National Toxicology Program

Peer Review of Draft Report on Carcinogens Monograph on Antimony Trioxide

January 24, 2018

National Institute of Environmental Health Sciences Research Triangle Park, NC

Peer-Review Report

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Contents

I. Attendees*

Peer-Review Panel

Rebecca Fry (Chair), University of North Carolina at Chapel Hill
Richard Peterson II, AbbVie Inc. (by webcast)
Elaine Symanski, University of Texas (by webcast)
Michael Waalkes, Retired, National Toxicology Program (by webcast)
Elizabeth Ward, Retired, American Cancer Society (by webcast)
John P. Wise, Sr., University of Louisville (by webcast)
Hao Zhu, Rutgers University at Camden (by webcast)

National Toxicology Program Board of Scientific Counselors Liaison

Kenneth McMartin, Louisiana State University (by webcast)

National Institute of Environmental Health Sciences Staff

Brian Berridge
John Bucher
Gloria Jahnke
Kelly Lenox
Ruth Lunn
Suril Mehta
Cynthia Rider
Andrew Rooney
Matt Stout
Amy Wang
Mary Wolfe

Report on Carcinogens Contract Support Staff

Stanley Atwood, ILS
Canden Byrd, ICF
Susan Dakin, Independent Consultant
Andrew Ewens, ILS
Sanford Garner, ILS
Lara Handler, ILS
Jeanne Luh, ICF
Alton Peters, ILS
Anna Stamatogiannakis, ICF
Joanne Trgovcich, ICF

Other NIEHS Contract Support Staff

Ernest Hood, FM Talent

Public Attendees

None in person (by telephone only)

II. Welcome and Introductions

The National Toxicology Program (NTP) peer-review panel for the *Draft Report on Carcinogens Monograph on Antimony Trioxide* was convened on January 24 in Rodbell Auditorium, Rall Building, National Institute for Environmental Health Sciences (NIEHS), Research Triangle Park, North Carolina. Dr. Rebecca Fry served as chair. Dr. Kenneth McMartin attended by webcast as the NTP Board of Scientific Counselors (BSC) liaison. Representing NTP were Dr. Brian Berridge, Associate Director, NTP; Dr. Mary Wolfe, Director, NTP Office of Liaison,

*The meeting was webcast. Individuals who viewed the webcast are not listed except as noted.

Policy, and Review; Dr. Ruth Lunn, Director, Office of the Report on Carcinogens (ORoC); Dr. Amy Wang, ORoC; Mr. Suril Mehta, ORoC, and Dr. John Bucher, Senior Scientist, NTP. Dr. Wolfe served as the Designated Federal Official. All of the peer-review panel members ("the Panel") attended by webcast.

Dr. Fry called the meeting to order at 8:35 a.m., welcomed everyone to the meeting, and asked the NTP representatives, Report on Carcinogens (RoC) presenters, and Panel members to introduce themselves. Dr. Bucher welcomed the Panel and thanked them for their service. Dr. Wolfe read the conflict of interest policy statement and briefed the attendees on meeting logistics. Dr. Fry informed the Panel and the audience of the format for the peer review.

III. Process for Preparing the Draft RoC Monograph

Dr. Lunn presented background information about the RoC and the process and methods used to prepare the draft RoC monograph. She noted that the RoC is congressionally mandated and identifies substances that pose a cancer hazard for U.S. residents. It is prepared for the Secretary of Health and Human Services (HHS) by NTP and is cumulative, including substance profiles for newly listed substances and for all substances listed in previous reports.

Dr. Lunn outlined the four-part formal process for preparing the RoC: (1) selection of substances for evaluation, (2) preparation of draft RoC monographs, (3) peer review and finalization of the monographs, and (4) approval of the substance profiles by the HHS Secretary and release of the RoC. The process incorporates opportunities for public comment, scientific input, and peer review of the scientific information.

Dr. Lunn outlined the steps of the process that had been completed for selection and evaluation of antimony trioxide. NTP selected antimony trioxide for review for the RoC based on the potential for substantial human exposure in workplaces and the availability of an adequate database of cancer studies in experimental animals. ORoC presented the draft concept document explaining the rationale and proposed approach for the RoC review to the NTP BSC in December 2016 and received two public comments, after which ORoC developed a protocol for preparation of the draft monograph. The evaluation included input from technical advisors, and the draft monograph underwent internal review prior to public release.

Dr. Lunn briefly discussed the legislative requirement for whether a significant number of people living in the United States are exposed to antimony trioxide, noting that it is a scientific judgment, not a formal exposure assessment, and takes into account exposure levels, including higher levels seen with occupational exposure. She noted that because antimony trioxide is converted to other forms of antimony and *vice versa,* information on other antimony compounds informed the evaluation. However, the data from studies in experimental animals were inadequate for evaluation of the potential carcinogenicity of other antimony compounds.

Dr. Lunn outlined the framework for the evaluation and types of evidence, noting that studies in humans and experimental animals and mechanistic data were included. She described the ORoC systematic review process for reaching cancer hazard conclusions, noting that software from the Health Assessment Workspace Collaborative was used to manage the literature search.

Dr. Lunn reviewed the RoC criteria for listing a substance as *known to be a human carcinogen* or *reasonably anticipated to be a human carcinogen*. She emphasized that the listing recommendations are based on scientific judgment considering all relevant information.

Dr. Lunn said the draft monograph would be revised based on NTP's review of the peer-review comments, with consideration of public comments. The revised monograph, the peer-review report, and NTP's response to the peer-review report would be provided to the NTP BSC at a public meeting, after which the monograph would be finalized.

The charge to the Panel was as follows:

- Comment on whether the Draft RoC Monograph on Antimony Trioxide is technically correct, clearly stated, and objectively presented.
- Provide an opinion on whether there is currently or was in the past significant human exposure to antimony trioxide.

The Panel was asked to vote on the following questions:

- Whether the scientific evidence supports NTP's conclusions on the level of evidence for carcinogenicity from cancer studies in humans.
- Whether the scientific evidence supports NTP's conclusions on the level of evidence for carcinogenicity from cancer studies in experimental animals.
- Whether the scientific evidence supports NTP's preliminary policy decision on the listing status of antimony trioxide in the *Report on Carcinogens*.

IV. Public Comments

IV.A. Written Public Comments

The chair noted that written public comments on the draft monograph were received from Ahmed Mostafa, Ryan Surmaitis, Maricel Dela Cruz, Michael Greenberg, and Muhammad Khalid, of the Drexel University College of Medicine Division of Medical Toxicology; Caroline Braibant, on behalf of the International Antimony Association; and Mark Carpels, on behalf of Campine. The written comments were posted to the meeting webpage and distributed to the Panel prior to the meeting.

IV.B. Oral Public Comments

Glade Squires, Product Manager for flame retardants, Omya Industries, Inc., presented comments on behalf of Omya by telephone. Omya has represented Campine in selling antimony trioxide in North America for over 40 years. Omya does not feel there is sufficient evidence to conclude that antimony trioxide is a human carcinogen; the evidence presented does not relate to human exposure to antimony trioxide. Levels have been set for worker exposure, and exposure has declined among workers given proper protective equipment and instructed on how to handle antimony trioxide. Consumers are mostly not exposed to antimony trioxide in flame retardants; the majority is used in thermoplastic and thermoset materials, where the antimony trioxide is mostly completely encapsulated and not free in powder form. Commercially available forms of antimony trioxide have been designed to reduce or completely eliminate worker exposure to the dust; these include material for use in polyvinyl chloride and thermoplastics. The value of antimony trioxide for fire safety in the United States is significant. Mr. Squires concluded by stating that Omya feels there is no direct evidence in humans that antimony trioxide causes cancer, and that no conclusion on human carcinogenicity can be drawn from the animal studies.

Craig Boreiko, an N.C.-based consultant, presented comments on behalf of the International Antimony Association (i2a) by telephone. Although the monograph appropriately focused on the well-conducted NTP bioassays of antimony trioxide (NTP 2017), i2a is concerned about several nuances of interpretation. In particular, i2a does not agree that the NTP genotoxicity data indicate a positive response or that these data are congruent with the observed lung-tumor response. Mr. Boreiko noted that Dr. Jon Mirsalis, chairperson of the peer review panel for the draft NTP technical report on antimony trioxide, considered the genotoxicity results to be negative.

Dr. Boreiko stated that the data in the monograph and elsewhere support pulmonary overload as the mechanism underlying the rat lung tumors. Although pulmonary overload did not explain the lung tumors in mice, the NTP technical report sends "mixed messages" concerning the potential mechanism. It is critical to determine whether carcinogenicity is specific to the inhalation route of exposure, as uptake of most antimony compounds administered orally is less than 1%. Another issue is the observation of tumors at sites distant from the lung, which i2a does not think should be attributed directly to antimony trioxide. Pheochromocytomas were likely a response to systemic hypoxia (due to the high inhalation exposure levels); B-cell lymphomas were likely a response to pulmonary toxicity; and direct attribution of skin tumors in mice to antimony trioxide also was inappropriate. Furthermore, NTP studies observed aggressively progressing inflammatory pulmonary responses at exposure levels that would be associated with relatively benign, nonprogressive pneumonitis in humans. Dr. Boreiko concluded by stating that translation of the findings of the NTP studies to humans is less clear-cut than it might first appear.

Rita Cortvrindt, an independent advisor, presented comments on behalf of Campine, a Belgian producer of antimony, by telephone. She stated that in 100 years of operation, no cases of lung cancer have been observed among Campine's workers. Health monitoring of workers by an independent company has found only a weak relationship between pulmonary function and years of exposure to antimony trioxide, and no relationship between liver or pulmonary function and mean urinary antimony concentration. In the past 20-plus years, chest X-rays of workers have shown no pulmonary lesions.

Ms. Cortvrindt stated that Campine does not agree with the draft monograph's conclusions drawn from the NTP antimony trioxide study data. The large reduction in body weight of exposed rats indicated that the maximum tolerated dose was exceeded; therefore, the results at the highest exposure levels were not relevant. The study also showed much higher blood levels of antimony in rats than in mice; this species-specific difference in toxicokinetics is supported by many other studies, indicating that mice are not a good model for human absorption or accumulation of antimony. Even at the lowest exposure level, the lung tissue burden of antimony was much higher in mice than in rats, which has implications for secondary effects of obstruction of the lung tissue by antimony trioxide. Therefore, lung tumors observed at the two highest exposure levels in rats and at all exposure levels in mice should not be considered in the evaluation because of pulmonary overload, which does not occur in humans. At the lowest exposure level in rats, the lung tumor incidences were within the historical control range, and the historical control range in mice is high. Furthermore, antimony in the lungs is found in the alveolar space in rodents, but is taken up by the interstitial tissue in humans, making the rat a poor model for lung effects in humans. Ms. Cortvrindt cited a recent review by Warheit *et al.* (2016) which concluded that the rat is over-sensitive to pulmonary overload and not representative of humans in studies of inhalation exposure to potential lung carcinogens. She

concluded by noting that the results showing skin tumors and lymphoma should be reevaluated, because hypoxia accelerates tumor growth in mice but reduces it in humans, and that pheochromocytoma was observed only in rats at high exposure levels under pulmonary overload conditions.

Dr. Bucher asked whether the data on health monitoring of Campine's workers have been published. Ms. Cortvrindt said that Campine is preparing a publication on the results of health monitoring of its workers and is willing to provide the data to NTP for use in its evaluation.

V. Peer Review of the Draft RoC Monograph on Antimony Trioxide

V.A. Cancer Evaluation Component

V.A.1 Properties and Human Exposure

V.A.1.1 Presentation on Properties and Human Exposure

Dr. Sanford Garner presented an overview of the key information on properties and human exposure. When the metalloid element antimony is combined with other elements, it can exist in several oxidation states, the most common of which are +3 and +5. Antimony species can undergo transformation both in the environment and biologically. The solubility of antimony(III) trioxide is quite limited in water, and the water solubility of antimony(V) pentoxide is even lower. However, antimony compounds are more soluble in simulated body fluids than in water; their solubility varies with pH and suggests bioavailability.

NTP concludes that a significant number of U.S. residents are or have been exposed to antimony trioxide. Its most widespread industrial use is as a flame-retardant synergist, and it is also used in the manufacture of polyethylene terephthalate (PET) plastics, art glass, and paints and glazes. Exposure of workers to antimony trioxide is most likely during its production and during manufacture of flame-retardant plastic. Consumers may be exposed through the use of products made of flame-retardant materials (such as furniture upholstery and electrical or electronic equipment).

The major route of exposure to antimony trioxide is inhalation of solid dust, and exposure levels during production of antimony trioxide have often exceeded the current American Conference of Governmental Industrial Hygienists threshold limit value of 500 $\mu g/m^3$. Urinary levels of elemental antimony in exposed workers are related to air levels of antimony trioxide. Urinary levels of antimony in the general population are low, but higher levels are found in younger children and are associated with lower socioeconomic status. Antimony trioxide is released to the air from industrial sources; through oxidation of other forms of antimony (such as from automobile brake materials, coal combustion, and recycling of automobile batteries); and through wear and tear of consumer products containing flame retardants. Oral and dermal exposure can also occur, especially among children crawling on and mouthing the materials.

V.A.1.2 Peer-Review Comments on Properties and Human Exposure

Dr. Hao Zhu, first reviewer, found the information on properties to be clear and complete; he had comments concerning the chemical structures, CAS numbers, or InChi Key for some of the antiomony compounds listed in Table 1-2.

Dr. Elaine Symanski, second reviewer, found the information on use, production, and human exposure to be clear and accurate. She suggested clarifying why ranges are reported for antimony consumption on page 14 and Table 2-1 and whether consumption data on page 14 are reported as gross weight or as weight of antimony content. She also suggested including more recent data from the updated U.S. Geological Survey *Minerals Yearbook.* She found the information on past and present exposure to be adequate. Automobile brake-wear particles could be mentioned as a potential source of exposure for workers in urban environments. She suggested adding information to Table 2-3 about the geographical locations of the industrial sites and years of monitoring; consistently indicating whether air antimony levels were based on personal or area samples; and indicating whether personal samples were full-shift samples. Dr. Symanski identified several studies that could be added to the table (Iavicoli *et al.* 2002, Goi *et al.* 2003, Miller *et al.* 2010, and Shelley *et al.* 2012). Concerning exposure of the general population, she suggested adding studies on exposure from cosmetics and jewelry (Weidenhamer and Clement 2007, Perez *et al.* 2017) in Section 2.4.1 and on exposure to metals (Pang *et al.* 2016, Whitworth *et al.* 2017) in Table 2-5. Dr. Garner noted that the ranges reported in the monograph for consumption data are the way companies report their data (i.e., no specific value was reported). He also clarified that the consumption data are for the gross weight of the material.

Dr. Elizabeth Ward, third reviewer, found the information on use, production, and human exposure to be clear and comprehensive, providing a sufficient basis for addressing the issue of significant exposure of U.S. residents to antimony trioxide. She suggested providing more detail on occupational and National Health and Nutrition Examination Survey (NHANES) urinary biomonitoring data; Table 2-5 could be expanded to show NHANES values for the 90th and 95th percentiles and results by age group, as urinary levels of antimony tend to be higher in younger children than in adults, possibly because of direct skin contact with materials containing antimony trioxide. The monograph provides sufficient evidence that occupational exposure to antimony trioxide is higher than exposure of the general population. However, it would be helpful to explain the limitations of the U.S. monitoring data from the Occupational Safety and Health Administration Exposure Health Dataset, to clarify why these data were not discussed in more detail.

V.A.1.3 Panel Discussion on Properties and Human Exposure

The Panel concurred with the statement that a significant number of persons living in the United States are exposed to antimony trioxide.

The meeting was recessed at 10:10 a.m. and reconvened at 10:23 a.m.

V.A.2 Studies of Cancer in Humans

V.A.2.1 Presentation on Studies of Cancer in Humans

Suril Mehta presented an overview of the key information on cancer studies in humans. Studies of lung-cancer mortality included two historical cohort studies of antimony-smelter workers, which were judged to be of high-to-moderate utility for informing the hazard evaluation, and a study of tin-smelter workers, whose utility was judged to be moderate. All studies found an increased risk of lung-cancer mortality, with estimated standardized mortality ratios of 1.39 and 1.55 in the higher-utility studies. However, the numbers of studies and of lung cancer deaths among exposed workers were small. The exposure-response relationship was examined only in

the tin-smelter study, which used air-sampling measurements and a job-exposure matrix to model antimony trioxide exposure. The antimony-smelter studies looked at ever-exposure to antimony and used external populations as comparators. The relationships seen were likely confounded by concurrent exposure to other metals and a high prevalence of smoking among workers in the older studies.

Studies of stomach cancer mortality included the same two cohort studies of antimony-smelter workers discussed above and a population-based case-control study examining death records in a region of Sweden where art glass was produced. The case-control study was judged to have low utility because of major concerns about potential exposure misclassification, confounding from occupational co-exposure, and low study sensitivity. Associations between antimony exposure and stomach cancer were inconsistent within and across the studies; the numbers of studies and of stomach cancer deaths among exposed workers were small; and the results were likely confounded by smoking and occupational lead exposure.

NTP's preliminary level-of-evidence conclusion was that the data available from studies in humans are inadequate to evaluate the relationship between human cancer and exposure specifically to antimony trioxide or other antimony compounds. Overall, the body of evidence was limited by small numbers of studies with small sample sizes for both lung and stomach cancer and potential confounding by smoking and occupational co-exposures.

V.A.2.2 Peer-Review Comments on Studies of Cancer in Humans

Dr. Ward, first reviewer, found the information on human cancer studies to be clear, complete, and well presented, and she agreed with the choice of studies for the evaluation. She noted that the statement on page 56 concerning the results of the Swedish case-control study was incorrect; the study found, if anything, a negative association between stomach cancer and antimony exposure. However, this statement did not influence the overall conclusion. She noted that the study of tin-smelter workers, which found a fairly large relative risk of lung cancer, used quite unusual analytic methods, involving the use of weighted exposure estimates derived from a different study; she suggested giving more emphasis to the risk estimate based on unweighted exposure estimates. She agreed with the limitations of the studies identified in the monograph, especially the substantial concern about confounding exposures.

In response to Dr. Ward's comments on the Swedish case-control study, Mr. Mehta explained that because of the likelihood of exposure misclassification, NTP had conducted a *post hoc* analysis pooling high and low exposure levels and found a weighted odds ratio of 1.36, which was not statistically significant. In the monograph, the risk associated with low exposure in the study was given more weight than the risk associated with high exposure, as the low-exposure estimate appeared to be more precise.

Dr. Symanski, second reviewer, suggested revising the statement on page 52 that confounding by smoking could be ruled out because of the magnitude of the effect estimate, as this is not always the case. Throughout this section, the lack of individually based exposure estimates was mentioned as a limitation of studies; however, individual-level exposure estimates generally are more precise than group-level estimates, though biased. This issue could be clarified in the text. Dr. Symanski also suggested removing the mention of Guo *et al.* (2016) in Section 4.3.3, as this cross-sectional study falls outside the types of studies included in the human cancer evaluation as stated on page 41.

V.A.2.3 Panel Discussion on Studies of Cancer in Humans and Vote on Preliminary Level-of-Evidence Conclusion

No other Panel members had comments on the evaluation of cancer studies in humans.

Dr. Ward moved that the Panel accept the preliminary level-of-evidence conclusion that the *data available from studies in humans are inadequate* to evaluate the relationship between human cancer and exposure specifically to antimony trioxide or other antimony compounds. Dr. Wise seconded the motion, which passed unanimously (6 yes, 0 no, 0 abstentions).

V.A.3 Studies of Cancer in Experimental Animals

V.A.3.1 Presentation on Studies of Cancer in Experimental Animals

Dr. Wang presented an overview of the key information on cancer studies in experimental animals. The most informative studies were the NTP (2017) studies of two-year exposures in mice and rats, which were judged to be of high utility in assessing carcinogenicity. Three other studies in rats had some limitations such as insufficient or flucturating exposure levels, small sample size, or concerns about the purity of the test material, and were judged to be of moderate or low utility.

In the NTP mouse study, increased incidences were found of malignant or combined benign and malignant lung tumors in both sexes, combined benign and malignant skin tumors in males, and malignant lymphoma in females. Dr. Wang noted that pulmonary overload alone does not induce lung tumors in mice, and that lung tumor incidence was increased at the low dose, where overload was not an issue.

In rats, three of four studies found increased incidences of lung tumors. In the NTP study, the incidences of alveolar/bronchiolar adenoma and carcinoma combined in male rats exceeded the concurrent and historical control incidences. Although these increases were not statistically significant, they were considered evidence of carcinogenicity because of the rarity of alveolar/bronchiolar carcinoma in Wistar Han rats, the possiblility for progression of the adenoma to carcinoma, and the intrinsic toxicity of antimony trioxide. The other two studies found significantly increased incidences of squamous-cell and scirrhous carcinoma of the lung in female rats. The NTP study also found increased incidences of pheochromocytoma of the adrenal medulla, a tumor known to increase in rats under hypoxic conditions.

NTP's preliminary level-of-evidence conclusion was that there is *sufficient evidence of carcinogenicity* for antimony trioxide from studies in experimental animals, based on increased incidences of malignant tumors and/or combined incidences of malignant and benign tumors at several tissue sites (lung, skin, adrenal gland, and lymphatic system) in two rodent species exposed to antimony trioxide by inhalation. Increased incidences were observed for lung tumors, skin tumors, and lymphoma (whole body) in mice and lung and adrenal-gland tumors in rats.

V.A.3.2 Peer-Review Comments on Studies of Cancer in Experimental Animals

Dr. Michael Waalkes, first reviewer, said that the presentation was generally technically correct and for the most part clear and objective. Four of the studies provided more-than-adequate evidence of carcinogenicity of antimony trioxide in experimental animals, which supports its listing as *reasonably anticipated to be a human carcinogen.*

Dr. Waalkes suggested that NTP consider and resolve the issue of the purity of the test substance used by Groth *et al.* (1986), because the reported 80% purity, which reduced the utility of the study, is probably incorrect. Volume 47 of the International Agency for Research on Cancer Monographs (IARC 1989) reports the purity as greater than 95%, so Dr. Waalkes consulted the original paper and concluded that 80% referred to the percentage of antimony in the test substance (KR-grade antimony trioxide, which today is 99.5% pure and used in flame retardant), not the purity of the test substance, which even if it were 100% pure could theoretically contain no more than 83.53% antimony by weight. Thus, the reported 80% antimony content would mean that the test substance was 95.8% antimony trioxide (consistent with >95% purity, as stated by IARC). He noted that concerns about lead and arsenic contamination drop sharply at the higher purity level, and he suggested consulting with producers of the KR-grade material or members of the IARC Working Group to resolve this issue. Dr. Wang concurred with Dr. Waalkes comments that the purity was greater than 95%.

Dr. Waalkes noted a formatting error in Table 5-8, p. 71, where lung adenoma data for male mice were included as data for female rats. He said that the section dealt very well with the issue of pulmonary overload. Whether overload is a direct cause of lung cancer is unresolved in the literature, but he felt it was worth stating that overload does not obligate tumor formation, as demonstrated by Newton *et al.* (1994), who found evidence of overload, but no tumors. He was bothered by the mention of non-statistically significant increases in lung tumor incidence and of pre-neoplastic changes as evidence for carcinogenicity, as he felt this was unnecessary and looked like overreach; the evidence for carcinogenicity was sufficient without it. The dose-response relationship for lung cancer in mice should be discussed in more depth; this is strong evidence of an agent-driven carcinogenic process and occurred in both sexes. With respect to the Watt (1983) dissertation, which was never published in the peer-reviewed literature, Dr. Waalkes suggested that NTP should clearly state in the text its own confidence in the paper, rather than relying on the IARC (1989) review.

Dr. Richard Peterson, second reviewer, concurred completely with the review by Dr. Waalkes. He found the section to be well written and focused on studies of high utility and quality. He noted that the carcinogenicity of antimony trioxide was obvious, especially based on the increased lung tumor incidences and dose-response relationship. With regard to pulmonary overload, the literature generally indicates that pulmonary neoplasia is not expected as a response in mice. He found it striking that pulmonary neoplasia was increased in mice both with and without pulmonary overload, and also in rats. He agreed that the adrenal medullary changes were likely secondary to hypoxia, and he suggested strengthening the statement on page 66 linking likely hypoxia and the development of pheochromocytoma. He also agreed with the assessment of the skin-tumor and lymphoma data, and that the data overall supported that antimony trioxide is a likely carcinogen in animal models.

V.A.3.3 Panel Discussion of Studies of Cancer in Experimental Animals and Vote on Preliminary Level-of-Evidence Conclusion

No other Panel members had comments on the evaluation of cancer studies in humans.

Dr. Waalkes moved that the Panel accept the preliminary level-of-evidence conclusion that there is sufficient evidence for the carcinogenicity of antimony trioxide from studies in experimental

animals. Dr. Peterson seconded the motion, which passed unanimously (6 yes, 0 no, 0 abstentions).

V.A.4 Disposition and Toxicokinetics

V.A.4.1 Presentation on Disposition and Toxicokinetics

Dr. Garner presented an overview of the key information on the disposition of antimony compounds and the toxicokinetics of antimony trioxide. Both trivalent and pentavalent forms of antimony can enter red blood cells, where the pentavalent form is reduced to the trivalent form. Absorption of antimony trioxide is greater via inhalation than oral exposure, but only about 5% to 10% of inhaled antimony trioxide is absorbed. Much of the inhaled material may be subject to mucociliary transport, resulting in oral absorption (which is about 1%). There is also potential for dermal absorption.

In exposed workers, air concentrations of antimony trioxide are related to elevated urinary levels of elemental antimony, confirming absorption. Antimony is excreted in both the urine and the feces. In the NTP studies, blood antimony levels were much higher in rats than in mice. In rats, blood antimony levels increased with increasing exposure level and exposure time, whereas in mice, they increased with increasing exposure level but only slightly over time. Lung burden increased over time in mice, but could not be adequately modeled, because of extremely high levels at the highest exposure level at day 551. In rats, lung burden over time was clearly related to exposure level and did not approach a steady state at the highest exposure level. Neither species reached the threshold for lung overload at the lowest exposure level, and both species greatly exceeded the threshold at the highest exposure level.

Dr. Waalkes asked how lungs were prepared for the assessment of antimony. Dr. Matt Stout, NTP, asked by Dr. Garner to respond, said that whole lungs were digested and analyzed by inductively coupled plasma atomic emission spectrometry. Dr. Stout confirmed that the measured lung burden would have included antimony that was not within the lung cells.

V.A.4.2 Peer-Review Comments on Disposition and Toxicokinetics

Dr. John Wise, first reviewer, found the section on disposition and toxicokinetics to be generally very clear, technically correct, and objectively presented. However, he commented that the text in Section 3.1.1 and the corresponding tables did not align well, in that it was difficult to follow how the tables supported the statements in the text, a problem that could be resolved by either revising the text or changing the table design; he noted that specific editorial suggestions were provided in his preliminary written comments. Also in Section 3.1.1, the process by which blood concentrations were normalized to exposure concentrations should be explained; the rationale for emphasizing increased antimony levels in bone marrow, thyroid, and blood was not clear; and in the last two sentences of page 30, paragraph 3, it was unclear what comparisons were being made. In Section 3.2.1, large differences in antimony tissue levels among rats, dogs, and cats should be clarified, to explain the source of the variation.

Dr. Garner explained that only very limited information was available on the tissue levels in dogs and cats.

Dr. Waalkes, second reviewer, found the section to be very well written, and had little to add to Dr. Wise's comments. He said it was worth noting that metabolism of other metalloids, such as

arsenic, also varies greatly in rats and mice, so the variation seen with antimony is not unexpected.

V.A.4.3 Panel Discussion on Disposition and Toxicokinetics

No other Panel members had comments on the section on disposition and toxicokinetics.

V.A.5 Mechanistic and Other Relevant Data

V.A.5.1 Presentation on Mechanistic and Other Relevant Data

Dr. Wang presented an overview of the key information on mechanistic and other relevant data. Data were included for antimony trioxide and for other compounds containing trivalent antimony. Evaluation of potential mechanisms of carcinogenicity was based on the key characteristics of carcinogens defined by Smith *et al.* (2016).

Antimony compounds are electrophilic and can interact with proteins and nucleic acids. Trivalent antimony is highly reactive with thiol groups, which are found in many enzymes involved in oxidation-reduction (redox) reactions and DNA binding. There is evidence that trivalent antimony compounds increase oxidative stress by decreasing intracellular levels of the reduced form of glutathione, increasing mitochondrial damage, and directly inhibiting redox enzymes.

Antimony trioxide caused DNA damage in prokaryotic and eukaryotic cells *in vitro* and in the lungs of mice after 12 months of inhalation exposure. It also caused chromosomal aberrations in human leukocytes *in vitro,* micronucleus formation in rodent cells *in vitro* and after inhalation exposure, and sister chromatid exchange in human and rodent cells *in vitro.* It did not cause point or frame-shift mutations. Antimony trichloride inhibits the repair of several specific types of DNA damage, and antimony potassium tartrate inhibits the differentiation of cultured skin cells by preventing the normal decrease in epidermal growth factor receptor (EGFR). Dr. Wang noted that skin is a cancer site in mice exposed to antimony trioxide, and that antimony trioxide exposure increased mutation of the EGFR gene in the lung tumors of mice and rats.

NTP concluded that the mechanistic studies provide supporting evidence for the cancer observed in experimental animals, and that there are no compelling data indicating that antimony trioxide acts through mechanisms which do not operate in humans.

V.A.5.2 Peer-Review Comments on Mechanistic and Other Relevant Data

Dr. Wise, first reviewer, found the discussion of mechanistic and other relevant data to be generally relevant, well considered, and reasonably thorough. His major concern was about the overall presentation. While he agreed with the premise of considering other antimony compounds, the first paragraph should address what is known about antimony trioxide, and other compounds should be addressed in separate paragraphs.

Dr. Wise said that using the Smith paradigm is appropriate, but he suggested reorganizing the discussion. The order in which the characteristics are discussed should be based on quantity of data, and should probably not start with electrophilic properties. The separate sections on transcriptomics and ToxCast high-throughput screening should be integrated into Smith's categories. The Smith approach needs to be better described in the introduction; Table E-1 might be moved into the monograph section. In the text, presentation of the cell-culture data was

oversimplified; there should be some consideration of dose, exposure time, and limitations of the model system, and more weight should be given to effects seen at low doses. Dr. Wise agreed that comparisons with arsenic were relevant, but its mentions seemed random and did not add anything. If arsenic is discussed, it should be done in a separate section and in a more thorough and deliberate manner.

Dr. Wise said that the beginning of the introduction detracted from its readability and flow. The discussion of "other relevant data" should be incorporated into the introduction. Section 6.1.1, carcinogenicity studies on other antimony compounds, seemed to belong in Section 5 and should be removed from the mechanism section. Although Section 6.1.2, non-cancer health outcomes, seemed to have been included to support the concept of lung as a target organ, it did not add anything and should be removed.

Section 6.3.1, mutagenicity, needs to include a sentence stating there are no mutagenicity studies in human cells, and an overall conclusion about mutagenicity in animal cells should be added. The tissue mutation data, while relevant to mechanism, should be moved from the mutagenicity section to a section dealing with *Egfr and Kras*. In Section 6.3.3, DNA damage, there is no discussion of antimony adducts or how antimony might interact with the DNA backbone; if there are no data, that should be stated, because this is such an important end point. Section 6.10, integration of mechanistic information, paragraph 4, needs to be revised for accuracy in the use of the term "mutagenic." Tables E.1-3 and E.1-4 are virtually identical and should be combined, and the tables in E.2 should be separated into tables for antimony trioxide and for all other antimony compounds. In response, Dr. Wang clarified that no studies on antimony adducts were found.

Dr. Zhu, second reviewer, agreed that the presentation of the mechanistic and other relevant data was confusing, and that the data for antimony trioxide and for other antimony compounds should be presented separately. He suggested that the discussion of mechanisms should include consideration of the metabolism of antimony compounds. He also suggested searching PubChem to confirm which antimony compounds were most active in high-throughput screening assays.

Dr. Waalkes, third reviewer, suggested placing more emphasis on the presumed role of the antimony(3+) ion as the active species underlying the mechanistic effects. He also suggested reformulating the discussion of arsenic to emphasize parallels between the involvement of antimony and arsenic with skin tumors, which fits with the RoC's consideration of structurally related chemical classes.

V.A.5.3 Panel Discussion on Mechanistic and Other Relevant Data

No other Panel members had comments on the section on mechanistic and other relevant data.

The meeting was recessed at 12:50 p.m. and reconvened at 1:57 p.m.

V.A.6 Overall Cancer Evaluation and Preliminary Listing Recommendation

V.A.6.1 Presentation and Peer-Review Comments on the Overall Cancer Evaluation

Dr. Wang summarized NTP's preliminary conclusions from the evaluation of antimony trioxide. A significant number of people living in the United States are exposed to antimony trioxide; the highest exposure levels occur in the workplace, and the general population is exposed through consumer products and via primary and secondary environmental releases. The evidence from

studies in humans is inadequate to evaluate the carcinogenicity of antimony in humans, because of the small numbers of studies, small sample sizes, and potential confounding by smoking and occupational co-exposures. There is sufficient evidence for the carcinogenicity of antimony trioxide from studies in experimental animals, based on increased incidences of malignant tumors and/or combined incidences of malignant and benign tumors at several tissue sites (lung, skin, adrenal gland, and lymphatic system) in two rodent species exposed to antimony trioxide by inhalation. Supporting mechanistic information comes from studies with antimony trioxide and other trivalent antimony compounds.

Dr. Zhu, first reviewer, agreed with the integration of evidence and the preliminary listing recommendation and had no additional comments.

Dr. Peterson, second reviewer, found the section to be well written and integrated. He said that it summarized the draft monograph well, but noted that Section 7.2 should be revised to reflect any changes made in Section 6.

V.A.6.2 Vote on the Preliminary Listing Recommendation

Dr. Peterson moved that the Panel accept NTP's preliminary listing recommendation that antimony trioxide should be listed in the *Report on Carcinogens* as *reasonably anticipated to be a human carcinogen* based on sufficient evidence from studies in experimental animals and supporting mechanistic data. Dr. Waalkes seconded the motion, which passed unanimously (6 yes, 0 no, 0 abstentions).

V.B. Draft RoC Substance Profile

Dr. Wang summarized the purpose and contents of the draft substance profile.

Dr. Symanski, first reviewer, noted that comments made concerning the monograph text should also be considered in the substance profile. In addition, the mention on page P-5 of non-cancer health outcomes should be removed, because it is not salient to the question of carcinogenicity. Potential exposure of workers to antimony trioxide from emissions in high-traffic areas should be added to the table of sources of exposure. In the section on exposure of the general population, reporting air levels as the inhalable fraction (PM_{10} or $PM_{2.5}$) would be preferable to reporting total suspended particulates. Dr. Symanski also suggested adding cosmetics and jewelry as potential sources of exposure.

Dr. Ward, second reviewer, said that the summary of lung-cancer studies in humans slightly overstated the findings. Some indication of the inconsistencies between studies depending on analytic approach would be helpful, and the statement concerning stomach cancer should be reconsidered, as it is inconsistent with the data presented in the monograph and with the original study.

Dr. Waalkes, third reviewer, mentioned the issue of test-substance purity in the study by Groth *et al.* (1986). He suggested eliminating the sentence on page P-1 about benign tumors progressing to malignancy, because it is too vague and is inconsistent with the RoC listing criteria. He also suggested removing the reference to the non-significant increase in combined benign and malignant lung tumors in male rats, as this is not appropriate or necessary. Dr. Lunn clarified that the potential for progression of benign tumors has been considered in past RoC evaluations.

Dr. Wise, fourth reviewer, said the profile section on mechanisms read quite well. He recommended deleting the second paragraph and the last sentence of the fourth paragraph, as these were speculative and judgmental and did not add much.

No other Panel members had comments on the draft substance profile.

VI. Closing Remarks on Draft RoC Monograph

Dr. Wise commended the RoC staff for their hard work and excellent job; this was seconded by the other panelists. Drs. Fry, Bucher, and Wolfe thanked the Panel members for their efforts, thorough review, and detailed comments.

The meeting was adjourned at 2:15 p.m.

VII. Literature Cited

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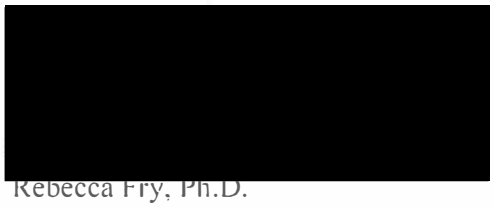
VIII. Approval of the Peer Review Report by the Chair of the Peer Review Panel

This peer review report has been read and approved by the chair of the January 24, 2018 NTP Report on Carcinogens Monograph Peer Review Panel.



Rebecca Fry, Ph.D.

Peer Review Panel Chair

Date:

3.7.2018