perform quantitative risk assessment? Was money spent developing a tool never to be used despite that it would support the efficient evaluation of submitted risk assessment models?

CTP discards QRA as a precise quantitative approach with no support from existing scientific research,<sup>62</sup> but CTP has used it in the past (as have other FDA Centers), and CTP held a public meeting with presentations on QRA applied to tobacco science.<sup>63</sup> Without a sound scientific risk assessment approach CTP is making decisions that discard any scientific consideration of variability, uncertainty, and error related to adverse health effects. CTP should address the substantive scientific issues raised by the concerned toxicologists.

The Expert panel has provided excellent guidance for CTP to improve its risk assessment process. CTP's remedial actions are vague and do not sufficiently address the panel's concerns. CTP asserts the proposed revisions to the memo are consistent with the expert panel recommendations<sup>64</sup> but does not demonstrate this to be the case. The Expert Report cautions that the unique and unfamiliar approach in the HPHC memo is not necessarily the ideal approach "because additional methods can be needed to assess the risk of toxicity"<sup>65</sup> and "these approaches can lead to varying decisions"<sup>66</sup> which may not produce consistent results.<sup>67</sup> The Expert Panel properly noted that more specific and transparent guidance and clear decision rules are needed in order to produce consistent decisions and to avoid reliance on judgment and impressions rather than reliable standards.<sup>68</sup> The Expert Panel critiques the approach in the HPHC memo and suggests specific means to make the review process scientifically sound.<sup>69</sup> CTP should explicitly address each recommendation by the expert panel with a substantive response (scientific references, scientific data, or both) regarding both risk assessment methods and processes and the uncertainty in the process.

The OSC Report addressed retaliation generally, but it did not address the full scope of retaliation used by management under their discretion to suppress scientific opinion of the concerned toxicologists (and others).<sup>70</sup> See again the reference to the appearance of DNCS management intent for unilateral global resolution of this scientific difference without input from the concerned toxicologists and the OS Appeal Decision which dismissed the concerned

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<sup>62</sup> OSC Report page 41.

<sup>63</sup> See Concerned Toxicologist's Memo.

<sup>64</sup> OSC Report page 46.

<sup>65</sup> OSC Report page 18, citing Expert Panel Report.

<sup>66</sup> OSC Report page 19, citing Expert Panel Report.

<sup>67</sup> OSC Report page 19, citing Expert Panel Report.

<sup>68</sup> OSC Report page 18-20, citing Expert Panel Report.

<sup>69</sup> OSC Report page 18-19, citing Expert Panel Report.

<sup>70</sup> Undisclosed.

## Whistleblower Response to FDA Report

toxicologists' issues without a substantive response.<sup>71</sup> Also noted above, CTP prevented these scientists from any risk assessment related functions (review, presenting) when others who had not expressed scientific concerns or objections were permitted to do so.<sup>72</sup>

The fact that CTP managers expressed surprise that the concerned toxicologists did not agree with the HPHC memo<sup>73</sup> does not seem consistent with the emails and reviews sent from the concerned toxicologist to DNCS management before and after the implementation of the HPHC memo. While CTP recites its decision to resolve the scientific dispute,<sup>74</sup> CTP has not contacted the concerned toxicologists (including the whistleblower) to resolve the scientific issues.<sup>75</sup>

Lastly, CTP asserts "toxicology reviewers have discretion" but at the same time all but predetermines the outcome for proposed tiers 1 to 3.<sup>76</sup> While CTP asserts reviewers are to exercise their own judgment,<sup>77</sup> the "OS Appeal Decision concludes that the HPHC memo 'is a well-considered and appropriate management directive that DNCS staff are expected to follow.'<sup>78</sup> This appears inconsistent with being able to voice dissenting scientific opinion. While the scientific dispute could be continued,<sup>79</sup> the concerned toxicologists felt dismissed and mistreated by management, subsequently lost trust in management, and even before departing CTP, continued to fear retaliation.

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<sup>71</sup> OSC Report page 52. Also note the appeal path the concerned toxicologist may not have been the proper route, but CTP provided no guidance on how to execute a proper appeal, scientific dispute, or other action to resolve any issues.

<sup>72</sup> See *supra* text after note 19.

<sup>73</sup> OSC Report page 33-34.

<sup>74</sup> OSC Report page 24, citing CTP Director's Decision.

<sup>75</sup> In fact, the OS Appeal Memo and the OS Director's decision dismissed these issues with conclusory statements.

<sup>76</sup> OSC Report page 46 items 2 ("[B]ut acknowledge that any analysis in a QRA departing from the typical outcomes for Tiers One through Three is unlikely to produce a different outcome, absent very compelling arguments grounded in science.")

<sup>77</sup> OSC Report page 27, citing CTP Addendum.

<sup>78</sup> OSC Report pages 12-13, citing CTP Appeal Decision.

<sup>79</sup> OSC Report page 62.

## Whistleblower Proposed Questions for FDA Report

1. When the Chemistry discipline in the Division of Product Sciences evaluates whether an HPHC is considered equivalent, other than considering the variability and uncertainty of the analytical measurement of an HPHC has CTP considered the impact of the health effects from these analytical differences (whether analytically equivalent or not)?
2. CTP has still not addressed some key issues, including how it addresses uncertainty.<sup>1</sup> How does CTP address uncertainty, variability, and error in the measurement of an HPHC? How does it address this analytically? How does it address this regarding the health effects of an HPHC?
3. It is unclear how an increase is offset by a decrease when CTP does not “rank toxicants as more or less ‘problematic.’”<sup>2</sup> Is an increased carcinogen offset by a mass or weight basis of an equal mass or weight of a different carcinogen with the assuming that both are considered equal carcinogenic, even though this assumption is likely incorrect? How are non-carcinogenic increases offset by decreases when CTP “does not group toxicants based on the end organ effected because toxicants can impact more than one organ”?<sup>3</sup>
4. (Using equivalence as implemented in CTP) If only one HPHC has a non-equivalent increase, but dozens of other HPHCs have a non-equivalent decrease, would CTP disregard these non-equivalent decreases? Conversely, if only one HPHC has a non-equivalent decrease, but dozens of other HPHCs have a non-equivalent increase, would CTP disregard these non-equivalent increases? Finally, how does CTP address this difference when there is a combination of increases and decreases?
5. (Using equivalence as implemented in CTP) If an application contains only increases in HPHCs but the increases are all analytical equivalent increases in the new tobacco product as compared to the predicate product, under the CTP’s proposed tiering structure, is the new product considered SE?
6. Can CTP cite any specific scientific evidence to support the use of the HPHC memo? Can CTP cite any specific scientific evidence to support the use of each step in the memo?

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<sup>1</sup> CTP argues giving any weight to analytically non-equivalent difference would “introduce error into the evaluation” (OSC Report page 35). This disregards the fact error already exists in the evaluation, and CTP chooses to dismiss this error. There is variability and uncertainty in analytical measurement, in considering potency, and in estimating the health effects. Thus, this conclusory statement dismisses but does not scientifically address error. The HPHC memo completely disregards this error, and the QRA provides a method to account for such error. The agricultural variability due to analytical limitations cited as not sufficiently reliable (OSC Report page 35) has been accounted for in QRAs performed by other government agencies on a variety of products, including variable environmental or agricultural products (OSC Report refers to FDA Report).

<sup>2</sup> OSC Report page 27, citing CTP Addendum (OSC Report refers to FDA Report).

<sup>3</sup> OSC Report page 27, citing HPHC memo (OSC Report refers to FDA Report).

## WB Response to Supplemental Report – OSC File No. DI-20-0372

The supplemental report submitted by FDA shows a strong starting effort, but ongoing staff support and program monitoring is needed. The updated CTP HPHC memo gives reviewing scientists some discretion. These scientists will still need courage to challenge a system that places great importance on collaboration and meeting deadlines given the risks involved. Briefly, the updated memo allows scientists discretion to consider the most important harmful chemicals impacting human health risk in a tobacco product. However, the improved review system still can remove chemicals from review based on how they are measured.

Doing so misses the most crucial aspect of review because it does not consider the health effects of the chemical in question. This is a primary concern despite the FDA's partial responsiveness to earlier inquiries. The whistleblower concerns were detailed previously (Whistleblower Response to FDA Report) and therefore not restated fully here. Rather, this document is a response to the FDA Supplemental Report (hereinafter FSR). The FSR provides inconsistent responses which address agency procedural issues rather than concrete scientific issues, as the whistleblower previously noted. It is important to address where this difference is substantive and may still fall short of protecting public health.

First, the FSR begins with an assertion that the Expert Panel concluded the original CTP HPHC Memo was consistent with sound regulatory science. This statement places selective emphasis on only part of the Expert Panel's conclusions (e.g., omits panel opinion on problems with the original HPHC memo) and thereby mischaracterizes the outcome. The statement also disregards the recommendation by the panel to clarify the memo to avoid making subjective decisions. CTP's stance on the Expert Panel is concerning. On one hand, they have selectively adopted those pieces of a report that seemingly support current agency practices. At the same time, CTP dismissed the panel for lacking tobacco expertise. This second stance potentially invalidates the first. If the panel has no tobacco expertise, adopting its recommendations for tobacco regulation may be questionable. Either the panel is qualified to make recommendations, or they are not.

Second, the FSR notes the whistleblower was involved in the new memo, but this late involvement was a compromise with management coupled with and contingent on management's promise to continue resolving issues with the HPHC memo. The whistleblower provided more recommendations than those incorporated into the new HPHC memo, but management declined many of those recommendations. Additionally, another scientist developing the memo informed the whistleblower that some problematic and potentially inaccurate language was provided by upper management and "could not be changed." Correctly developing the memo requires the use of scientifically sound materials such as quality peer-reviewed publications, data, and related evidence to provide a robust, toxicologically sound basis for evaluating the health impact of tobacco-related chemicals. The whistleblower took management's promise and FDA response to have been made in good faith and is hopeful but has reservations after being disappointed. The FDA asserts the memo was revised to provide more clarity (FSR response to goals 1-3), but CTP did not update the memo until OSC required the FDA to act. While it includes more clarity by allowing consideration of risk drivers in a tobacco product, more work is needed.

Third, the culture of scientific intimidation continues at CTP. Some scientists working on or reviewing the memo noted they had concerns but were afraid to challenge upper management's direction on the memo. If this continues and reviewing scientists fear reprisal, solutions that merely give reviewers discretion to challenge rather than specific review guidelines may still fall short.

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Fourth, genuine change requires a shift in focus from chemical amounts to chemical harms posed to individuals and the population. The recommendation by the whistleblower is to allow reviewers to evaluate chemicals driving the risk in a product (risk drivers). Doing so provides a good basis of considering the health effects of these chemicals. The evaluation of chemicals in tobacco products should not be limited to the measurement of HPHCs that are “not equivalent.” Health-based criteria should be considered (i.e., criteria that can be used to determine if a change in the amount of chemical will impact human health). Thus, CTP needs to continue working on and evolving the HPHC memo to consider the health impact of these chemicals.

Fifth, robust consideration of health impact requires multidisciplinary review. CTP cannot continue to rely solely on the chemistry evaluation of which chemicals have changed. Instead, reviews must include toxicological assessment of the amount of change for these chemicals, and whether that change - equivalent or not - poses an increased risk of harm to users. As previously recommended, CTP should address the recommendations of the expert panel and the concerned toxicologists.

Sixth, the FDA's response is concerningly vague and promises of change have no metric for measurement or tracking of progress. In response to goal 4, the FDA asserts that it will continue to revise the memo “as this is an emerging area of regulatory science,” and will evaluate and refine the process “as the agency gains additional insight and experience.” The whistleblower is hopeful the agency will follow this course but has concerns since FDA did not act until compelled. The language of FDA's response easily allows for inaction and enables management to disregard any insights that uncomfortably challenge its preferred stance and current policy. Management has made significant investment in chemistry-centric review of HPHC changes and may not welcome adding an equivalent toxicological focus to ensure that noted changes do not harm the public.

Seventh, FDA asserts (response to goals 1 and 2 and the additional question) that it has a clear and transparent process for evaluating HPHCs and that it provides staff with the necessary training to conduct this evaluation. This does not appear to be correct as evidenced by FDA's lack of specific training on the memo despite requests for such training by CTP scientists. FDA has not developed clear and transparent training on the memo. FDA is not addressing specific issues with current HPHC memo review processes and practices, developing a timeline for improvement, or prioritizing these changes.

Eighth, the FDA will need to improve its efforts to ensure credible scientific issues are considered without retaliation. FDA explains it has eliminated ambiguity in the scientific dispute resolution process, created an FDA point of contact, and provided additional training (FSR goal 5). However, the whistleblower is unsure these measures are complete without continued vigilance. As noted earlier, some scientists are afraid to raise scientific issues with management, and others have stated they are unsure how to raise a disagreement. These CTP scientists have taken the required scientific dispute training and still do not feel that they have a workable path forward in a dispute. In addition, the whistleblower has asked managers who have taken this training how to raise a scientific dispute, and the managers have responded that they do not know. Whatever CTP training that supposedly addresses the scientific dispute process and how to lodge a dispute is insufficient.

The whistleblower acknowledges that the FDA cannot eliminate all ambiguity from scientific disputes; science and disputes are not a purely objective process. FDA is an agency that makes regulatory decisions and has discretion to manage its employees and scientific disputes. The FDA distinguishes informal from formal disputes and encourages resolution at the earliest stage, preferably informal.

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The FDA dispute process creates ambiguity in disputes and impedes performance. Managers determine the validity of an informal scientific dispute. This creates ambiguity and leaves non-management scientists vulnerable to capricious, informal, and undocumented decisions of – and potential retaliation from – their supervisors if they disagree with CTP management. The FDA scientific dispute process encourages resolution at the lowest organizational level possible and preferably informally (pages 2-3 of FDA scientific dispute resolution policy). A manager evaluates a scientist's performance in part to determine the extent of that scientist's collaboration. This evaluation of performance affects assignments, promotion potential, and even awards. Some examples of required performance language include: "fostering a cooperative work environment; seeks resolution of workplace conflicts at earliest stage; known for collaboration with others; demonstrate successful collaboration; works in a collaborative manner; facilitates agreement by resolving differences of opinions; conveys a positive and willing attitude; demonstrate collegial, professional demeanor."

This agency language discourages dissenting voices, and pressures junior scientists and managers to capitulate to current FDA practices and policies even if these are insufficient or problematic. Disputing employees may be seen as not collaborating, cooperating, or resolving a dispute, or as having a less than positive and willing attitude. Given that scientist work on a deadline, raising a dispute risks the ability to complete such work in a timely manner. Note that managers or supervisors are excluded from scientific disputes (page 4, item 3 under FDA SDR), but managers under senior management may have valid scientific concerns. There is no guidance on how they might engage in scientific dispute.

The FDA has taken good first steps to support the best available regulatory science by giving scientists discretion to evaluate the most harmful chemicals (risk drivers) in a tobacco product applications and revisiting FDA scientific dispute policies and training. However, first steps do not cross the finish line. FDA should remain vigilant that these changes support the use of the best available scientific evidence to support regulatory decisions, and that FDA policies protect scientists from retaliation when raising these issues. Over the course of years for this dispute, the actions by management have left scientists afraid to challenge scientific positions. Some will not speak up at all out of fear of retaliation, while others have given up and state that it does not matter, as management will disregard their input. This has also been a major contributor to the loss of qualified, excellent, and experienced risk assessors.

The DOJ has evaluated organizations to determine if they have effective compliance programs, including whether a program fosters a culture of compliance and protects challengers from retaliation. While the DOJ does not investigate FDA programs, it does provide guidance on how programs are evaluated (US DOJ, June 2020. Evaluation of Corporate Compliance Programs). DOJ asks questions to determine if a program is well-designed; if the program is applied earnestly and in good faith; and if the program actually works?

These seem like effective questions the FDA should be asking itself to determine if it values voices that provide credible scientific reasons for concern. The FDA has started with some good principles but needs to go further to distinguish what it has written from a paper program (i.e., a program that only exists on paper) to one that can be effectively implemented and evaluated. This may entail actions such as internal monitoring and auditing for effectiveness, creating and communicating disciplinary guidelines for non-compliance (right now FDA has no policy for non-compliance), and developing policies to promptly detect problems and undertake corrective action.