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October 11, 2019

Via E-Mail

Rick Woychik, Ph.D.
Acting Director
National Institute of Environmental Health Sciences
National Toxicology Program
P.O. Box 12233
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Durham, NC 27709

Re: RoC Review of Antimony Trioxide

Dear Dr. Woychik:

On behalf of the International Antimony Association (i2a),[1] this is a Request for Correction (RfC) of the unlimited characterization of the cancer hazard for antimony trioxide disseminated by the Office of the Report on Carcinogens (RoC) of the National Toxicology Program (NTP) in the final Monograph on Antimony Trioxide, released October 19, 2018.[2] To the extent that the information of concern in the Monograph is based on NTP's September 2016 "Draft Report on Carcinogens Concept: Antimony Trioxide," [3] the NTP 2017 Study Report,[4] or

1 The i2a is a commodity association based in Brussels, Belgium, that represents the collective interests of antimony producers and importers worldwide. The mission of i2a is to conduct studies and to disseminate information from a product stewardship standpoint concerning the safe use and benefits of antimony and antimony compounds. These activities entail generating and providing access to pertinent data; providing an informed viewpoint on the interpretation of scientific studies; and promoting awareness of worldwide environmental, health, and safety regulations that may be relevant to antimony compounds.

2 NTP, Report on Carcinogens, Monograph on Antimony Trioxide (Oct. 2018), available at https://ntp.niehs.nih.gov/ntp/about_ntp/bsc/2016/december/meetingmaterials/draftantimonytrioxide_508.pdf (Monograph).

3 NTP, Draft Report on Carcinogens Concept: Antimony Trioxide (Sept. 2016), available at https://ntp.niehs.nih.gov/ntp/roc/monographs/antimony_final20181019_508.pdf (Concept Document).

other foundational documents, this request necessarily encompasses correcting the corresponding information there as well. As discussed more specifically below, this RfC is made under the Information Quality Act (IQA)[5] and the 2002 implementing guidelines issued by the Office of Management and Budget (OMB),[6] to which all federal agencies are subject, and also under guidelines of the U.S. Department of Health and Human Services (HHS),[7] based on OMB's principles, which apply to all agencies under its auspices. As further addressed below, key aspects of OMB's April 24, 2019, additional guidance are also highly pertinent to this RfC.

Summary -- Key Points

Among the issues raised by this RfC and discussed more fully below, the following are critical to the review i2a seeks:

- Our primary concern is the breadth of the Office of the RoC's recommendation for antimony trioxide to encompass forms of the chemical and exposure pathways for which the carcinogenic potential has

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4 NTP, Draft Toxicology and Carcinogenesis Studies of Antimony Trioxide (CAS No. 1309-64-4) in Wistar Han [Crl:WI (Han)] Rats and B6C3F1/N Mice (Inhalation Studies), NTP TR 590, NTP, NIH (2017). This document is numbered 981 in the August 17, 2017, docket entry by NTP of its "Preliminary References" listing, available at https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/ongoing/antimonyt/index.html#comments (NTP 2017 Study Report).

5 Section 515, Treasury and General Government Appropriations Act for Fiscal Year 2001 (Public Law 106-554; H.R. 5658).

6 67 Fed. Reg. 8451 (Feb. 22, 2002) (republished and corrected version). Recently, OMB issued a memorandum intended "to reinforce, clarify, and interpret agency responsibilities" under the IQA, which also is referenced in this RfC. Russell T. Vought, Acting Director, OMB, Memorandum to the Heads of Executive Departments and Agencies, "Improving Implementation of the Information Quality Act" (Apr. 24, 2019), available at https://www.whitehouse.gov/wp-content/uploads/2019/04/M-19-15.pdf (2019 Improving IQA Implementation Memorandum).

7 HHS, Office of the Assistant Secretary for Planning and Evaluation, HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public (Oct. 1, 2002), available at https://aspe.hhs.gov/information-quality-guidelines (HHS Guidelines).

not been demonstrated. Therefore, we are requesting that the open-ended language used in the final Monograph, supporting documents, and, ultimately, the forthcoming RoC be changed to indicate that the characterization of antimony trioxide as "reasonably anticipated to be a human carcinogen" be limited to the powder form of the compound only and the inhalation route of exposure. The RfC is consistent with NTP's scientific findings. The language in either i2a's proposed Option 1 or Option 2 on pages 8-9 below would satisfy the request, and precedent for such a limited listing is well established.

- We request affirmation that the April 24, 2019, Implementation Update 4.5 to the IQA is met in that the staff reviewing the RfC is independent and sufficiently senior to disagree effectively with their NTP colleagues who prepared the RoC recommendation.

- We request affirmation that the April 24, 2019, Implementation Update 4.3 to the IQA is met in that the NTP's peer review committee actually considered the issue of limiting the scope of the Monograph recommendation for antimony trioxide to the actual chemical species and route of exposure shown to be carcinogenic.

Background -- NTP/Office of RoC Review of Antimony Trioxide

Antimony (atomic number 51), a metalloid, offers a combination of metal and non-metal properties that make it highly versatile in its many forms and uses. As NTP recognizes, antimony trioxide is by far the most commercially significant form of antimony.[8] The predominant use of antimony trioxide is for flame retardants in textiles, plastics, and rubber. Antimony trioxide acts as a synergist in halogenated flame retardants via interaction with bromide or chloride to form antimony halogens. Through such interaction, antimony trioxide decreases the amount of halogen needed for flame resistance.[9] It thus confers an opportunity benefit as a component of a life-saving product and also by its role in diminishing the quantity of halogen necessary to make that product effective.

In September 2019, Roskill, a UK-based market consultant with 50 years' experience of research and consulting in metals, minerals, and chemical industries, and their end-

8 Concept Document at 3.

9 *Id*.

use industries, analyzed the socio-economic footprint of the production and use of antimony and its compounds in the European Economic Area (EEA).[10] The analysis contained various statistics relating to production and use of antimony in the United States. According to these statistics, the U.S. hosts 16% of the world's production of antimony, including only 0.6% of the world production of antimony oxides, while it accounts for 14% of the worldwide consumption of antimony. The high dependence on non-U.S. sources makes antimony a critical mineral resource for the U.S. This criticality furthermore is confirmed by the reliance of military applications, which require flame-retardant textiles and polymers among others, on antimony.

NTP announced in September 2016 that antimony trioxide was one of four substances nominated for possible review for a future edition of the RoC and requested information on the nominations.[11] In response, a substantial body of information was provided to NTP by i2a, including a Chemical Safety Report that was "largely . . . adopted from the European Union Risk Assessment Report" for antimony trioxide that was carried out on the evaluation and control of the risks of "'existing' substances." Together with providing the Chemical Safety Report, i2a submitted its preliminary assessment of NTP's long-term carcinogenicity studies on antimony trioxide that had been made available for review earlier in 2016, before antimony trioxide was nominated as a possible candidate for inclusion in a future RoC.[12] In the preliminary assessment, i2a raised study-specific issues, including issues going to the interpretation and relevance of the available animal data on antimony trioxide for human health. In its companion letter, i2a reminded NTP that antimony trioxide would be subject to a

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10 Roskill, *Socio-Economic Analysis of the Antimony Industry in the EEA* (Sept. 16, 2019). The U.S. Environmental Protection Agency (EPA), in the Toxic Substances Control Act (TSCA) Risk Assessment discussed below at pages 14-15 had referenced a 2011 report by Roskill. EPA, Office of Chemical Safety and Pollution Prevention, *TSCA Work Plan Chemical Risk Assessment, Antimony Trioxide*, CASRN: 1309-64-4, EPA Document No. 740-Z1-4001 (Aug. 2014) at 22, 66, available at https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/tsca-work-plan-chemical-risk-assessment-antimony (TSCA Risk Assessment).

11 81 Fed. Reg. 62513 (Sept. 9, 2016).

12 Caroline Braibant, Geert Krekel, and Nathalie Branche letter to Dr. Ruth Lunn (Oct.11, 2016) (October 11, 2016, Letter); Attachment 1 (Preliminary Assessment); and Attachment 2 (Chemical Safety Report). This submission and the subsequent comments submitted by i2a may be found in the public comment docket, available at https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/ongoing/antimonyt/index.html#comments.

Substance Evaluation in the European Union (EU) under the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) beginning in 2018, to be preceded by a Compliance Check in 2017 of the joint Registration Dossier that had been submitted collectively by all EU manufacturers and importers of antimony trioxide to the European Chemicals Agency (ECHA). In light of the imminent review processes to be commencing in the EU, i2a requested that NTP postpone the assessment of antimony trioxide until the next RoC review to align the regulatory processes in both jurisdictions "so that a more efficient, complete and internationally coherent deliverable can be achieved to the benefit of both programs."[13]

Despite the relative paucity of its database, NTP proceeded as scheduled with the review without reference to the upcoming EU processes. The extent to which NTP considered the information i2a had submitted in response to its request is uncertain. NTP proceeded as planned, and i2a participated through the submission of comments at each stage of the review where the opportunity was afforded on those documents that NTP made available to the public. i2a's comments underscored items on which i2a concurred with NTP, as well as items on which i2a raised substantive questions or points of divergence.

Following on its original submissions and in preparation for the December 15, 2016, Board of Scientific Counselors (BSC) meeting convened by NTP, i2a submitted comments on NTP's Concept Document on October 30, 2016.[14] Dr. Craig J. Boreiko, scientific counselor to i2a, addressed the BSC meeting,[15] where he raised specific cautions about the interpretations to be attached to the rat and mouse studies relied upon by NTP and explained why NTP's description of antimony as "persistent" was inappropriate.[16] Beyond issues of science and

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13 October 11, 2016, Letter at 2.

14 Caroline Braibant, Geet Krekel, and Nathalie Branche letter to Dr. Ruth Lunn (Oct.30, 2016) (October 30, 2016, Letter). This letter is mislabeled in the docket as a November 30, 2016, submission. The docket is available at https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/ongoing/antimonyt/index.html#comments.

15 Dr. Boreiko's written statement accompanying his appearance at the BSC meeting was submitted to the docket by i2a's Secretary General Braibant on January 30, 2017, (Boreiko Written Statement). The docket is available at https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/ongoing/antimonyt/index.html#comments.

16 Boreiko Written Statement at 1-2.

regulatory categorization, however, Dr. Boreiko highlighted the importance of "the current convergence of regulatory processes in the US and the European Union," with evaluation of antimony and its compounds beginning shortly under REACH, in support of which i2a was embarking on a research program focused on fundamental issues going to hazard classification and risk assessment for antimony and its compounds. Dr. Boreiko alerted the BSC that new information would soon be generated pertinent to uncertainties associated with the carcinogenic and mutagenic properties of antimony and its compounds.[17]

After NTP released the Draft Monograph for review and comment on November 29, 2017 -- which was the next opportunity for public input -- i2a submitted detailed comments in response,[18] addressing both that document and interpretations drawn from a (then) recently-issued final NTP report on toxicology and carcinogenesis studies of antimony trioxide in rats and mice (NTP 2017 Study Report). In the comments, i2a stated that it had identified factual inaccuracies in the Draft Monograph that it questioned, as well as questionable technical interpretations found in the NTP 2017 Study Report.[19]

Among the points on which i2a expressed reservations and submitted specific comments are those that go to the heart of this RfC. With the workplace as the locus for antimony trioxide health effects, i2a observed that the levels of exposure set out in an informational table in the Draft Monograph were out of date, did not reflect current industry practice, and created a misleading profile of the industry. After a discussion of specifics, i2a requested that the Monograph be revised so that it relied on recent and relevant exposure data for estimating exposure and to inform any discussion of current occupational exposure levels. In that connection, i2a also suggested that NTP omit a table (2.3) depicting old data and rely on the fresher and more accurate data from the EU Risk Assessment of antimony trioxide depicted in a second table (2.4).[20]

A related but even more critical issue raised by i2a was the absence in the Draft Monograph of what NTP considered to be actual workplace-relevant particle size distribution

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17 *Id*.at 1.

18 i2a Comment on Draft NTP Report on Carcinogens Monograph on Antimony Trioxide, dated 30 November 2017 (Jan. 10, 2018) (i2a Comment Document on Draft Monograph).

19 *See*, for example, i2a's discussion in points numbered 8 through 12 in the i2a Comment Document on Draft Monograph at 3-5.

20 *Id*.at 1-2.

information for its assessment. Such study data were available; the EU's Risk Assessment Report had contained studies of the particle size distribution occupational aerosols associated with antimony trioxide production. This should have been key because the inhalation route is the only realistic occupational exposure pathway through which antimony trioxide poses a carcinogenic hazard,[21] and the workplace, in turn, is the only realistic setting in which that exposure hazard can occur. As i2a stated in its comments: "Given the subsequent focus of the Monograph upon carcinogenic impacts associated with the exposure of experimental animals to respirable antimony trioxide aerosols, it is difficult to understand why these data were not mentioned in a technical characterization of occupational exposure to antimony trioxide."[22]

i2a further suggested that a comparative review of the different protocols used in the animal studies should include the particle size of the antimony trioxide preparations used (all respirable aerosols) and differences in the particle size distribution among those studies indicated. Since particles of differing form or size are not comparable in terms of their amenability to inhalation or subsequent deposition patterns within the lung, the omission of this part of the exposure equation was problematic.[23]

The Draft Monograph reached the conclusion that while no evidence existed based on epidemiological studies, experimental animal study data supported designating antimony trioxide as "reasonably anticipated to be a human carcinogen." After detailing 20 specific substantive comments, i2a requested that NTP review the designation and determine whether it was indeed justified and/or whether it would have any real-world relevance under current standards regulating human exposure.[24]

Issuance of Final Monograph and Subsequent i2a Correspondence with NTP

In the Final Monograph, issued on October 19, 2018, NTP adhered to its conclusion in the Draft Monograph, in recommending that "antimony trioxide is *reasonably anticipated to be a human carcinogen* based on *sufficient* evidence of carcinogenicity from

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21 As i2a pointed out, the Draft Monograph contained no rationale as to why dermal exposure data might even be relevant. *Id*.at 2.

22 *Id*.

23 *Id*.at 3.

24 *Id*.at 8.

studies in experimental animals and supporting evidence from mechanistic studies."[25] The recommendation rested on the rodent studies, as NTP acknowledged that "[t]he data available from studies in humans are *inadequate* to evaluate the relationship between human cancer and exposure specifically to Sb_2O_3 or antimony in general."[26]

Although the Monograph was in its final form and the RoC review process complete, i2a remained deeply troubled by the breadth of the recommendation, that overlooked those data that demonstrated persuasively and, in i2a's view conclusively, that it could and should be limited as discussed. The absence of a robust database at a minimum counseled that greater precision should have been brought to crafting the recommendation, a concern heightened by NTP's unwillingness to align its review process with the review already in progress in the EU.

Accordingly, several weeks after the Monograph was issued, i2a, through its legal counsel, wrote to Dr. Ruth Lunn, Director of NTP's Office of the RoC, seeking such a refinement: "i2a believes it would be sound, appropriate, and scientifically necessary for NTP to refine its contemplated recommendation for Sb(III) by limiting it to the powder form of the compound only and the inhalation exposure route."[27] As noted above, i2a had emphasized in its submissions to NTP during the review process the role of particle size and form in occupational exposure to antimony trioxide via inhalation, which was the only viable exposure route indicated by the data. i2a requested, therefore, that NTP revise the Monograph language in question to read either as stated in what it termed "Option 1" or "Option 2." The suggested language (in italics) was presented in the December 2018 Letter as a refinement to the existing Monograph text, as follows:

> Option 1: NTP recommends that antimony trioxide, *in the form of respirable powder** is reasonably anticipated to be a human carcinogen *by inhalation* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting evidence from mechanistic studies. The data available from studies in humans are inadequate to evaluate the relationship

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25 Monograph at iii (emphasis in original).

26 *Id*. (emphasis in original).

27 Letter from Lynn L. Bergeson, Esquire, and Bethami Auerbach, Esquire, Bergeson & Campbell, P.C., to Ruth M. Lunn, Dr.P.H., Director, Office of the RoC (Dec. 3, 2018) (December 2018 Letter). A copy of the letter is appended as Attachment 1.

> between human cancer and exposure specifically to Sb_2O_3 or antimony in general.
> ** Powders of particle size at or below 4 µm*.
>
> Option 2: NTP recommends that antimony trioxide, *in the form of respirable powders with a particle size at or below 4 µm*, is reasonably anticipated to be a human carcinogen *by inhalation* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting evidence from mechanistic studies. The data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure specifically to Sb_2O_3 or antimony in general.[28]

The letter set out i2a's rationale, building upon i2a's prior review and analyses of the database, along with comments it had submitted since the time antimony trioxide had been announced as a candidate for RoC listing and the hazard evaluation process began. As the letter recapitulated:

> The narrower focus of the recommendation [to reflect particle size and form] better reflects the data, the physical properties of the compound used in inhalation studies, discussion in the Monograph, the literature, and the public comments of the exposure hazard associated with Sb_2O_3 than does the current, open-ended language. Whether in the workplace or where the general population is concerned, the predominant sources of exposure identified in those materials are via inhalation. Uptake after dermal or oral exposure is extremely limited. Moreover, 90-day oral feeding studies with Sb_2O_3 have not exhibited carcinogenicity or toxicity[29] at the tissues' sites suggested to be targets for cancer in the NTP studies.[30]

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28 *Id*. at 1-2.

29 The letter (in its footnote 1) refers the NTP to Hext PM, Pinto PJ, Rimmel BA (1999). Subchronic feeding study of antimony trioxide in rats. *J. Appl. Toxicol.* 19:205-209.

30 December 2018 Letter at 2 (typo in original letter corrected in the passage quoted here).

To elaborate briefly, 90 days is too short for a cancer study, but one would expect to observe histopathological changes that signal pre-malignant alterations. NTP's inhalation

In further support of its request that NTP refine and limit the extent to which antimony trioxide was described as "reasonably anticipated to be a human carcinogen" in the Monograph, i2a cited examples from both the federal RoCs and from California's Office of Environmental Health Hazard Assessment (OEHHA), which, like NTP, is an authoritative body. In those instances, found in previous RoCs, NTP had limited or otherwise qualified its recommendations in some aspects; additionally, i2a found ample support for specifying inhalation exposure routes. The cited NTP precedents included RoC listings for crystalline silica, certain glass wool fibers, ceramic fibers, and cobalt and its compounds.[31] i2a's discussion of these precedents is set out in the next part of this RfC.

Dr. Lunn responded to the December 2018 Letter on March 14, 2019 (NTP's March 2019 letter), declining to pursue either of i2a's suggested limitations to the "reasonably anticipated to be a human carcinogen."[32] The reasons stated by Dr. Lunn are addressed below in connection with i2a's IQA violation discussion, but her basic points, briefly, were that "[c]onsidering the exposure route and particle size, as you propose for the antimony trioxide listing, would be part of a formal risk assessment" and "not within the RoC's purview" and also that the precedents cited by i2a were not apt because, with the less developed database for antimony trioxide, the "current mechanistic understanding" of its carcinogenicity was insufficient to limit the recommendation as requested.[33]

i2a replied to Dr. Lunn on April 24, 2019, expressing its disappointment and briefly reiterating its reasons why the NTP recommendation for antimony trioxide should be limited.[34] Subsequently, on May 20, 2019, i2a informed Dr. Lunn about the very concrete

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studies showed such changes in the lung in the 2-week range finder studies. It is therefore expected that similar findings should have been made in the oral studies, if antimony trioxide were to have a comparative effect via routes other than inhalation

31 December 2018 Letter at 4-7.

32 Letter from Ruth M. Lunn, Dr.P.H., Director, Office of the RoC to Lynn L. Bergeson, Esquire, and Bethami Auerbach, Esquire, Bergeson & Campbell, P.C. (Mar. 14, 2019) (March 2019 Lunn Response Letter). A copy of the letter is appended as Attachment 2.

33 *Id*. at 1, 2.

34 Letter from Lynn L. Bergeson, Esquire, and Bethami Auerbach, Esquire, Bergeson & Campbell, P.C., to Ruth M. Lunn, Dr.P.H., Director, Office of the RoC (Apr. 24, 2019). A copy of the letter is appended as Attachment 3.

outcome of the ongoing REACH Substance Evaluation on antimony trioxide, by sharing a copy of the draft decision of the authorities received on April 18, 2019. In this draft decision, European authorities requested that an additional study be performed by the industry, one which is virtually a repetition of the genotoxicity assays performed by NTP (Micronucleus and COMET). These precise assays had been recognized to present interpretative limitations key to the proper determination of the true nature and human relevance of the carcinogenicity hazard of antimony trioxide. i2a further invited Dr. Lunn to consider this development in the ongoing RoC listing process for antimony trioxide.

On May 29, 2019, following Dr. Lunn's response welcoming the announced new information, i2a shared with her the overall research strategy developed by i2a to address both scientific questions remaining after the 2017 NTP carcinogenicity studies and the regulatory requests formulated by the EU authorities under REACH Evaluation.[35] While Dr. Lunn has appeared receptive to receiving these updates on the highly relevant developments in the EU, there is no indication that NTP is inclined to revisit the conclusions on antimony trioxide in the Final Monograph or align the RoC listing process to account for the new data being generated under REACH. Such reluctance to revisit conclusions that already rest on shaky scientific ground in the new light to be cast by forthcoming additions to the database is yet another reason why NTP's dissemination of the information in question fails to satisfy the "utility" principle of the IQA, which is discussed below.

Request for Correction

IQA Background

In its December 2018 Letter, i2a raised the concern that an unlimited "reasonably anticipated to be a carcinogen" recommendation in the Monograph and, thus, in the upcoming RoC could run afoul of the IQA and OMB's implementing guidelines, which are binding on all federal agencies and are reflected in the parallel HHS Guidelines. The fundamental principles that underlie the statute and the OMB guidelines by now are well-known -- that each subject federal agency must issue and adhere to guidelines that ensure and maximize "the quality, objectivity, utility, and integrity" of information (including statistical information) that the

[35] Copies of the May 2019 correspondence between Caroline Braibant and Dr. Lunn are appended as Attachment 4. In her correspondence, Ms. Braibant references an April 18, 2019, ECHA document relating to antimony trioxide, "Draft decision notified to the registrant(s) under Article 50(1) of REACH for comments."

agency disseminates;[36] and that each such agency must establish administrative mechanisms to allow affected persons "to seek and obtain correction of information maintained and disseminated by the agency that does not comply with the guidelines."[37] As discussed below, it is the "utility" prong that is implicated here, with "utility" referring to "the usefulness of the information to the intended users."[38]

By now, also well-established is the elevated standard of review in accordance with "stricter quality standards" that applies to an agency's dissemination of information considered "influential." [39] As OMB stated:

> We recognize that some government information may need to meet higher or more specific information quality standards than those that would apply to other types of government information. The more important the information, the higher the quality standards to which it should be held, for example, in those situations involving "influential scientific, financial, or statistical information."[40]

According to OMB, "influential" when applied to agency information describes a scenario in which "the agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact on important public policies or important private sector decisions." [41] "Influential" accurately depicts the nature of the scientific information that NTP disseminated through its conclusions in the Office of the RoC's Final Monograph that antimony trioxide is "reasonably likely to be a human carcinogen." Indeed, it is impossible to describe such information when disseminated as anything but "influential."

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36 "Dissemination" is defined to mean "agency initiated or sponsored distribution of information to the public," for example, "a risk assessment prepared by the agency to inform the agency's formulation of possible regulatory or other action." 67 Fed. Reg. at 8454.

37 67 Fed. Reg. at 8452.

38 *Id.* at 8453.

39 *Id.* at 8455.

40 *Id.* at 8452.

41 *Id.* at 8455. This definition was reiterated in the 2019 Improving IQA Implementation Memorandum at 3.

NTP's Final Monograph is influential on its own and, inevitably too, as a signal that how it characterizes a chemical substance will be incorporated into a forthcoming RoC. As observed in i2a's December 2018 Letter to Dr. Lunn, regulatory agencies are likely to treat NTP's recommendations as authoritative in their own decision-making on whether a substance is carcinogenic and, if so, how to regulate or otherwise restrict it. In the case of antimony trioxide, the data do not support persuasively the NTP recommendation when unlimited by particle form or size. The i2a submissions throughout the review process help to illuminate why. As currently written, the NTP recommendation invites unnecessary over-regulation of a substance whose value in flame retardant compounds is widely recognized.

Misfit between Database and NTP Recommendation for a Beneficial Chemical Compound

From its submissions, as well as from its commitment -- backed by action -- to creating a more robust database internationally and addressing existing data gaps, it goes without saying that i2a recognizes that antimony trioxide is possibly a human carcinogen. But the real-world hazard arises predominantly in occupational settings and only when antimony trioxide is available for inhalation exposure in a respirable particle size. In that context, the hazard must be mitigated and responsive measures put into place should they not be in place already.[42] i2a fully supports and advocates for such measures as a fully-engaged product steward.

Whether in the workplace or elsewhere, if relevant, the database supports the predominance of the inhalation pathway as posing the hazard, and it fails to support other routes. As noted in i2a's December 2018 Letter -- and reflecting prior submissions in which these points were made and referenced in substantial detail -- the uptake after dermal or oral exposure to antimony trioxide is extremely limited. Ninety-day oral feeding studies, for example, did not yield an exhibition of carcinogenicity, precancerous changes, or toxicity at tissue sites that the NTP studies had suggested were targets for cancer. In short, the available data contradict any assumption that the carcinogenic potential of antimony trioxide will be expressed via oral or dermal exposure routes and to the non-respirable species of the compound. Nonetheless, NTP proceeded, despite an acknowledged dearth of information adequate to support carcinogenic impacts via any exposure except through inhalation of respirable particles, to make an unlimited recommendation in the Monograph. The absence of the necessary supporting data should have been a reason to forbear from this conclusion and all that it entails. Especially given the manifest paucity of the database as a foundation, NTP should have taken scientifically responsible account of the detailed comments on precisely this point submitted by i2a at every available stage of

[42] i2a additionally observed in its submissions that NTP has relied on an outdated picture of how 21st century workplaces operate to prevent antimony trioxide exposure.

review. The conclusions might well have been different if NTP had relied on recent and relevant exposure data. Because it failed to do so, the interest of "utility" under IQA has been poorly served as a result.

In light of what the data show and what they do not -- and for the other reasons discussed here, in the December 2018 Letter, and in the submitted comments -- i2a's requested correction of NTP's language is sensible and realistic. It is a far better fit for the known physical properties of antimony trioxide used in inhalation studies, the database on which the NTP review proceeded, and the information presented on exposure hazard than is the Monograph language as it stands.

Significantly, EPA took a more measured approach in a peer-reviewed risk assessment for antimony trioxide issued in 2014, undertaken in accordance with a work plan that had identified various chemicals for further assessment under TSCA.[43] While the primary focus was on ecological risks, EPA also addressed risks to human health from exposure to antimony. In that connection, it stated:

> Based on a review of the available data regarding antimony concentrations in food and environmental media, and biomonitoring data obtained from the latest National Health and Nutrition Examination Survey (NHANES), general population exposure to antimony is expected to be low (CDC, 2009; 2012). Because food and water are the primary sources of general population exposure, and the less toxic (*i.e.*, pentavalent) form of antimony predominates in these media, significant human health risks are not anticipated. This conclusion is supported by recent risk assessments completed for ATO in Canada and Europe.[44]

Limiting NTP's recommendation to reflect exposure route and particle properties also would be consistent with the TSCA Risk Assessment, which, in addition to the passage quoted above, recognized in its "Human Health Assessment" Appendix that "[s]ystemic

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43 EPA explained: "The Agency is performing risk assessments on chemicals in the work plan. If an assessment identifies unacceptable risks to humans or the environment, EPA will pursue risk management." TSCA Risk Assessment at 10.

44 *Id.* EPA noted that a NTP carcinogenicity study on antimony trioxide was in progress and indicated that it would review the study results when available. *Id.*

absorption of antimony compounds following inhalation exposure is mainly influenced by chemical form, particle size, and solubility."[45] By reflecting these characteristics, the corrections that i2a seeks would enhance the utility of this influential scientific information to those who will use it, while the current, open-ended language detracts from it.

According to Section VII of the relevant HHS Guidelines:

> NIH makes every effort to ensure that the presentation and dissemination of information about environmental health is comprehensive, informative, and understandable, and that scientific conclusions are based on: (1) The best available science and supporting studies, particularly peer-reviewed studies, conducted in accordance with sound and objective scientific practices; and (2) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies use of the data).[46]

In its dissemination of the recommendation in the Monograph for antimony trioxide, NTP has fallen far short of what the above-quoted guidelines call for. The scientific uncertainty associated with the NTP recommendation for antimony trioxide is indisputable. In the absence of human epidemiological studies, NTP relied on rodent studies, but issues arising from those studies and data gaps overall led NTP to rely also on mechanistic studies -- by their nature, a weaker link, and in this instance providing only a modest database.[47] We question whether this degree of scientific uncertainty on multiple levels has driven NTP to look to the precautionary principle to justify implicitly the breadth of its recommendation. The standard of

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45 *Id*., Appendix A, "Human Health Assessment," Section A-1 (Toxicokinetics) at 71. The Risk Assessment stated further: "In general, large particles (≥ 2.5 μm) tend to deposit in the upper airway and are cleared more rapidly (via mucociliary transport) than smaller particles that can deposit in the lower lung, where clearance times depend more on solubility (i.e., less soluble particles will be cleared more slowly) (*citing* a study denoted there as Brain *et al.,* 1994 and listed in the references section). *Id.*

46 *See* HHS Guidelines at Part II.I Section VII.

47 The Concept Document stated: "Based on a preliminary review of the literature, the mechanistic database is smaller and less established than for other metals, although antimony appears to be associated with some similar biological activities as other metals, such as oxidative damage." Concept Document at 9.

proof NTP employed to conclude that sufficient potential for harm exists cannot be discerned. It appears that because such potential cannot be specified within an identifiable range of probabilities, NTP has opted for a level of caution that will cover the indeterminable. If this was the approach, it lacks the necessary articulation or justification. We also must ask why NTP rushed into this conclusion in the absence of a more robust and informative database when the EU's study initiative for antimony was known.[48] Alignment with the EU process, or at least NTP's staying its hand, would have far better served the IQA's utility principle.

Precedents That Support a Limited Listing

In support of the limitation of the NTP recommendation language sought by i2a, the December 2018 Letter to Dr. Lunn provided a number of precedents to show that a recommendation or listing need not be couched in blanket terms. The text of that discussion (including the original footnotes[49]), which supports this RfC as well, is inserted verbatim as follows:

* * * * *

Opting to narrow the scope of the recommendations for Sb_2O_3 finds support in past practice by NTP and such other authoritative bodies as California's Office of Environmental Health Hazard Assessment (OEHHA). Prior RoCs contain recommendations that are limited or otherwise qualified in some ways; the precedent clearly exists, as does ample precedent for specifying inhalation exposure routes. The chemical substances involved include crystalline silica; certain glass wool fibers; ceramic fibers; and, most recently, cobalt and cobalt compounds.

Looking more specifically at these particular recommendations, "Silica, Crystalline (Respirable Size)" was listed first in the 6th RoC in 1991 and revisited in the 9th RoC in 2000, when it was revised to "known to be a human carcinogen." Found primarily in the form of quartz dusts occurring in industrial settings, according to the RoC, the listing for crystalline silica was limited to "respirable size," as noted above. Likewise, the recommendation that ceramic fibers were "reasonably anticipated to be human carcinogens" in the 7th RoC (1994) also was specifically limited to those of "respirable size." NTP studied closely the size and properties of glass wool fibers before listing "Glass Wool (Respirable Size)" as "reasonably anticipated to be a human carcinogen" in the 7th RoC; after additional studies were conducted to

48 *See* footnote 13 and the accompanying text, above.

49 The original footnotes have been renumbered to harmonize with those that surround them in this document.

evaluate the physicochemical properties of those fibers related to carcinogenicity, the listing caption was changed to "Certain Glass Wool Fibers (Inhalable)," in the 12th RoC (2011).[50]

The 2016 listing for cobalt and cobalt compounds in the 14th RoC was the culmination of a process that began with the nomination of cobalt in 2013 and demonstrates that

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[50] The discussion in the 12th RoC of the size and properties of the fibers that were the subject of the recommendation, rather than painting with a broad brush, was quite specific: "[t]he class of glass wool fibers consists of fine glass fibers forming a mass resembling wool; individual fibers are defined as being over 5 μm long and having a length-to-width (aspect) ratio of at least 3:1 (i.e., the fiber is at least three times as long as its width) (Walton 1982, Breysse et al. 1999). There is considerable variation in the physicochemical properties of individual fibers within this class, depending on the manufacturing process and end use. Glass fibers can be classified into two categories based on end use: insulation and special purpose (see Use, below). The physicochemical properties within each category also vary, and there is some overlap of properties between the two use categories. Moreover, a specific glass wool product often contains fibers with a wide range of diameters, as a result of the manufacturing process (see Properties, below, for a discussion of nominal diameter). For cancer hazard identification, it is important that fibers be classified according to their biological activity. For the purpose of this profile, 'inhalable' fibers include all fibers that can enter the respiratory tract. Inhalable fibers are of concern because most human lung cancer occurs within the first five generations of the tracheobronchial tree (Quinn et al. 1997, Husain 2010). The class of glass wool fibers consists of fine glass fibers forming a mass resembling wool; individual fibers are defined as being over 5 μm long and having a length-to-width (aspect) ratio of at least 3:1 (i.e., the fiber is at least three times as long as its width) (Walton 1982, Breysse et al. 1999). There is considerable variation in the physicochemical properties of individual fibers within this class, depending on the manufacturing process and end use. Glass fibers can be classified into two categories based on end use: insulation and special purpose (see Use, below). The physicochemical properties within each category also vary, and there is some overlap of properties between the two use categories. Moreover, a specific glass wool product often contains fibers with a wide range of diameters, as a result of the manufacturing process (see Properties, below, for a discussion of nominal diameter). For cancer hazard identification, it is important that fibers be classified according to their biological activity. For the purpose of this profile, 'inhalable' fibers include all fibers that can enter the respiratory tract. Inhalable fibers are of concern because most human lung cancer occurs within the first five generations of the tracheobronchial tree (Quinn et al. 1997, Husain 2010)."

NTP can and will not only change but will eventually limit the final recommendation.[51] By the time that NTP issued a Concept Document and a Protocol, both in October 2014, the scope of the candidate substance had been expanded to encompass "Cobalt and Certain Cobalt Compounds," with "certain" referring to "cobalt metal, those compounds that release cobalt ion or are cobalt particles" and excluding compounds with confounding exposures. The listing category continued to evolve, however. Based on what was described as "expert input" at the Cobalt Information Group Meeting, it was suggested that the listing generally "be limited to cobalt compounds that produce cobalt ions in vivo." This change was reflected in documents prepared as the RoC development continued. While the June 2015 draft Monograph was titled "Peer-Review Draft: Report on Carcinogens Monograph on Cobalt and Certain Cobalt Compounds," by the time the November 2015 revised draft Monograph was released, the change in the title also reflected the agreed-upon limitation -- "Report on Carcinogens Monograph on Cobalt and Cobalt Compounds That Release Cobalt Ions *In Vivo*." Ultimately, that was the designation of the narrowed category that was adopted in the 14th RoC.

Beyond NTP's past practices in developing the RoCs, there are numerous instances as well of California's OEHHA limiting the scope of its listings based with some specificity on particle nature, respirable size, or length. Under Proposition 65, OEHHA over the years has made many listings that are subject to one or more of these limitations. In some of those instances, the listing is specifically limited to powder or dust and thus also supports what i2a is requesting here. Examples of Proposition 65 listings that illustrate the foregoing include the following:

- Carbon black (airborne, unbound particles of respirable size) (2/21/03): https://oehha.ca.gov/proposition-65/chemicals/carbon-black-airborne-unbound-particles-respirable-size;

- Ceramic fibers (airborne particles of respirable size) (7/1/90): https://oehha.ca.gov/proposition-65/chemicals/ceramic-fibers-airborne-particles-respirable-size;

- Chlorinated paraffins (average chain length, C12; approximately 60 percent chlorine by weight) (7/1/89): https://oehha.ca.gov/proposition-65/chemicals/chlorinated-paraffins-avg-chain-length-c12-approx-60-percent-chlorine;

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51 *See* RoC Review of Cobalt and Cobalt Compounds that Release Cobalt Ions In Vivo, available at https://ntp.niehs.nih.gov/pubhealth/roc/listings/cobalt/index.html.

- Cobalt metal powder (7/1/92): https://oehha.ca.gov/proposition-65/chemicals/cobalt-metal-powder;
- Glass wool fibers (inhalable and biopersistent) (7/1/90): https://oehha.ca.gov/proposition-65/chemicals/glass-wool-fibers-inhalable-and-biopersistent;
- Leather dust (4/29/11): https://oehha.ca.gov/proposition-65/chemicals/leather-dust;
- Nickel refinery dust from the pyrometallurgical process (10/1/87): https://oehha.ca.gov/proposition-65/chemicals/nickel-refinery-dust-pyrometallurgical-process;
- Palygorskite fibers (> 5µm in length) (12/28/99): https://oehha.ca.gov/proposition-65/chemicals/palygorskite-fibers-5um-length;
- Silica, crystalline (airborne particles of respirable size) (10/1/88): https://oehha.ca.gov/proposition-65/chemicals/silica-crystalline-airborne-particles-respirable-size;
- Titanium dioxide (airborne, unbound particles of respirable size) (9/2/11): https://oehha.ca.gov/proposition-65/chemicals/titanium-dioxide-airborne-unbound-particles-respirable-size;
- Vanadium pentoxide (orthorhombic crystalline form) (2/11/05): https://oehha.ca.gov/proposition-65/chemicals/vanadium-pentoxide-orthorhombic-crystalline-form; and
- Wood dust (12/18/09): https://oehha.ca.gov/proposition-65/chemicals/wood-dust.

In light of the discussion above and the content of the Monograph itself, i2a believes that there is a substantial and legally compelling basis for NTP to limit its recommendations for Sb(III) as requested in this letter, and we urge it to pursue that change. Should NTP opt not to implement the requested modifications, NTP needs to provide stakeholders, regulators, other authoritative bodies, and the interested public an explanation as to why the open-ended recommendation was retained. The prospect of reliance by regulators on what NTP has recommended, and the implications for manufacturers, sellers, and consumers,

especially if the production and use of flame-retardant products should be compromised, would merit a more clearly articulated and adequately supported foundation. Adoption of the refinement that i2a suggests would obviate this concern.[52]

* * * * *

While Dr. Lunn's March 2019 letter also rejected the relevance of the above-cited listing precedents, i2a believes that they supported its December 2018 request to NTP, as well as this RfC. Where a qualified listing (or "recommendation") is a more appropriate fit for the data, opting for a blanket listing detracts from its utility.

Role of Exposure

A separate and further compelling reason why this RfC should be granted is grounded in NTP's stated viewpoint that a RoC listing will be used by regulators simply for identifying a substance as a cancer hazard without reference to exposure considerations. As Dr. Lunn put it in her March 2019 response to i2a's December 2018 Letter:

> While a listing in the RoC identifies a substance as a cancer hazard, the RoC does not estimate cancer risks to individuals associated with exposures in their daily lives or attempt to rank listed substances according to their potency. Considering the exposure route and particle size, as you propose for the antimony trioxide listing, would be part of a formal risk assessment. Risk assessments are not within the RoC's purview. Rather, federal, state, and local health agencies are responsible for such risk assessments.[53]

NTP has cited this rationale to support the denial of past RfCs, and it reflects the HHS's IQA guidelines.[54] Nonetheless, it is a facile and unsatisfying one in the larger context of

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52 December 2018 Letter at 4-7. The foregoing text concludes the discussion inserted from the Letter into this RfC.

53 March 2019 Lunn Response Letter at 1.

54 The HHS Guidelines, in Part II.I Section VII, state: "With respect to health, safety, and environmental information, NIH does not have a mandate to conduct formal risk assessments, which are the purview of the appropriate Federal, State, and local health regulatory and research agencies [citing Guideline Section V.2.iv]."

how regulatory systems and business entities work. NTP is considered an authoritative body in its pronouncements about substances it considers to be, or reasonably anticipates to be, carcinogenic. The absence of an accompanying risk assessment is not highlighted when the carcinogenicity listing is disseminated to the public. Indeed, specification of an exposure pathway or particle size range of concern is not a risk assessment -- it is a hazard identification statement that seeks to define the exposure conditions and material characteristics associated with potential carcinogenic hazard. As noted earlier, past NTP listing decisions for silica, glass wool, and cobalt/cobalt compounds have established precedents for the use of exposure considerations in the refinement of hazard classification conclusions. The classification of cobalt and cobalt compounds based upon metal ion release in vivo merits particular attention, providing yet another demonstration that exposure considerations can be integral to refinement of the hazard classification process.

Once NTP makes known how it characterizes the carcinogenicity of a substance, regulatory agencies further disseminate the cancer designation whether or not they end up performing a full risk assessment for purposes of specific actions. To workers, business entities, and non-governmental organizations (NGO), the label connotes danger and liability when actual exposure situations may be extraordinarily unlikely.

The opportunity benefits of antimony trioxide as a flame-retardant synergist, including the life-saving potential of the product in which it is incorporated, easily could be eclipsed, misleadingly, by the carcinogenic label, even if "only" reasonably anticipated to be such. In a practical sense, however, the hazard does not exist in isolation. Exposure is the other essential part of the equation. Not everyone is a scientist, and not everyone is knowledgeable about the role of a formal risk assessment and about what the absence of a risk assessment actually means. Even if formal risk assessment is not within NTP's portfolio in listing substances for RoC purposes, qualifying a listing to reflect the state of the database is certainly justified if not legally mandated. The public, and even most regulators, will be as aware of the relative strength of the database or of the data gaps relating to antimony trioxide as NTP is. If NTP could have refined its listing to reflect better the data, it is appropriate to call it out on IQA grounds for its failure to take that step. As currently written, NTP's recommended categorization is materially less useful than it could be if the listing were qualified as i2a seeks.

Beyond this, too, is the reality that exposure considerations, even if not addressed in the context of a full-scale risk assessment, run throughout the NTP review process that culminates in a determination of whether a substance is deemed carcinogenic. It is indeed impossible to separate exposure considerations from the body of the review. Exposure is mentioned throughout the documentation, and even though it does not drive the nature of the review, is intertwined with it.

Thus, for NTP to demur from considering the form of exposure to a substance in preparing its recommendation denies this relationship in a way that simply makes no sense on reading the record. For example, the initial section of NTP's Concept Document is devoted to "Human exposure."[55] The subsequent July 2017 Protocol Document, in its Section 2, "Methods for Evaluating Chemical Properties and Human Exposure," poses the following "Key questions":

- What are the sources of exposure? How are people exposed to antimony compounds?
- Is a significant number of people residing in the United States exposed to antimony?
- What are the antimony chemical forms that occur in human exposure? Can the current analytical methods and available monitoring studies address this question? [56]

Likewise, NTP's Protocol Document, in Section 3, "Methods for Evaluating Human Cancer," states that the human cancer hazard component of the Draft Monograph would evaluate "relevant epidemiologic studies on antimony *exposure* and cancer."[57] As it transpired, NTP could not rely on human epidemiological studies in its review of antimony trioxide, but its protocol acknowledges the obvious -- that "hazard" is made meaningful only in the presence of "exposure." The potential link between exposure and cancer hazard also runs through the "Key questions" NTP poses in this portion of the Protocol Document[58] and continues relevant as the

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55 Concept Document, Section 1 (including Subsections 1.1.1 – 1.1.4), at 4-7; *see also id.* Section 1.2 at 7. The same document depicts that in the vast majority of the rodent studies on antimony trioxide, the exposure pathway was via inhalation. *Id*. Section 2.2, Table 2, at 8-9.

56 NTP, Report on Carcinogens Protocol: Methods for Preparing the Draft Report on Carcinogens Monograph on Antimony Trioxide and Other Antimony Compounds (July 28, 2017) at 3, available at https://ntp.niehs.nih.gov/ntp/roc/protocols/antimonytrioxide_508.pdf (Protocol Document). The Protocol Document also specifies a "Literature search strategy for exposure." *Id*., Table 2-1.

57 *Id*. at 4 (emphasis added).

58 *Id*.

discussion proceeds. It also appears, inevitably, in the discussion of exposure pathways and dosages in the animal studies.

The Final Monograph in which the NTP review culminated devotes an entire section of just under 20 pages to "Human Exposure."[59] Thus, while the Office of the RoC has declined to limit its recommendations for antimony trioxide to account for specific, valid exposure conditions, the justification that exposure considerations must be left to regulators down the road does not hold up. Even without a full risk assessment, NTP's own documents show that exposure is part and parcel of the hazard evaluation process. This further supports the proposition that the RfC should be granted and that NTP's rejection on this ground is not a viable response.

OMB's 2019 Improving IQA Implementation Memorandum

Earlier this year, OMB issued a rare update to its IQA in the form of a memorandum to the heads of executive branch departments and agencies. With its stated purpose "to reinforce, clarify, and interpret agency responsibilities" under the IQA, OMB issued the memorandum because "additional guidance is required to address changes in the information landscape and to incorporate best practices developed over time."[60] Section 4 of the 2019 Improving IQA Implementation Memorandum specifically addresses RfCs, and certain of the implementation updates set out there have particular resonance for this Request, as follows:

(i) *Implementation Update 4.5* states: "To ensure the integrity of the appeals process, agencies should ensure that those individuals reviewing and responding to the appeals request were not involved in the review and initial response to the RFC."[61]

While *Implementation Update 4.5* specifically addresses appeals of an agency's (presumably unfavorable) disposition of an RfC, in the circumstances here it should apply to the consideration of the RfC itself. NTP already has rejected i2a's December 4, 2018, request to modify the recommendations in the Monograph to reflect more accurately the NTP-referenced database on the carcinogenic potential of antimony trioxide. Dr. Lunn's March 14, 2019, response did not indicate that she and her colleagues had given more than superficial attention to

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59 Monograph at 11-28.

60 2019 Improving IQA Implementation Memorandum at 1. See the initial citation for the Memorandum above, at footnote 6 of this RfC.

61 *Id*. at 10.

the reasoning that underlays i2a's request or that they were open to revisiting with fresh eyes the limitations of what the data would support. We have no reason to believe that an RfC reviewed by the same personnel who were involved in the preparation of the 2017 NTP Study Report or the Monograph or who likely assisted Dr. Lunn in reviewing and rejecting the refinements to the Monograph suggested in i2a's December 2018 Letter, would approach this RfC with open minds.

Accordingly, we request assurance that the personnel involved in preparing the RoC recommendation in the Monograph or the NTP materials that underlay it are not involved in preparing the response to the RfC. The staff reviewing the RfC should be independent and sufficiently senior that they can effectively disagree with their NTP colleagues who prepared the RoC, should they be persuaded that disagreement is warranted, as we believe is the case here. In addition, the appropriate official (whether Dr. Lunn as Director, or, preferably, a more detached overseer) must be able to document that she has created an effective mechanism to ensure that the issues raised in the RfC have been given independent consideration by a competent and fair-minded panel of referees. Otherwise, the consideration and disposition of this RfC will not satisfy the requirements of *Implementation Update 4.5*, in that the objectivity of the response is compromised. Further, this appropriate official should provide a description of the procedure in place to handle correction requests as they pertain to information disseminated by the Office of the RoC. As the saying goes, "The pitcher cannot call the balls and strikes." Consequently, it is absolutely critical that the RfC be evaluated by individuals who had no role in preparing the RoC recommendation.

(ii) *Implementation Updates 4.2, 4.3, and 4.4* all go to the instruction that agencies are to share draft responses to RfCs with OMB prior to their release.

Implementation Update 4.2 states: "In its response to an RFC, agencies should not opine on the requestor's or the agency's policy position."

Implementation Update 4.3 states: "The agency response should contain a point-by-point response to any data quality arguments contained in the RFC and should refer to a peer review that directly considered the issue being raised, if possible."

Implementation Update 4.4 states: "Agencies should share draft responses to RFCs and appeals with OMB prior to release to the requestor for assessment of compliance with the above norms."[62]

62 *Id*.

In connection with the above, i2a urges that NTP's satisfaction of *Implementation Update 4:3* include an indication whether the peer review committee actually considered the issue raised in the RfC. It is essential that it clearly be stated whether or not the peer review committee actually considered the issue of limiting the scope of the Monograph recommendation to the actual chemical species and route of exposure shown to be carcinogenic. If the peer review committee did not specifically address the issue raised in the RfC, then the corresponding IQA implementation requirement has not been met.

(iii) *Implementation Update 4.1* goes to processing timelines and states: "Agencies should revise their procedures to reflect more realistic timelines for RFCs. Revised procedures should, at a minimum, provide that agencies will not take more than 120 days to respond to an RFC without the concurrence of the party that requested the request for correction."[63]

OMB admonished against the practice of agencies "frequently unilaterally extend[ing] their own deadlines for replying" to an RfC, "taking a year or more to provide a substantive response."[64] In the case of this RfC, even 120 days appears excessive to address the issue presented, especially given that the HHS Guidelines state that NIH will respond to all requests for corrections within 60 calendar days of receipt.[65] With the adverse impacts of the recommendation in the Monograph already in play, and with the above-noted EU review underway, time is of the essence in resolving the correction request.

Conclusion

Through its dissemination to the public and to state, federal, and international regulatory agencies of an unlimited characterization of the hazards posed by antimony trioxide, NTP has fallen far short of satisfying the IQA's "utility" principle. One of the components of "information quality," "utility," means "the usefulness of the information to its intended users," whether public or governmental.[66] For the reasons discussed in this RfC, the characterization of antimony trioxide in the Monograph and in the NTP documents on which it is based do not serve or satisfy that "utility" principle. The reality of the hazards posed by antimony trioxide is

63 *Id*.

64 *Id*.

65 HHS Guidelines at Part II.I Section VI.

66 67 Fed. Reg. at 8459.

presented along with those hazards arising in settings, and through exposure routes, that do not realistically occur.

Unless the characterization of antimony trioxide in the Monograph is refined and until it rests on a more complete database, it is difficult to understand how it can be useful to regulatory bodies or the public. As presented, the characterization instead threatens to be counterproductive in its impacts. If the recommendation remains open-ended and thus covers exposures of any magnitude to antimony trioxide in any form, and via any exposure route, the practical effect may well be to open the door to regulating the compound to such an extent that its viable uses as a flame retardant, among others, are compromised. Accordingly, i2a believes it would be sound, appropriate, and scientifically necessary for NTP to correct its recommendation for antimony trioxide by limiting it to the powder form of the compound only and the inhalation exposure route.

i2a appreciates consideration of this request and would be pleased to address any questions you might have or provide additional information.

Sincerely,

Lynn L. Bergeson

Bethami Auerbach

Attachments
cc: Ruth M. Lunn, Dr.P.H. (w/attachments) (via e-mail)
Director, Office of the Report on Carcinogens
National Institutes of Health
U.S. Department of Health and Human Services

Attachment 1

Lynn L. Bergeson
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BERGESON & CAMPBELL PC

December 3, 2018

Via E-Mail

Ruth M. Lunn, Dr.P.H.
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National Institutes of Health
U.S. Department of Health and Human Services
P.O. Box 12233
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Re: RoC Review of Antimony Trioxide

Dear Dr. Lunn:

This letter is submitted on behalf of the International Antimony Association (i2a) following the October 9, 2018, meeting of the Board of Scientific Counselors (BSC) and the October 19, 2018, release by the Office of the Report on Carcinogens (RoC) of the RoC's final Monograph on Antimony Trioxide (Monograph). As you and your colleagues are aware from our previous submissions and our close attention as stakeholders, i2a has followed from the start the National Toxicology Program's (NTP) cancer hazard assessment review process for antimony trioxide (Sb_2O_3 or Sb(III)) for possible listing in the RoC. At this juncture, i2a believes it would be sound, appropriate, and scientifically necessary for NTP to refine its contemplated recommendation for Sb(III) by limiting it to the powder form of the compound only and the inhalation exposure route.

The current Monograph language is as follows:

> NTP recommends that antimony trioxide is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting evidence from mechanistic studies. The data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure specifically to Sb_2O_3 or antimony in general.

We request that NTP revise the above-quoted language to read either as stated in Option 1 or Option 2, with the added language in italics, as follows:

> Option 1: NTP recommends that antimony trioxide, *in the form of respirable powder** is reasonably anticipated to be a human carcinogen *by inhalation* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting evidence from mechanistic studies. The data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure specifically to Sb_2O_3 or antimony in general.
> ** Powders of particle size at or below 4 µm*.

> Option 2: NTP recommends that antimony trioxide, *in the form of respirable powders with a particle size at or below 4 µm*, is reasonably anticipated to be a human carcinogen *by inhalation* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting evidence from mechanistic studies. The data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure specifically to Sb_2O_3 or antimony in general.

The narrower focus of the recommendation better reflects the data, the physical properties of the compound used in inhalation studies, discussion in the Monograph, the literature, and the public comments of the exposure hazard associated with Sb_2O_3 than does the current, open-ended language. Whether in the workplace or where the general population is concerned, the predominant sources of exposure identified in those materials are via inhalation. Uptake after dermal or oral exposure is extremely limited. Moreover, 90 oral feeding studies with Sb_2O_3 have not exhibited carcinogenicity or toxicity[1] at the tissues' sites suggested to be targets for cancer in the NTP studies. If the recommendation remains open-ended and thus covers exposures of any magnitude to Sb_2O_3 in any form, and via any exposure route, the practical effect may well be to open the door to regulating the compound to such an extent that its viable uses as a flame retardant, among others, are compromised.

[1] Hext PM, Pinto PJ, Rimmel BA (1999). Subchronic feeding study of antimony trioxide in rats. *J. Appl. Toxicol.* 19:205-209.

As the Monograph acknowledges, while much is known about properties and effects of Sb_2O_3, the database is not complete and human study data are inadequate to underpin a conclusion about the relationship between exposure and incidences of cancer in humans. These circumstances, of course, do not preclude NTP from reaching conclusions based on animal studies and other evidence, but they are one of the reasons for exercising care and precision in crafting NTP's recommendations. Caution in analysis and interpretation is particularly important when lesion induction is also suggested (*e.g.*, pheochromocytomas in rats or lymphomas in mice) for endpoints not observed in other studies and for which responses are believed to arise as an indirect reaction to the direct impacts of inhalation mediated pulmonary toxicity.[2]

An overly broad recommendation risks running afoul of the Information Quality Act (IQA)[3] and the implementing guidelines issued by the Office of Management and Budget (OMB),[4] which are binding on all federal agencies and also are reflected in the parallel guidelines to which U.S. Department of Health and Human Services agencies are subject. Adherence to the guidelines and to the purposes they are intended to serve is especially crucial where "influential scientific, financial, or statistical information" is involved. As OMB observed, "[t]he more important the information, the higher the quality standards to which it should be held," with such "influential" information cited as the example."[5]

"Influential" describes a situation in which "the agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact on important public policies or important private sector decisions."[6] It captures precisely the information disseminated by way of NTP's conclusions as to the carcinogenicity of a chemical substance that is included in a RoC; among other impacts, regulatory agencies are likely to treat NTP's recommendations as authoritative in their own decision-making on whether a substance is

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2 Greim H, Hartwig A, Reuter U, Richter-Reichhelm HB, Thielmann HW (2009). Chemically induced pheochromocytomas in rats: mechanisms and relevance for human risk assessment. *Crit. Rev. Toxicol.* 39(8):695-718; Ward JM (2006). Lymphomas and leukemias in mice. *Exp. Toxicol. Pathol.* 57(5-6):377-381.

3 Section 515, Treasury and General Government Appropriations Act for Fiscal Year 2001 (Public Law 106-554; H.R. 5658).

4 67 Fed. Reg. 8451 (Feb. 22, 2002) (republished and corrected version).

5 *Id.* at 8452.

6 *Id.* at 8455.

carcinogenic and, if so, how to regulate or otherwise restrict it. An overly broad recommendation from NTP that the evidence does not persuasively support will open the door to over-regulation of that substance by an agency proceeding on the basis of that recommendation. An unnecessarily broad delineation of the substance involved also, for obvious reasons, will run contrary to the IQA principle of "utility," a component of "quality" that refers to "the usefulness of the information to its intended users," whether public or governmental.[7]

Opting to narrow the scope of the recommendations for Sb_2O_3 finds support in past practice by NTP and such other authoritative bodies as California's Office of Environmental Health Hazard Assessment (OEHHA). Prior RoCs contain recommendations that are limited or otherwise qualified in some ways; the precedent clearly exists, as does ample precedent for specifying inhalation exposure routes. The chemical substances involved include crystalline silica; certain glass wool fibers; ceramic fibers; and, most recently, cobalt and cobalt compounds.

Looking more specifically at these particular recommendations, "Silica, Crystalline (Respirable Size)" was listed first in the 6th RoC in 1991 and revisited in the 9th RoC in 2000, when it was revised to "known to be a human carcinogen." Found primarily in the form of quartz dusts occurring in industrial settings, according to the RoC, the listing for crystalline silica was limited to "respirable size," as noted above. Likewise, the recommendation that ceramic fibers were "reasonably anticipated to be human carcinogens" in the 7th RoC (1994) also was specifically limited to those of "respirable size." NTP studied closely the size and properties of glass wool fibers before listing "Glass Wool (Respirable Size)" as "reasonably anticipated to be a human carcinogen" in the 7th RoC; after additional studies were conducted to evaluate the physicochemical properties of those fibers related to carcinogenicity, the listing caption was changed to "Certain Glass Wool Fibers (Inhalable)," in the 12th RoC (2011).[8]

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7 *Id.* at 8459.

8 The discussion in the 12th RoC of the size and properties of the fibers that were the subject of the recommendation, rather than painting with a broad brush, was quite specific: "[t]he class of glass wool fibers consists of fine glass fibers forming a mass resembling wool; individual fibers are defined as being over 5 μm long and having a length-to-width (aspect) ratio of at least 3:1 (i.e., the fiber is at least three times as long as its width) (Walton 1982, Breysse et al. 1999). There is considerable variation in the physicochemical properties of individual fibers within this class, depending on the manufacturing process and end use. Glass fibers can be classified into two categories based on end use: insulation and special purpose (see Use, below). The physicochemical properties within each category also vary, and there is some overlap of properties between the two use categories. Moreover, a specific glass wool product often contains fibers with a wide range of diameters, as a result of the manufacturing process (see

The 2016 listing for cobalt and cobalt compounds in the 14th RoC was the culmination of a process that began with the nomination of cobalt in 2013 and demonstrates that NTP can and will not only change but will eventually limit the final recommendation.[9] By the time that NTP issued a Concept Document and a Protocol, both in October 2014, the scope of the candidate substance had been expanded to encompass "Cobalt and Certain Cobalt Compounds," with "certain" referring to "cobalt metal, those compounds that release cobalt ion or are cobalt particles" and excluding compounds with confounding exposures. The listing category continued to evolve, however. Based on what was described as "expert input" at the Cobalt Information Group Meeting, it was suggested that the listing generally "be limited to cobalt compounds that produce cobalt ions in vivo." This change was reflected in documents prepared as the RoC development continued. While the June 2015 draft Monograph was titled "Peer-Review Draft: Report on Carcinogens Monograph on Cobalt and Certain Cobalt Compounds," by the time the November 2015 revised draft Monograph was released, the change in the title also reflected the agreed-upon limitation -- "Report on Carcinogens Monograph on Cobalt and

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Properties, below, for a discussion of nominal diameter). For cancer hazard identification, it is important that fibers be classified according to their biological activity. For the purpose of this profile, 'inhalable' fibers include all fibers that can enter the respiratory tract. Inhalable fibers are of concern because most human lung cancer occurs within the first five generations of the tracheobronchial tree (Quinn et al. 1997, Husain 2010). The class of glass wool fibers consists of fine glass fibers forming a mass resembling wool; individual fibers are defined as being over 5 μm long and having a length-to-width (aspect) ratio of at least 3:1 (i.e., the fiber is at least three times as long as its width) (Walton 1982, Breysse et al. 1999). There is considerable variation in the physicochemical properties of individual fibers within this class, depending on the manufacturing process and end use. Glass fibers can be classified into two categories based on end use: insulation and special purpose (see Use, below). The physicochemical properties within each category also vary, and there is some overlap of properties between the two use categories. Moreover, a specific glass wool product often contains fibers with a wide range of diameters, as a result of the manufacturing process (see Properties, below, for a discussion of nominal diameter). For cancer hazard identification, it is important that fibers be classified according to their biological activity. For the purpose of this profile, 'inhalable' fibers include all fibers that can enter the respiratory tract. Inhalable fibers are of concern because most human lung cancer occurs within the first five generations of the tracheobronchial tree (Quinn et al. 1997, Husain 2010)."

9 *See* RoC Review of Cobalt and Cobalt Compounds that Release Cobalt Ions In Vivo, available at https://ntp.niehs.nih.gov/pubhealth/roc/listings/cobalt/index.html.

Cobalt Compounds That Release Cobalt Ions *In Vivo*." Ultimately, that was the designation of the narrowed category that was adopted in the 14th RoC.

Beyond NTP's past practices in developing the RoCs, there are numerous instances as well of California's OEHHA limiting the scope of its listings based with some specificity on particle nature, respirable size, or length. Under Proposition 65, OEHHA over the years has made many listings that are subject to one or more of these limitations. In some of those instances, the listing is specifically limited to powder or dust and thus also supports what i2a is requesting here. Examples of Proposition 65 listings that illustrate the foregoing include the following:

- Carbon black (airborne, unbound particles of respirable size) (2/21/03): https://oehha.ca.gov/proposition-65/chemicals/carbon-black-airborne-unbound-particles-respirable-size;

- Ceramic fibers (airborne particles of respirable size) (7/1/90): https://oehha.ca.gov/proposition-65/chemicals/ceramic-fibers-airborne-particles-respirable-size;

- Chlorinated paraffins (average chain length, C12; approximately 60 percent chlorine by weight) (7/1/89): https://oehha.ca.gov/proposition-65/chemicals/chlorinated-paraffins-avg-chain-length-c12-approx-60-percent-chlorine;

- Cobalt metal powder (7/1/92): https://oehha.ca.gov/proposition-65/chemicals/cobalt-metal-powder;

- Glass wool fibers (inhalable and biopersistent) (7/1/90): https://oehha.ca.gov/proposition-65/chemicals/glass-wool-fibers-inhalable-and-biopersistent;

- Leather dust (4/29/11): https://oehha.ca.gov/proposition-65/chemicals/leather-dust;

- Nickel refinery dust from the pyrometallurgical process (10/1/87): https://oehha.ca.gov/proposition-65/chemicals/nickel-refinery-dust-pyrometallurgical-process;

- Palygorskite fibers (> 5µm in length) (12/28/99):

https://oehha.ca.gov/proposition-65/chemicals/palygorskite-fibers-5um-length;

- Silica, crystalline (airborne particles of respirable size) (10/1/88): https://oehha.ca.gov/proposition-65/chemicals/silica-crystalline-airborne-particles-respirable-size;

- Titanium dioxide (airborne, unbound particles of respirable size) (9/2/11): https://oehha.ca.gov/proposition-65/chemicals/titanium-dioxide-airborne-unbound-particles-respirable-size;

- Vanadium pentoxide (orthorhombic crystalline form) (2/11/05): https://oehha.ca.gov/proposition-65/chemicals/vanadium-pentoxide-orthorhombic-crystalline-form; and

- Wood dust (12/18/09): https://oehha.ca.gov/proposition-65/chemicals/wood-dust.

In light of the discussion above and the content of the Monograph itself, i2a believes that there is a substantial and legally compelling basis for NTP to limit its recommendations for Sb(III) as requested in this letter, and we urge it to pursue that change. Should NTP opt not to implement the requested modifications, NTP needs to provide stakeholders, regulators, other authoritative bodies, and the interested public an explanation as to why the open-ended recommendation was retained. The prospect of reliance by regulators on what NTP has recommended, and the implications for manufacturers, sellers, and consumers, especially if the production and use of flame-retardant products should be compromised, would merit a more clearly articulated and adequately supported foundation. Adoption of the refinement that i2a suggests would obviate this concern.

We hope this discussion is helpful. As always, we would be happy to address any questions you or your colleagues may have or provide additional information.

Sincerely,

Lynn L. Bergeson

Bethami Auerbach

cc: Amy Wang (Hui Shan Wang), Ph.D. (via e-mail)
Health Scientist, Office of the Report on Carcinogens (ORoC)
Division of National Toxicology Program (DNTP)
National Institute of Environmental Health Sciences (NIEHS)

Mary S. Wolfe, Ph.D. (via e-mail)
Deputy Division Director for Policy
Director, Office of Liaison, Policy, and Review, NIEHS

North American Flame Retardants Alliance (NAFRA) (via e-mail)

PET Resin Association (PETRA) (via e-mail)

National Association for PET Container Resources (NAPCOR) (via e-mail)

Battery Council International (via e-mail)

Attachment 2

NATIONAL TOXICOLOGY PROGRAM
U.S. Department of Health and Human Services

NATIONAL INSTITUTE OF
ENVIRONMENTAL HEALTH SCIENCES
111 T.W. ALEXANDER DRIVE
P.O. BOX 12233
RESEARCH TRIANGLE PARK, NC 27709

March 14, 2019

Lynn L. Bergeson
Bergeson & Campbell, PC
2200 Pennsylvania Avenue, NW, Suite 100W
Washington, DC 20037

Dear Ms. Bergeson:

Thank you for your letter on behalf of the International Antimony Association regarding the National Toxicology Program's (NTP) recommended listing status of antimony trioxide in the Report on Carcinogens (RoC) as *reasonably anticipated to be a human carcinogen*. We understand that you want the listing of antimony trioxide to be limited to inhalation exposure of particles of a specific size. To address your specific comments on antimony trioxide, we will provide general information from the RoC, the NTP review process, and specific information relevant to the recommended antimony trioxide listing.

The RoC is a congressionally mandated report that identifies agents, substances, mixtures, or exposure circumstances (collectively called "substances") that may pose a cancer hazard for people residing in the United States. Responsibility for preparing the RoC has been delegated to the NTP, an interagency program headquartered at the National Institute of Environmental Health Sciences of the National Institutes of Health. The NTP's review of antimony trioxide has been a rigorous process[1] based on unbiased and sound science, including multiple opportunities for public and technical comment, external peer review, and application of established listing criteria. The International Antimony Association has provided input to the review and the related peer-review meeting on several occasions, and we appreciate your interest in this important topic. Among the scientific issues raised by the International Antimony Association, in both written and oral comments to the peer review panel, were consideration of exposure route as a qualifier and particle overload in the lung. The peer review panel agreed unanimously with NTP's preliminary recommendation that antimony trioxide should be listed in the RoC as *reasonably anticipated to be a human carcinogen*. The panel did not recommend qualifying the listing by exposure route or particle size.

While a listing in the RoC identifies a substance as a cancer hazard, the RoC does not estimate cancer risks to individuals associated with exposures in their daily lives or attempt to rank listed substances according to their potency. Considering the exposure route and particle size, as you propose for the antimony trioxide listing, would be part of a formal risk assessment. Risk assessments are not within the RoC's purview. Rather, federal, state, and local health agencies are responsible for such risk assessments.

[1] RoC review process is available at https://ntp.niehs.nih.gov/pubhealth/roc/process/index-2.html

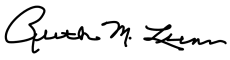
You note several examples of RoC listings that have a "narrow" or "qualified" scope: cobalt and cobalt compounds that release cobalt *in vivo*,[2] certain glass wool fibers (inhalable),[3] and silica, crystalline (respirable size).[4] We do not feel that these listings are analogous to the antimony trioxide listing for the following reasons:

- Qualification of the cobalt and glass wool listings in the RoC refers to limiting substances within the class based on strong mechanistic data, whereas you request to narrow the scope of the exposure conditions for a single chemical. Of note, the specific compounds or fibers in each listed class are not identified, as that would be part of a formal risk assessment by the relevant regulatory agencies.
    - For the cobalt-related listing, there is strong mechanistic data which indicates that the release of cobalt ions is a key event in cobalt-induced carcinogenicity.
    - For the glass wool listing, "certain" refers to fibers that are biopersistent in the lung or tracheobronchial area based on experimental animal studies showing that not all fibers are carcinogenic and mechanistic data indicating that biopersistence is a key factor for predicting carcinogenicity.
- The rationale for qualifying the RoC listing of silica is based largely on:
    - Evidence from human studies finding an association of an increased risk of cancer with exposure to respirable quartz and cristobalite but not to amorphous silica,[4] and;
    - Evidence from mechanistic studies showing persistence of silica in the lung leads to pathways of lung disease and cancer; deposition of particle size is related to their size.[5]

In contrast to these three RoC listings with a more developed database, the current mechanistic understanding of antimony trioxide carcinogenicity is insufficient to limit the scope of the antimony trioxide listing to a specific particle size or route of exposure.

Again, thank you for contacting us. Please do not hesitate to let me know if you have further questions or concerns. An identical letter has been sent to Ms. Bethami Auerbach.

Sincerely,



Ruth M. Lunn, Dr.P.H.
Director, Office of the Report on Carcinogens
Division of the NTP
National Institute of Environmental Health Sciences

[2] RoC substance profile is available at https://ntp.niehs.nih.gov/ntp/roc/content/profiles/cobalt.pdf
[3] RoC substance profile is available at https://ntp.niehs.nih.gov/ntp/roc/content/profiles/glasswoolfibers.pdf
[4] RoC substance profile is available at https://ntp.niehs.nih.gov/ntp/roc/content/profiles/silica.pdf
[5]RoC Background Document on Silica, Crystalline (Respirable Size) is available at https://ntp.niehs.nih.gov/ntp/newhomeroc/other_background/silica_no_app_508.pdf

Attachment 3

Lynn L. Bergeson
phone: 202.557.3801
lbergeson@lawbc.com

BERGESON & CAMPBELL PC B&C

April 24, 2019

Via E-Mail

Ruth M. Lunn, Dr.P.H.
Director, Office of the Report on Carcinogens
National Institutes of Health
U.S. Department of Health and Human Services
P.O. Box 12233
Mail Drop K2-14
Durham, North Carolina 27709

Re: RoC Review of Antimony Trioxide

Dear Dr. Lunn:

Thank you for taking the time to respond to our December 3, 2018, letter submitted on behalf of the International Antimony Association (i2a) concerning the final Monograph on Antimony Trioxide (Monograph), released several weeks prior by the Office of the Report on Carcinogens (RoC). The Monograph recommends that antimony trioxide (Sb(III)) be listed in the RoC as "reasonably anticipated to be a human carcinogen." Needless to say, we and the i2a are disappointed that your office was not receptive to the i2a's carefully considered suggestions as to how and why the contemplated across-the-board listing for Sb(III) should be limited to a specific physical form of the compound -- respirable powders with a particle size at or below 4 µm -- and to a specific exposure route -- inhalation.

You observe in your letter that the role of an RoC listing does not encompass the estimation of cancer risks to individuals through exposures in daily life and that listed substances are not ranked according to their potency. It is strictly correct to state that the role of exposure typically is left to the individual agencies when they take steps to regulate an RoC-listed substance. Those statements, however, overlook the real-world impacts of an RoC listing by the National Toxicology Program (NTP) as an authoritative body. As described in our earlier letter, there is ample precedent -- the essential relevance of which you inexplicably reject -- for NTP to limit or otherwise qualify its RoC listings, as well as to specify an inhalation exposure pathway.[1] Regulatory agencies are not unaware that limiting an RoC listing is an option, and NTP's

[1] Our letter enumerated as well many instances of California's Office of Environmental Health Hazard Assessment limiting the scope of its Proposition 65 listings based specifically on particle nature, respirable size, or length.

declining to do so sends a message that necessarily affects an agency's risk assessment for a chemical substance. What NTP states, or does not state, about the form of a substance or its exposure pathways may be reflected in a subsequent risk assessment by a regulatory body, taking its cue from NTP's approach. Where, as in the case of Sb(III), the all-inclusive listing rests on a paucity of human data and the underlying oral and dermal exposure data are scarce, it makes sense to refine the listing by basing it squarely on those data that actually are available and persuasive. Otherwise, regulatory agencies may begin their assessment processes on the unsupportable assumption that all forms of the compound pose similar risks in daily life, a conclusion plainly not supported by the data and a preventable over-reach that NTP can and should avert inviting.

In sum, i2a respectfully continues to differ with NTP on how the listing for Sb(III) should be presented, and it remains concerned about the ramifications for the regulatory process, as noted above and in our earlier letter. Sb(III), when combined with typically used halogenated flame retardant chemicals, allows for smaller quantities of those halogen chemicals to be incorporated into the resulting product, thereby increasing the overall chemical resource efficiency and environmental safety, without jeopardizing the essential flame retardancy performance. The chemicals are furthermore embedded and retained inside the polymeric matrix to which they are added. At the same time, inhalation of Sb(III) in particle form, to the extent it may occur at a few industrial workplaces, is amenable to mitigation through control measures, and i2a is an active proponent of those controls. NTP's rejection of i2a's proposal to focus the listing on known dangers -- indeed, on the only known dangers, based on the data -- ultimately could encourage the production of flame retardants comprised of relatively greater quantities of halogen chemicals that pose more risks. Going forward, i2a will continue to advocate for product stewardship and for a more realistic and scientifically robust understanding of Sb(III) before regulators, stakeholders, and the interested public.

Sincerely,

Lynn L. Bergeson

Bethami Auerbach

cc: Ms. Caroline Braibant (via e-mail)
Secretary-General
International Antimony Association

Amy Wang (Hui Shan Wang), Ph.D. (via e-mail)
Health Scientist, Office of the Report on Carcinogens
Division of National Toxicology Program
National Institute of Environmental Health Sciences (NIEHS)

Mary S. Wolfe, Ph.D. (via e-mail)
Deputy Division Director for Policy
Director, Office of Liaison, Policy, and Review, NIEHS

North American Flame Retardants Alliance (via e-mail)

PET Resin Association (via e-mail)

National Association for PET Container Resources (via e-mail)

Battery Council International (via e-mail)

Attachment 4

From: Caroline Braibant [mailto:caroline.braibant@antimony.com]
Sent: Wednesday, May 29, 2019 9:34 AM
To: Lunn, Ruth (NIH/NIEHS) [E]
Cc: Lynn L. Bergeson; Bethami Auerbach; Wang, Amy (NIH/NIEHS) [E]; Wolfe, Mary (NIH/NIEHS) [E]; Kathleen M. Roberts; Chad H. Howlin; Nathalie Francis; Marjorie Huppert; Craig Boreiko
Subject: RE: RoC Review of Antimony Trioxide: news from EU REACH Evaluation

Dear Dr Lunn,

Many thanks for your positive response!

We have responded to the REACH Evaluations yesterday and the preparation of updated Decisions is now in the hands of ECHA.
There is no timeline specified in the REACH Regulation text as to when the final Decision can be expected, but we have calculated that this may come between Spring and Autumn 2020.

Meanwhile, i2a is continuing its research strategy, which covers 10 Sb substances, as per the attached program, which has been refined to take into consideration the REACH Evaluation process steps.
The first lung toxicity research step ('blue' line of the program), the in vitro lung assay, should start this summer at the IOM in Edinburgh (UK). The German authorities have indicated that they "*appreciate this voluntary initiative for the in vitro studies on different Sb compounds. Results might give valuable additional input for read-across considerations and possible mechanisms of action.*" IOM is just ensuring that the assay meets the minimum quality guidelines to enhance its validity and acceptability for more formal scientific and regulatory processes, including NTP's. We would be happy to share the protocol if you wish to review it too.

Systemic effects will also be investigated, as you can see in the 'pink' line of the program.

Kind regards, and many thanks for considering this on-going research and the evidence it should bring to the table.

Caroline

From: Lunn, Ruth (NIH/NIEHS) [E] <lunn@niehs.nih.gov>
Sent: 29 May 2019 15:17
To: Caroline Braibant <caroline.braibant@antimony.com>
Cc: Lynn L. Bergeson <lbergeson@lawbc.com>; Bethami Auerbach <BAUERBACH@lawbc.com>; Wang, Amy (NIH/NIEHS) [E] <huishan.wang@nih.gov>; Wolfe, Mary (NIH/NIEHS) [E] <wolfe@niehs.nih.gov>; Kathleen M. Roberts <kroberts@lawbc.com>; Chad H. Howlin <chowlin@lawbc.com>; Nathalie Francis <nathalie.francis@antimony.com>; Marjorie Huppert <Marjorie.Huppert@antimony.com>
Subject: Re: RoC Review of Antimony Trioxide: news from EU REACH Evaluation

Dear Ms. Braibant,

Thank you for providing information concerning the European Chemical Agency's request for additional genotoxicity studies on antimony trioxide. We would welcome receiving the new information. Please let us know when the proposed studies are published.

Sincerely,

Ruth M. Lunn
Director, Office of the Report on Carcinogens
National Institute of Environmental Health Sciences
Division of the National Toxicology Program
P.O. Box 12233, MD K2-14
Research Triangle Park, NC 27709
Phone: 984-287-3155
Fax: 301-480-2970

From: Caroline Braibant <caroline.braibant@antimony.com>
Date: Monday, May 20, 2019 at 8:46 AM
To: "Lunn, Ruth (NIH/NIEHS) [E]" <lunn@niehs.nih.gov>
Cc: "Lynn L. Bergeson" <lbergeson@lawbc.com>, Bethami Auerbach <BAUERBACH@lawbc.com>, Amy Wang <huishan.wang@nih.gov>, Mary Wolfe <wolfe@niehs.nih.gov>, Caroline Braibant <caroline.braibant@antimony.com>, "Kathleen M. Roberts" <kroberts@lawbc.com>, "Chad H. Howlin" <chowlin@lawbc.com>, Nathalie Francis <nathalie.francis@antimony.com>, Marjorie Huppert <Marjorie.Huppert@antimony.com>
Subject: RoC Review of Antimony Trioxide: news from EU REACH Evaluation

Dear Dr Lunn,

In follow-up of the letter sent to you by Bergeson & Campbell on 24 April, I wanted to inform you about the preliminary outcome of the on-going EU-REACH Substance Evaluation on Antimony Trioxide (ATO).
You will see in the documentation attached that the European authorities are not convinced that the available evidence clarifies the carcinogenicity mode of action of ATO, and are hence requesting an additional study to shed light on the genotoxicity of this compound, before concluding on the applicable classification.
Although this was not minuted in the meeting recordings, we remember that at the Peer Review meeting at which the draft US NTP ATO Study results were discussed, your experts had also questioned the relevance of the Micronucleus and COMET assay results…

Our Board and General Assembly agreed last week that i2a would perform the test requested by the European authorities.
I am hence writing to you in the event this new development would be of relevance to improve the scope and impact of the on-going RoC Listing process for ATO.
In our view, the process would very much benefit from this additional information.
What's your view on this?

Kind regards, and many thanks in advance for considering this request,

Caroline

Caroline Braibant
Secretary-General

Av. de Broqueville 12, B-1150 Brussels
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caroline.braibant@antimony.com
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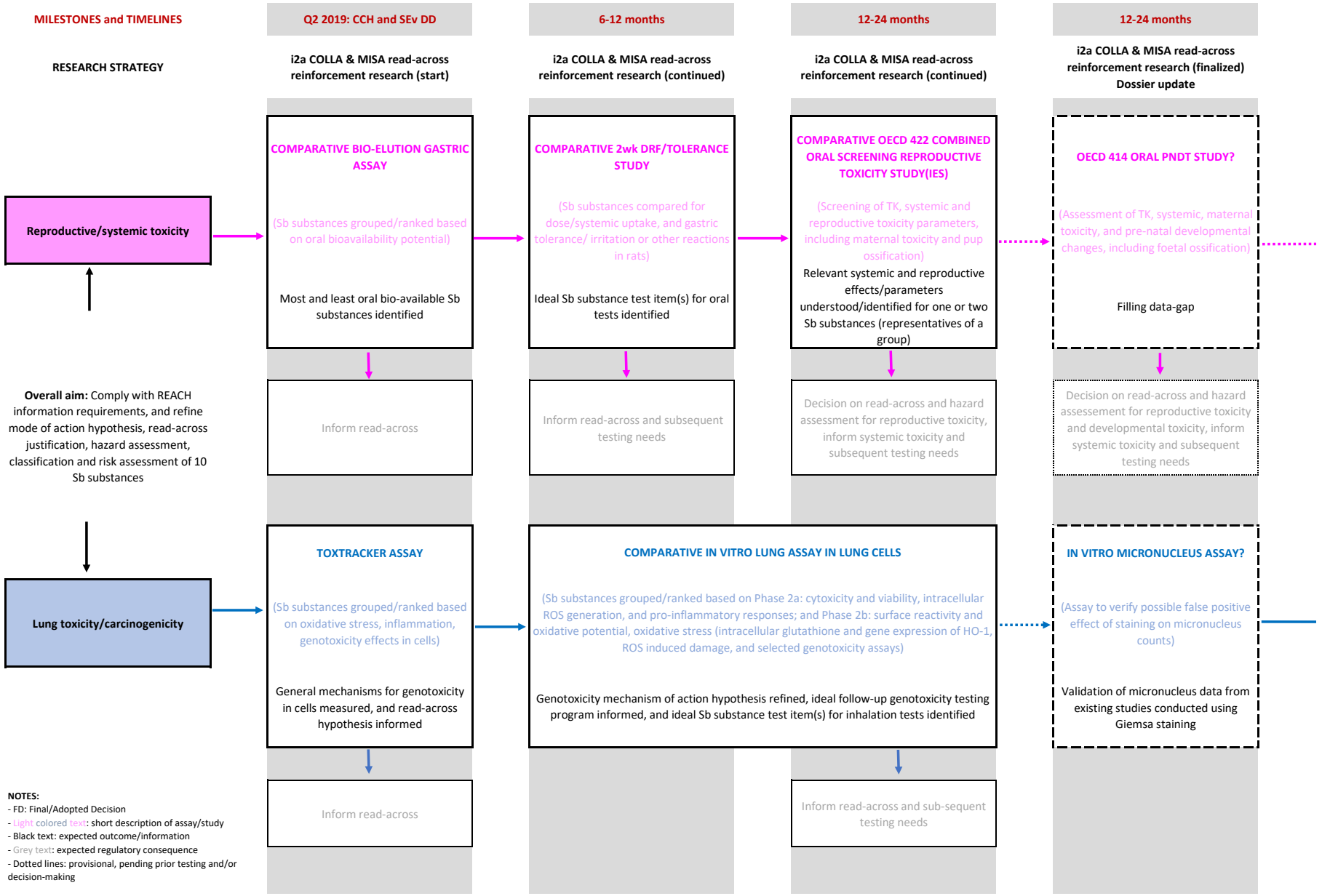
i2a International Antimony Association

Visual Overview of i2a's Sequential/Integrated Research Strategy for its 10 REACH Registered Sb substances
(focussing any in vivo testing on Sb 3+ species first)

22 May 2019 - FINAL



Visual Overview of i2a's Sequential/Integrated Research Strategy for its 10 REACH Registered Sb substances
(focussing any in vivo testing on Sb 3+ species first)

22 May 2019 - FINAL