National Toxicology Program
National Institute of
Environmental Health Sciences
P.O. Box 12233
Research Triangle Park, NC 27709
Website: https://ntp.niehs.nih.gov

July 10, 2020

Lynn L. Bergeson
Bethami Auerbach
Bergeson & Campbell P.C.
2200 Pennsylvania Avenue, NW, Suite 100W
Washington, DC 20037-1701

Dear Ms. Bergeson and Ms. Auerbach:

I am responding to your Information Quality Request for Correction of Information ("the RfC") dated October 11, 2019, submitted by the International Antimony Association (i2a) pursuant to Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001[1] (the Information Quality Act or IQA) and the guidelines issued by the Office of Management and Budget (OMB Guidelines),[2] the U.S. Department of Health and Human Services (HHS Guidelines),[3] and the National Institutes of Health (NIH Guidelines).[4] i2a requests correction to the "Final Report on Carcinogens Monograph on Antimony Trioxide" dated October 19, 2018, specific to the "unlimited characterization of the cancer hazard for antimony trioxide" as well as any reference to that information within the "Draft Report on Carcinogens Concept: Antimony Trioxide," "Draft Toxicology and Carcinogenesis Studies of Antimony Trioxide," or other foundational documents. In the RfC, i2a specifically asserts that the final monograph fails to meet the 'utility' requirements of the OMB, HHS, and NIH Guidelines. I have reviewed the request and would like to respond to your concerns.

## IQA and Applicability to Draft Documents

The RfC states that it encompasses correcting other documents where information within the final Report on Carcinogens (RoC) monograph is based upon them—draft RoC concept, draft NTP toxicology and carcinogenesis studies, or other foundational documents. With regard to applicability of the OMB, HHS, and NIH Guidelines, the front cover of the draft NTP Technical Report on toxicology and carcinogenesis studies of antimony trioxide has the following disclaimer:

[1] P.L. 106-554, 44 U.S.C. 3516 note.
[2] *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity of Information Disseminated by Federal Agencies,* 67 Fed. Reg. 8452 (February 22, 2002).
[3] *HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public*, accessible at https://aspe.hhs.gov/infoquality/Guidelines/part1.shtml.
[4] *HHS Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated to the Public*, Part II.I (National Institutes of Health), available at http://aspe.hhs.gov/infoquality/Guidelines/NIHinfo2.shtml.

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Report on toxicology and carcinogenesis studies of antimony trioxide has the following disclaimer:

> *This DRAFT Technical Report is distributed solely for the purpose of predissemination peer review under the applicable information quality guidelines. It has not been formally disseminated by the NTP. It does not represent and should not be construed to represent NTP determination or policy.*

Similarly, the front cover of the "Draft Report on Carcinogens Monograph on Antimony Trioxide" has the following disclaimer:

> *This information is distributed solely for the purpose of pre-dissemination peer review under applicable information quality guidelines. It has not been formally disseminated by the National Toxicology Program. It does not represent and should not be construed to represent any NTP determination or policy.*

Each disclaimer clearly explains that the information contained within the draft document is not an official view of the U.S. Government, but only a preliminary draft circulated for purposes of obtaining public comment and peer review. NIH Guidelines, consistent with HHS and OMB Guidelines, apply to information that Agency disseminates to the public and represents as "fact or the agency's views."[5] Each is clearly marked as a draft and does not represent agency views, and, therefore, is not subject to the NIH Guidelines. Likewise, the draft concept document for antimony trioxide is clearly marked as 'draft' and, therefore, is not subject to the NIH Guidelines.

## Report on Carcinogens Monograph on Antimony Trioxide

Before I respond to issues raised in the RfC, I would like to briefly provide information about the review of antimony trioxide for the RoC and development of the RoC monograph. NTP's review of antimony trioxide followed a rigorous process[6] that was based on unbiased and sound science, including multiple opportunities for public and technical comment, external peer review, and application of established listing criteria for assessing whether antimony trioxide should be recommended for listing in the RoC. The monograph presents information on human exposure, especially U.S. exposure, and an assessment of the evidence from cancer studies in humans and experimental animals, mechanisms of carcinogenicity, and other data (such as absorption, distribution, metabolism, and excretion) relevant for evaluating a substance's potential carcinogenicity.

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[5] OMB Guidelines, Section V(5), 67 Fed. Reg. 8460; HHS Guidelines, Section D(2)(e); NIH Guidelines, Section II(2).

[6] (NTP RoC Process). NTP Process for Preparation of the Report on Carcinogens is available at https://ntp.niehs.nih.gov/ntp/roc/process/process_508.pdf.

The draft RoC monograph on antimony trioxide, which was released for public comment and external peer review, presented NTP's preliminary conclusions regarding the level of evidence for carcinogenicity from studies in humans and experimental animals and its preliminary RoC listing recommendation. These conclusions were reached by applying the RoC listing criteria[7] to the cancer hazard assessment. NTP convened a seven-member, external scientific panel to peer review the draft RoC monograph at a public meeting on January 24, 2018 (82 Fed. Reg. 52066, November 9, 2017),[8] with opportunities for the public to attend via webcast and provide input as both written and oral comments. The chair was present in-person at the National Institute of Environmental Health Sciences on January 24, 2018, and panel members participated remotely. Written comments received became part of the public record that was reviewed by the expert panel prior to the meeting and posted on the RoC website.

The panel was given a three-part charge:

1) Comment on whether the draft monograph was technically correct, clearly stated, and objectively presented.
2) Provide opinion on whether there is currently or was in the part significant human exposure to antimony trioxide for persons residing in the United States.
3) Vote on whether the scientific evidence supports (a) the level of evidence conclusions regarding carcinogenicity from cancer studies in humans and animals and (b) NTP's preliminary policy decision on the listing status of antimony trioxide in the Report on Carcinogens.

The panel advised NTP on the content and completeness of the draft monograph taking into consideration individual publications and public comments. Prior to the meeting, three sets of written comments were provided to the panel including those submitted by i2a dated January 10, 2018,[9] and three speakers presented oral remarks at the meeting including Craig Boreiko, Ph.D. on behalf of i2a.[10]

In the RfC, page 11, i2a specifically states that final RoC monograph "fails to meet the 'utility' principle of the IQA." NTP believes, in fact, that the 'utility' criterion[11] with respect to the RoC monograph is satisfied. NTP finalized the monograph based upon comments and actions by the panel at the peer-review meeting. The panel voted unanimously that the scientific evidence supported NTP's preliminary recommendation to list antimony trioxide in the RoC as *reasonably anticipated to be human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting mechanistic data. The panel also agreed that the available data from studies in humans were inadequate to evaluate the relationship between

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[7] (RoC Listing Criteria). Report on Carcinogens listing criteria is available at https://ntp.niehs.nih.gov/go/rocprocess.
[8] Notice is available at https://ntp.niehs.nih.gov/ntp/pressctr/frn/2017/82frn216roc20171109_htm.pdf.
[9] Written public comments are available at https://ntp.niehs.nih.gov/go/809361, see Jan 24, 2018, Peer Review of Draft Report on Carcinogens Monograph on Antimony Trioxide, Meeting Materials.
[10] (Peer-Review Report). *National Toxicology Program Peer Review of Draft Report on Carcinogens Monograph on Antimony Trioxide, January 24, 2018, Peer-Review Report,* available at https://ntp.niehs.nih.gov/ntp/about_ntp/monopeerrvw/2018/january/antimonypeerreview_508.pdf, Section IV at 5.
[11] According to the OMB Guidelines, "[u]tility refers to the "usefulness of the information to its intended users, including the public." 67 Fed. Reg at 8459.

human cancer and exposure specifically to antimony trioxide or other antimony compounds. The panel's comments, deliberations, and votes are captured in the peer-review report.[12]

**Discussion of Requested Corrections to the Final RoC Monograph on Antimony Trioxide**

Several issues raised on pages 6-7 of the RfC pertain to comments submitted by i2a on the draft monograph. Those issues are addressed in this response only if they are relevant to content within the final RoC monograph.[13]

1. On page 6 of the RfC, i2a states that Table 2-3 with old U.S. occupational exposure data should be omitted and only newer more accurate data from the EU Risk Assessment be used (Table 2.4).

   NTP response: No correction to the final RoC monograph for antimony trioxide is needed. NTP included occupational exposure data in the monograph to document past or present U.S. exposure. The exposure information in Table 2-3 is technically correct and relevant. As stated in the monograph, "[a]lthough these data are over 30 years old, cancer has a long latency and thus this exposure information is still relevant"[14]; therefore, the monograph includes both Table 2-3 and the EU Risk Assessment information in Table 2.4.

2. On pages 6-7 of the RfC, i2a states that the monograph did not contain "actual workplace-relevant particle size distribution," such as is available in the EU's Risk Assessment Report (2008). i2a also references comments submitted on the draft monograph (January 10, 2018) regarding workplace monitoring and the Hughson *et al.* (2005)[15] study on particle-size distributions associated with antimony trioxide production.

   NTP response: No correction to the final RoC monograph on antimony trioxide is needed. Although Hughson *et al.* (2005) provides dermal exposure and workplace aerosols for antimony trioxide production, the report is not publicly available and, therefore, was not included in the RoC monograph. Per procedures for preparing monographs, "[i]nformation on exposure and properties of the candidate substance must come from publicly available sources."[16] Use of information from Hughson *et al.* (2005) in the monograph is only within the context of its inclusion in the EU Risk Assessment report.

3. On page 7 of the RfC, i2a proposes that "…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

[12] Peer-Review Report, Section V at 7.
[13] (RoC Monograph). *Report on Carcinogens Monograph on Antimony Trioxide*. October 2018, available at https://ntp.niehs.nih.gov/ntp/roc/monographs/antimony_final20181019_508.pdf.
[14] *Ibid.*, 15.
[15] Assessment of dermal and exposure and classification of workplace aerosols for antimony trioxide production. Prepared by the Institute of Occupational Medicine for the International Oxide Industry Association. This report was submitted as part of ia2 public comments (see footnote 17).
[16] (RoC Handbook). *Handbook for Preparing Report on Carcinogens Monographs*. July 20, 2015, available at https://ntp.niehs.nih.gov/ntp/roc/handbook/roc_handbook_508.pdf, at 2.

hazard can occur." Footnote 21 in the RfC states that the monograph "contained no rationale as to why dermal exposure data might even be relevant."

NTP response: No correction to the final RoC monograph on antimony trioxide is needed. Section 2, Human Exposure of the monograph[17] provides information on how people are exposed (e.g., route of exposure). Key questions for this section as detailed in the Objectives and Methods section of the monograph include "What are the sources of exposure?" and "How are people exposed to antimony(III) trioxide?"[18]

The EU report, which is referenced in the monograph, provides extensive and systematic occupational monitoring data specific to antimony(III) trioxide, or exposures converted to antimony(III) trioxide equivalents. Table 2-4[19] in the monograph includes information from the EU report on both inhalation and dermal exposure levels for different antimony trioxide exposure scenarios. The broad range of occupational exposure scenarios for which antimony trioxide data are available suggests that while inhalation is the most likely exposure route, dermal exposure is also a relevant route. Also, as noted in the monograph, members of the U.S. general population are potentially exposed to antimony trioxide when using consumer products containing antimony trioxide or by breathing contaminated indoor and outdoor air (Section 2.3).[20]

4. On page 7 of the RfC, i2a suggests that the monograph should include "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.

   NTP Response: No correction to the final RoC monograph on antimony trioxide is needed. Data on particle size used in the animal cancer studies are reported in Table 5.8 of the monograph.[21] The animal cancer studies reported particle sizes in the inhalable range for the animal species used in the study. The comparison of particle size versus deposition pattern is typically done for detailed dose-response modeling, which was not a part of the RoC cancer hazard evaluation for antimony trioxide.

5. On page 7 of the RfC, i2a states "[t]he 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."

   NTP response: No correction to the final RoC monograph on antimony trioxide is needed. NTP would like to point out that the monograph does not conclude "no evidence existed based on the epidemiological studies." The monograph (Section 8.3) states "[t]he data from

[17] RoC Monograph, 11-28.
[18] *Ibid.*, x.
[19] *Ibid.*, 20.
[20] *Ibid.*, 20-28.
[21] *Ibid.*, 70-80.

epidemiological studies are inadequate to evaluate the relationship between human cancer and exposure specifically to antimony(III) trioxide or other antimony compounds."[22] A concise summary of four epidemiological studies is also included. The expert panel unanimously supported these conclusions.[23]

**Discussion of Requested Corrections to the Listing Recommendation in the Final RoC Monograph on Antimony Trioxide**

1. On pages 8-9 of the RfC, i2a requests that NTP limit the listing of antimony trioxide in the RoC to the powder form of the compound only, and by the inhalation route of exposure. i2a suggests that NTP revise the listing language to be one of two options termed "Option 1" or "Option 2." This language (in italics below) was presented in the December 3, 2018 letter from your firm on behalf of i2a 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 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."

   NTP response: No correction to the final RoC monograph for antimony trioxide is needed because the available evidence does not support limiting the listing with regard to particle size and route of exposure for hazard identification. The monograph discusses data on exposure, absorption, and systematic distribution of antimony trioxide by multiple routes of exposures in humans or experimental animals.

   Although the major route of exposure to antimony trioxide is from inhalation, workers and the general public can also be exposed to antimony trioxide via ingestion or through the skin. For example, antimony trioxide is present in household dust due to the wear and tear of consumer products treated with flame retardant, and the oral exposure level of antimony trioxide via hand-to-mouth activity has been estimated for consumers.[24]

   Both the absorption and systemic distribution of antimony following oral exposure of antimony trioxide have been reported in animals. As detailed in the monograph, rats exposed

[22] *Ibid.*, 95.
[23] Peer-Review Report, Section V.A.2.3. at 10.
[24] RoC Monograph, Table 2-7 at 24.

orally to antimony trioxide showed increased antimony levels in multiple tissues and organs (thyroid, lung, spleen, heart, kidney, liver, bone marrow, muscle, and whole blood). Although no absorption data are published for oral exposure to antimony trioxide in humans, absorption is likely low based on computational models using animal data and considering human physiology, as presented by the European Union in their 2008 risk assessment.[25]

Studies in experimental animals and humans provide evidence of systemic distribution or systemic effects after inhalation exposure. Because antimony has been detected in the blood and urine from antimony trioxide-exposed workers,[26] there is evidence for systemic distribution in humans. Inhalation exposures of antimony trioxide in rats and mice have resulted in increased levels of antimony in the blood and caused tumors at multiple sites,[27] and those sites were not limited to the respiratory tract.

2. On page 10 of the RfC, i2a provides examples from other RoC listings in which the scope was limited including certain glass wool fibers (inhalable), certain refers to fibers that are biopersistent in the lung or tracheobronchial region; silica, crystalline (respirable size); and cobalt and cobalt compounds that release cobalt in vivo.

   NTP response: As the December 2018 letter, submitted on behalf of i2a, raised this same issue, we will summarize the rationale provided in our March 14, 2019 response. A major difference between the databases for antimony trioxide and those for cobalt, glass wool fibers, and silica is the extent and confidence in the mechanistic data. The mechanistic understanding of how antimony causes cancer has not been elucidated such that there is scientific confidence to narrow the RoC listing by exposure route, whereas the scientific evidence for the listing of cobalt, glass wool fibers, or silica indicates that the mechanism of action involves the release of cobalt ions, or the persistence of inhaled fibers, or particles, respectively.

   - For the listing of cobalt-related compounds, there is strong mechanistic data which indicates that the release of cobalt ions is a key event in cobalt-induced carcinogenicity.[28]
   - For the glass wool listing, "certain" refers to fibers that are biopersistent in the lung or tracheobronchial area based on (1) experimental animal studies showing that not all fibers are carcinogenic and (2) mechanistic data indicating that biopersistence is a key factor for predicting carcinogenicity.[29]
   - For silica, the rationale for qualifying its RoC listing is based largely on (1) evidence from human studies (especially studies of sand blasting releasing silica dust) that found an association of an increased risk of cancer with exposure to respirable quartz and

[25] *Ibid.,* 30.
[26] *Ibid.*, 24.
[27] *Ibid.*, 30.
[28] RoC substance profile for Cobalt and Cobalt Compounds That Release Cobalt Ions *In Vivo*, available at https://ntp.niehs.nih.gov/ntp/roc/content/profiles/cobalt.pdf.
[29] RoC substance profile for Certain Glass Wool Fibers (Inhalable), available at https://ntp.niehs.nih.gov/ntp/roc/content/profiles/glasswoolfibers.pdf.

cristobalite but not to amorphous silica,[30] and (2) evidence from mechanistic studies, which showed that persistence of silica in the lung leads to leads to pathways of lung disease and cancer; deposition of particles is related to their size.[31]

3. On page 13 of the RfC, i2a states that "[n]inety-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 inhalation of respirable particles, to make an unlimited recommendation in the Monograph."

   NTP response: No correction to the final RoC monograph for antimony trioxide is needed. Cancer is typically developed with a long latency period, and, therefore, chronic studies are used for cancer evaluation. As noted in the monograph, NTP followed methods outlined in the handbook for its preparation. The handbook states that "[t]he animals should be exposed to high enough doses (resulting in tolerable toxicity) for a sufficiently long duration to assess carcinogenicity (usually approaching the lifetime of the animal for nonpersistent substances)."[32] NTP identified five studies from four publications, which met the criterion and were of sufficient quality, and they were used to assess the carcinogenic potential of antimony trioxide.[33] Per the handbook's guidance, the 90-day feeding study[34] cited by i2a was not sufficiently long enough for carcinogenesis assessment; therefore, it was not included in our evaluation.

4. On page 14 of RfC, i2a proposes that limiting NTP's recommended listing status for antimony trioxide in the RoC would be consistent with the 2014 risk assessment issued under the Toxic Substance Control Act (TSCA) by the Environmental Protection (EPA). EPA stated "[b]ased on a review…., 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."

   NTP response: This issue raised by i2a is not specific to the RoC monograph on antimony trioxide and, therefore, outside the scope of this RfC. NTP would note that the purpose and utility of the RoC monograph and EPA risk assessment differ. The RoC monograph is a document for determining whether antimony trioxide is a *cancer hazard* and should be listed

[30] RoC substance profile Silica, Crystalline (Respirable Size), available at https://ntp.niehs.nih.gov/ntp/roc/content/profiles/silica.pdf.
[31] RoC Background Document for Silica, Crystalline (Respirable Size), available at https://ntp.niehs.nih.gov/ntp/newhomeroc/other_background/silica_no_app_508.pdf.
[32] RoC Handbook, Section 4.2.2 at 63.
[33] RoC Monograph, Section 5 at 59.
[34] Hext PM, Pinto PJ, Rimmel BA (1999). Subchronic feeding study of antimony trioxide in rats. *J. Appl. Toxicol*. 19:205-209.

in the RoC. The EPA evaluation of antimony trioxide goes beyond carcinogenic hazard and assesses the *human health risk* to antimony trioxide.

NTP would point out that text within the RoC monograph is consistent with the EPA evaluation. As stated in the monograph, "[t]he highest exposures to antimony(III) trioxide and total antimony occur in the workplace"[35] and "[e]vidence for exposure of the U.S. general population to antimony is provided by biomonitoring data showing its presence in urine, whole blood, and saliva. Data from the National Health and Nutrition Examination Survey (NHANES) indicate low level of exposure to antimony".[36]

5. On pages 15-16 of the RfC, i2a asserts, "[t]he 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 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."

   NTP response: No correction to the final RoC monograph for antimony trioxide is needed. Experimental animal cancer studies are an important and recognized scientific method for carcinogenicity testing to identify substances as potential human carcinogens. Although animals are not perfect surrogates for humans, experimental evidence has demonstrated that rodents are sufficiently similar to humans in their physiological, biochemical, metabolic, and genetic or genomic characteristics to warrant their use in predicting whether a substance is expected to cause cancer in humans. Moreover, all chemicals known to cause cancer in humans also cause cancer in experimental animals, and about a third of them were first identified in experimental animals.[37]

   NTP followed the RoC process and appropriately applied the RoC listing criteria to the scientific evidence to recommend the listing of antimony trioxide in the RoC. The handbook[38] provided the methods and considerations for using evidence from experimental animal studies in the RoC evaluation, and those methods were followed for preparation of the RoC monograph on antimony trioxide. As noted above, the peer-review panel agreed that the experimental animal studies supported the level-of-evidence conclusion of *sufficient evidence*

[35] RoC Monograph at 15.
[36] *Ibid*., 21.
[37] See Introduction in the RoC, available at https://ntp.niehs.nih.gov/ntp/roc/content/introduction_508.pdf.
[38] RoC Handbook, Part E: Cancer Studies in Experimental Animals at 56.

*of carcinogenicity*,[39] which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors in multiple species or at multiple tissue sites, per the RoC listing criteria.[40]

Studies of cancer mechanisms and other relevant data, such as how the substance is processed in the body, are also part of the standard cancer hazard assessment in RoC monographs[41] and may be used alone as the basis for listing a substance in the RoC.[42] In the case of antimony trioxide, the mechanistic information was considered by NTP to provide supporting evidence for the recommended listing as *reasonably anticipated to be a human carcinogen*. The expert panel agreed with the integration of the scientific evidence within the RoC monograph and the listing conclusion.[43]

**IQA and New Research Under REACH**

The RfC raises the issue of new research and data being generated under the REACH evaluation. As noted on page 11 of the RfC, Dr. Lunn acknowledged in her May 29, 2019 email NTP's receptivity to receiving new published data that are being generated under the REACH evaluations. The RoC process allows for a listed substance to be re-reviewed–"[a] nomination may seek to list a new substance in the RoC, *reclassify the listing status of a substance already listed*, or *remove a listed substance*."[44] [emphasis added]. As this RfC pertains to the final RoC monograph, which NTP has disseminated as "agency initiated or sponsored distribution of information to the public,"[45] the new research and data forthcoming under the REACH evaluation are not subject to the IQA and OMB, HHS, and NIH implementing guidelines.

**Specific RfC Process Requests**

1. On page 3 of the RfC, i2a requests confirmation that 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.

   NTP response: As noted below, the Implementation Update 4.5 to the IQA[46] applies to the appeals process, not to the agency response to the RfC.

   > *"Implementation Update 4.5: 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."* [emphasis added]

[39] Peer-Review Report, V.A.3.2 at 10 and V.A.3.3 at 11.
[40] RoC Listing Criteria, available at https://ntp.niehs.nih.gov/go/rocprocess.
[41] RoC Handbook, Part F: Other Relevant Data at 72.
[42] RoC Listing Criteria.
[43] Peer-Review Report, Sections V.A.6.1 at 14 and V.A.6.2 at 15.
[44] NTP RoC Process, Step 1 at https://ntp.niehs.nih.gov/ntp/roc/process/process_508.pdf.
[45] OMB Guidelines, 67 Fed. Reg. at 8454 (February 22, 2002).
[46] Memorandum from Russell T. Vought, Improving Implementation of the Information Quality Act (April 24, 2019), available at https://www.whitehouse.gov/wp-content/uploads/2019/04/M-19-15.pdf, at 10.

2. On page 3 of the RfC, i2a requests affirmation that the April 24, 2019, Implementation Update 4.3 to the IQA was met in that NTP's peer review committee actually considered limiting the scope of the Monograph recommendation for antimony trioxide to the chemical species and route of exposure shown to be carcinogenic.

   NTP Response: The Implementation Update 4.3 to the IQA states,

   > *"Implementation Update 4.3: 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 available."*

   The NTP held the peer-review meeting for the draft RoC monograph on antimony trioxide on January 24, 2018, more than a year prior to the April 24, 2019, memorandum from Russell T. Vought, "Improving Implementation of the Information Quality Act, which contains Implementation Update 4.3. The memorandum directs agencies to *update their guidelines*; it does not require retroactive application.[47] Therefore, this issue raised by i2a is not specific to the RoC monograph on antimony trioxide and outside the scope of this RfC. That being said, NTP has comprehensively addressed the issues raised by i2a in this response.

   In addition, as pointed out on page 6 of the RfC, "After NTP released the Draft Monograph for review and comment on November 29, 2017…i2a submitted detailed comments…" Per the RoC process, NTP distributed the written comments (dated January 10, 2018) submitted on behalf of i2a to the panel prior to the peer-review meeting and posted to the meeting webpage. At the meeting, the chair acknowledged receipt of written comments from three groups including i2a. In written comments[48] and during presentation of oral comments[49] at the meeting on January 24, 2018, Craig Boreiko, Ph.D. on behalf of i2a, and Rita Cortvrindt on behalf of Campine, discussed issues of carcinogenicity in the NTP studies. These issues were related or specific to the inhalation route of exposure such as particle overload and size, absorption via the oral route, and tumors at sites distal from the respiratory track in the inhalation studies. Per the meeting format,[50] the chair offered the panel an opportunity following each oral presentation to ask questions of the speaker.

**Conclusion**

As noted above, the final RoC monograph is a reference document for antimony trioxide and its evaluation for the RoC that compiles and summarizes the publicly available information from both positive and negative studies in determining whether antimony trioxide should be listed in the RoC. Released for public comment, the draft monograph was finalized following external peer review. In conclusion, we believe that the final RoC monograph on antimony trioxide

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[47] *Ibid.,* 2.
[48] Written comments are available at https://ntp.niehs.nih.gov/ntp/about_ntp/monopeerrvw/2018/january/publiccomm/braibant20180110_508.pdf.
[49] Peer-Review Report, Section IV at 5.
[50] Public comment format, slide 3 at https://ntp.niehs.nih.gov/ntp/about_ntp/monopeerrvw/2018/january/presentations/meeting-format_508.pdf.

satisfies the OMB, HHS, and NIH Guidelines pursuant to the IQA. NTP has identified no required edits in response to the RfC.

i2a may appeal our agency's decision either in writing or electronically within 30 days of receiving this response. Your request should state the reasons for your appeal. It does not need to reference a tracking number. The request may be sent electronically to Erica.Grant@nih.gov or by mail to:

Director, Office of Evaluation, Performance, and Reporting
Division of Program Coordination, Planning, and Strategic Initiatives
Office of the Director
National Institutes of Health
Building 1, Room 260, 1 Center Drive
Bethesda, MD 20892.

If the appeal is sent in hard copy, please clearly mark the appeal and outside envelope with the phrase "Information Quality Appeal."

Sincerely,

Brian R. Berridge -S

Digitally signed by Brian R. Berridge -S
Date: 2020.07.10 05:12:02 -04'00'

Brian R. Berridge, D.V.M., Ph.D., DACVP
Associate Director, NTP
Scientific Director, Division of NTP
National Institute of Environmental Health Sciences