Safe Drinking Water and Toxic Enforcement Act of 1986
Proposition 65

Final Statement of Reasons

Title 27, California Code of Regulations

Section 25705(b) Specific Regulatory Levels Posing No Significant Risk

No Significant Risk Level: Antimony Trioxide

August 2023

California Environmental Protection Agency

Office of Environmental Health Hazard Assessment

General Information

Overview of Proposed Regulation

This is the Final Statement of Reasons (FSOR) for the adoption of a No Significant Risk Level (NSRL) for antimony trioxide in Title 27, California Code of Regulations, section 25705(b).[1] The NSRL of 0.13 micrograms per day (µg/day) (inhalation) for antimony trioxide is based on a carcinogenicity study in rodents and was derived using the methods described in Section 25703. The NSRL is based upon the results of the most sensitive scientific study deemed to be of sufficient quality.[2]

Process and Timeline

Antimony trioxide was listed as a chemical known to the state to cause cancer for purposes of Proposition 65[3] on October 1, 1990. On August 26, 2022, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Proposed Rulemaking to adopt into section 25705(b) an NSRL for antimony trioxide. The Initial Statement of Reasons (ISOR) that accompanied the Notice of Proposed Rulemaking set forth the grounds for the amendment to the regulation. On July 12, 2023, OEHHA issued a notice of modification to limit the proposed NSRL to exposure via inhalation and to add documents to the rulemaking file, in compliance with the requirements of California Code of Regulations, Title 1, Section 44. The availability period was July 12, 2023, through July 27, 2023. The NSRL being adopted is 0.13 micrograms per day (µg/day) (inhalation).

Updates to Information Contained in the Initial Statement of Reasons

During the comment period on the original proposal, OEHHA received comments regarding the route of exposure to antimony trioxide. Specifically, comments pointed out that the absorption rate by the oral and inhalation exposure routes appears to differ. As stated in the ISOR, the animal carcinogenicity studies that were used to determine the cancer potency exposed the animals to aerosols of antimony trioxide (particles) via the inhalation route. The carcinogenicity of antimony trioxide in inhalation studies reflects effects from both the inhaled particles and, subsequent to inhalation, the dissolved form.

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[1] All further regulatory references are to sections of Title 27 of the Cal. Code of Regs., unless otherwise indicated.
[2] Section 25703(a)(4).
[3] The Safe Drinking Water and Toxic Enforcement Act of 1986, codified at Health and Safety Code section 25249.5 *et. seq*., hereafter referred to as “Proposition 65” or “The Act.”

After careful review of available scientific literature reviews such as those by the European Commission (2008), ATSDR (2019), WHO (2003), IARC (1989), and Boreiko and Rossman (2020)[4] and toxicokinetic data from studies such as Gross et al. (1955), Groth et al. (1986), Hiraoka (1986), Newton et al. (1994), Sunagawa (1981), and Westrick (1953),[5] OEHHA determined there are not enough data to assess the relative contributions of particulate and dissolved forms of antimony trioxide to the carcinogenic effects observed in the inhalation studies to confidently inform quantitative route-to-route extrapolation. With this uncertainty, and the apparent differences in absorption between the oral and inhalation routes, OEHHA determined that it could not derive an NSRL of this chemical for exposures via the oral route.

Therefore, OEHHA proposed in its Notice of Modification, dated July 12, 2023, to limit the NSRL to exposure via inhalation. This does not preclude the possibility of the development of an NSRL for the oral route in the future when sufficient information becomes available.

In addition to the documents referenced in the ISOR,[6] the following documents were added to the record during the rulemaking process, in the interest of completeness and

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[4] European Commission (2008). European Union risk assessment report. Diantimony trioxide. CAS No: 1309-64-4. EINECS No: 215-175-0. Risk Assessment. Luxembourg, Luxembourg: Office for Official Publications of the European Communities. Available from: https://echa.europa.eu/documents/10162/553c71a9-5b5c-488b-9666-adc3af5cdf5f. Agency for Toxic Substances Disease Registry (ATSDR 2019). Toxicological profile for antimony and compounds. Atlanta, GA. Available from: https://www.atsdr.cdc.gov/toxprofiles/tp23.pdf. WHO (2003). Antimony in drinking-water – background document for development of WHO Guidelines for Drinking-water Quality. Geneva. Available from: https://cdn.who.int/media/docs/default-source/wash-documents/wash-chemicals/antimony.pdf. International Agency for Research on Cancer (IARC 1989). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 47, Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting. IARC, World Health Organization, Lyon, France. Available from: https://publications.iarc.fr/65. Boreiko CJ and Rossman TG (2020). Antimony and its compounds: Health impacts related to pulmonary toxicity, cancer and genotoxicity. Toxicol. Appl. Pharmacol. 403:115156.

[5] Gross P, Brown JH, Westrick ML, Srsic RP, Butler NL, Hatch TF (1955). Toxicologic study of calcium halophosphate phosphors and antimony trioxide. I. Acute and chronic toxicity and some pharmacologic aspects. AMA Arch Ind Health 11(6):473-478. Groth DH, Stettler LE, Burg JR, Busey WM, Grant GC, Wong L (1986). Carcinogenic effects of antimony trioxide and antimony ore concentrate in rats. J Toxicol Environ Health 18(4):607-626. Hiraoka N (1986). The toxicity and organ-distribution of antimony after chronic administration to rats. Journal of Kyoto Prefectural University of Medicine 95: 997-1017. Newton PE, Bolte HF, Daly IW, Pillsbury BD, Terrill JB, Drew RT, Ben-Dyke R, Sheldon AW, Rubin LF (1994). Subchronic and chronic inhalation toxicity of antimony trioxide in the rat. Fundam Appl Toxicol. 22(4):561-576. Sunagawa S (1981). Experimental studies on antimony poisoning. Igaku Kenkyu 51(3):1-14. Westrick ML (1953). Physiologic responses attending administration of antimony, alone or with simultaneous injections of thyroxin. Proc Soc Exp Biol Med 82(1):56-60.

[6] Anderson EL and the Carcinogen Assessment Group of the US EPA (1983). Quantitative approaches in use to assess cancer risk. Risk Analysis 3:277-295. Bailer AJ and Portier CJ (1988). Effects of treatment-induced mortality and tumor-induced mortality on test for carcinogenicity in small samples. Biometrics

in accordance with Government Code sections 11347.1, subdivision (a) and 11346.9(a)(1):

- Agency for Toxic Substances Disease Registry (ATSDR 2019). Toxicological profile for antimony and compounds. Atlanta, GA. Available from: https://www.atsdr.cdc.gov/toxprofiles/tp23.pdf
- Boreiko CJ and Rossman TG (2020). Antimony and its compounds: Health impacts related to pulmonary toxicity, cancer and genotoxicity. Toxicol. Appl. Pharmacol. 403:115156.
- European Commission (2008). European Union risk assessment report. Diantimony trioxide. CAS No: 1309-64-4. EINECS No: 215-175-0. Risk Assessment. Luxembourg, Luxembourg: Office for Official Publications of the European Communities. Available from: https://echa.europa.eu/documents/10162/553c71a9-5b5c-488b-9666-adc3af5cdf5f
- Gross P, Brown JH, Westrick ML, Srsic RP, Butler NL, Hatch TF (1955). Toxicologic study of calcium halophosphate phosphors and antimony trioxide. I. Acute and chronic toxicity and some pharmacologic aspects. AMA Arch Ind Health 11(6):473-478.
- Groth DH, Stettler LE, Burg JR, Busey WM, Grant GC, Wong L (1986). Carcinogenic effects of antimony trioxide and antimony ore concentrate in rats. J Toxicol Environ Health 18(4):607-626.
- Hiraoka N (1986). The toxicity and organ-distribution of antimony after chronic administration to rats. Journal of Kyoto Prefectural University of Medicine 95: 997-1017.
- International Agency for Research on Cancer (IARC 1989). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 47, Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting. IARC, World Health Organization, Lyon, France. Available from: https://publications.iarc.fr/65

44(2):417-431. National Toxicology Program (NTP 2017). 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 Technical Report Series No. 590. US Department of Health and Human Services, NTP, Research Triangle Park, NC. Available at: https://ntp.niehs.nih.gov/go/tr590. National Toxicology Program (NTP 2018). Report on Carcinogens Monograph on Antimony Trioxide. RoC Monograph 13. US Department of Health and Human Services, NTP, Research Triangle Park, NC. Available at: https://ntp.niehs.nih.gov/ntp/roc/monographs/antimony_final20181019_508.pdf. US EPA (2005). US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. Washington, DC. EPA/630/P-03/001B. March 2005.

- Newton PE, Bolte HF, Daly IW, Pillsbury BD, Terrill JB, Drew RT, Ben-Dyke R, Sheldon AW, Rubin LF (1994). Subchronic and chronic inhalation toxicity of antimony trioxide in the rat. Fundam Appl Toxicol. 22(4):561-576.
- Sunagawa S (1981). Experimental studies on antimony poisoning. Igaku Kenkyu 51(3):1-14.
- Westrick ML (1953). Physiologic responses attending administration of antimony, alone or with simultaneous injections of thyroxin. Proc Soc Exp Biol Med 82(1):56-60.
- WHO. 2003. Antimony in drinking-water – background document for development of WHO Guidelines for Drinking-water Quality. Geneva. Available from: https://cdn.who.int/media/docs/default-source/wash-documents/wash-chemicals/antimony.pdf

Informative Digest

Proposition 65 prohibits a person in the course of doing business from knowingly and intentionally exposing any individual to a chemical that has been listed as known to the state to cause cancer or reproductive toxicity without first giving clear and reasonable warning to such individual.[7] The Act also prohibits a business from knowingly discharging a listed chemical into water or onto or into land where such chemical passes or probably will pass into any source of drinking water.[8]

For carcinogens, an exemption from the warning requirement is provided by the Act when the exposure for which the person is responsible can be demonstrated to produce no significant risk, or when a discharge which otherwise complies with all applicable requirements would not cause any significant amount of the discharged or released chemical to enter any source of drinking water.[9]

A determination that a level of exposure poses no significant risk may be made utilizing regulations that have previously been adopted by OEHHA (Sections 25701-25721). Section 25701 describes alternative methods for making such a determination. Section 25703 sets forth the process for determining “no significant risk” levels for purposes of Proposition 65 and Section 25705 establishes those levels for certain listed chemicals.

[7] Health and Safety Code section 25249.6.
[8] Health and Safety Code section 25249.5.
[9] Health and Safety Code sections 25249.9, 25249.10.

The NSRL for antimony trioxide (inhalation), being adopted in Section 25705, is based upon the results of the most sensitive scientific study deemed to be of sufficient quality.[10]

Details on the basis for the proposed NSRL for antimony trioxide, including documents relied upon by OEHHA, are provided in the ISOR for this regulatory amendment, as updated above. The ISOR is available on request from Esther Barajas-Ochoa at esther.barajas-ochoa@oehha.ca.gov and is posted on the OEHHA website at www.oehha.ca.gov.

Anticipated Benefits of the Proposed Regulation

Some businesses may not be able to afford the expense of establishing an NSRL and therefore may be exposed to litigation for a failure to warn or for a prohibited discharge of the listed chemical. By providing an NSRL, this regulatory proposal spares businesses the expense of calculating their own NSRL and may also enable them to reduce or avoid litigation costs. In addition, the NSRL does not require, but may encourage, businesses to reduce exposures to the listed chemical to a level that does not cause a significant exposure, thereby providing a public health benefit to Californians. This in turn may reduce resident, worker and environmental exposures to antimony trioxide.

No Inconsistency or Incompatibility with Existing Regulations

As explained in the ISOR, as updated above, the NSRL for antimony trioxide was determined in a manner consistent with existing regulations regarding the establishment of NSRLs. The proposed amendment would make amended section 25705 the only regulation addressing No Significant Risk Levels for this specific chemical under Proposition 65. Therefore, OEHHA has determined that the proposed regulation is neither inconsistent nor incompatible with existing state regulations.

Summary of and Response to Peer Review Comments

OEHHA provided the Notice of Proposed Rulemaking and the ISOR as well as the Notice of Modification and added documents for the proposed NSRL for antimony trioxide to the members of the Carcinogen Identification Committee for their review and comment, as required by Section 25701(e). OEHHA received peer-review comments from committee member Mariana C. Stern, Ph.D on the original proposal. No peer-

[10] Health and Safety Code section 25703(a)(4).

review comments were received from members of the Carcinogen Identification Committee on the modification to the proposal or the documents added to the rulemaking file.

Comment 1 (Dr. Stern): The ISOR is comprehensive and provides all the necessary details to evaluate the process used to arrive to an NSRL for this chemical.

Response: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 2 (Dr. Stern): "Overall, this evaluation is based on this one study conducted by NTP, in one strain of mice. Ideally, more studies in different strains of mice might be valuable to make a more informed decision to recapitulate the variability of metabolic pathways in the human population, as these differences may impact the threshold of carcinogenicity of this chemical."

Response: NSRLs are derived according to procedures established in Section 25703, which provides that NSRLs are based on the most sensitive study(ies) of sufficient quality available at the time of development. This is consistent with standard risk assessment practice and consistent with advice by scientific authorities.[11] Following the procedures laid out in regulations in section 25703, OEHHA reviewed the available studies. The available pharmacokinetic and metabolic data on the chemical were not sufficient to support an alternative approach to cancer potency estimation.

No changes to the proposed regulation were made based on this comment.

Comment 3 (Dr. Stern): The study relied on was an inhalation study. "Whereas inhalation is a likely route of exposure, contact exposure through the skin is also a concern, and there are no studies to evaluate this."

Response: OEHHA acknowledges that skin contact with antimony trioxide is possible. As the commenter notes, however, there are no sufficient studies to evaluate this.

Comment 4 (Dr. Stern): "I think the data is premature to establish a NSRL for antimony trioxide, and that at a minimum, this decision should merit a discussion with the entire committee to discuss some of these concerns and hear the opinion of various experts."

Response: Members of the Carcinogen Identification Committee provide peer review on proposed NSRLs in accordance with Section 25701(e), which specifies that whenever OEHHA proposes to adopt "a level of exposure to a listed carcinogen that shall be deemed to pose no significant risk of cancer, the lead agency shall provide to each member of the Carcinogen Identification Committee notice of the proposed action,

[11] National Research Council (2009). Science and Decisions: Advancing Risk Assessment. Washington, DC: The National Academies Press. Available at: https://doi.org/10.17226/12209.

the proposed change to the regulation, and a copy of the initial statement of reasons supporting the proposal for their review and comment."[12] OEHHA followed the process outlined in regulation, which does not include a requirement for the Carcinogen Identification Committee to meet.

No changes to the proposed regulation were made based on this comment.

Comment 5 (Dr. Stern): "[G]iven that the mechanistic and genotoxicity data suggest that there might be multiple mechanisms of action for this chemical, the multistage model might not capture well the cancer potency of this chemical."

Response: As stated in the regulations, "The absence of a carcinogenic threshold dose shall be assumed and no-threshold models shall be utilized. A linearized multistage model for extrapolation from high to low doses, with the upper 95 percent confidence limit of the linear term expressing the upper bound of potency shall be utilized."[13] For antimony trioxide, while there are data suggesting multiple mechanisms, there are no specific mechanistic data to support deviation from the standard assumptions set forth in regulation for the cancer dose-response analysis.

This general approach is also consistent with other regulatory agencies, such as US EPA. As described in the US EPA Benchmark Dose Technical Guidance, "it is a current practice of U.S. EPA's IRIS program to prefer the multistage model for cancer dose-response modeling of cancer bioassay data (Gehlhaus et al., 2011). The multistage model (in fact a family of different stage polynomial models) is sufficiently flexible for most cancer bioassay data, and its use provides consistency across cancer dose-response analyses."[14]

No changes to the proposed regulation were made based on this comment.

Comment 6 (Dr. Stern): "Whereas a dose associated with 5% increased risk of developing tumors seems the standard for the cancer potency calculations, it begs the question of what would happen if a lower threshold would have been used (e.g. 1%). In the human population, such small increase in risk can translate into large numbers of individuals depending on the incidence rate of a given cancer. Given the observed risk of this chemical with lung cancer, the #2 cancer in the US and #1 cause of cancer death, an increase of risk of 1% over the baseline population is of concern, as it can translate into a significant number of preventable deaths."

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[12] Section 25701(e).
[13] Section 25703(a)(5).
[14] US EPA (2012). Benchmark Dose Technical Guidance. Washington, DC: US EPA. Available at: https://www.epa.gov/risk/benchmark-dose-technical-guidance.

Response: The NSRL does not correspond to a 5 percent increase in cancer risk. The dose associated with the 5% risk is a starting point for use in extrapolating to lower doses. The NSRL corresponds to a cancer risk in humans of 1 in 100,000 for human exposure every day over a lifetime. OEHHA agrees that a 1% increase in risk would translate into large numbers of individuals. The NSRL reflects a risk level of 1/100,000 (10^{-5}), not 1%.

No changes to the proposed regulation were made based on this comment.

Comment 7 (Dr. Stern): "The interspecies scaling procedure considered the average body weight in humans of 70 Kg, which is the assumed value for men according to the risk assessment guidelines used by OEHHA. Among women, the assumed weight is 58, which would give an NSRL of 0.11 ug/day instead of 0.13 ug/day. The animal experiments do show data for females, in fact, dose-response results are stronger for women."

Response: Standard cancer risk assessment practice (as provided in Section 25703) does not assume that male and female animals apply separately to male and female humans. Rather, OEHHA uses the most sensitive study, whether in male or female animals, to be protective of the entire human population. In this case, the most sensitive study, in female mice, served as the basis for deriving an NSRL for all humans. OEHHA applied the default approach in Section 25703 to convert from an estimate of cancer potency in animals to a human cancer potency estimate. The default body weight of 70 kg is taken as representative of the human population and is intended to protect the entire general population.[15]

No changes to the proposed regulation were made based on this comment.

Comment 8 (Dr. Stern): "There is no data presented about the impact this chemical may have on fetuses, infants, children, and adolescents."

Response: No data were identified in the literature or other sources that examined the carcinogenic effects of antimony trioxide exposure on the cancer risk of fetuses, infants, children, or adolescents. The NSRL is based on the most sensitive studies of sufficient quality available at the time of development, following the criteria, principles and assumptions specified in Section 25703.

No changes to the proposed regulation were made based on this comment.

[15] Section 25703(a)(8).

Summary of and Response to Public Comments on Originally Proposed Regulation – August 2022

A public comment period was provided from August 26, 2022, to October 11, 2022. The notice stated that a public hearing would be held upon request. No request for a public hearing was received. OEHHA received written public comments on the proposed rulemaking from the following organizations:

- Ben Gann on behalf of the American Chemistry Council's North American Flame Retardant Alliance (NAFRA)
- Center for Environmental Health, Defend Our Health, Center For Food Safety, The Last Beach Cleanup, Safer States, Energy Innovation Center, Ecology Center, and The Story of Stuff Project (CEH)
- Claigan Environmental Inc. (Claigan) (late submission)
- Gina Solomon, Bruce Lanphear, and Leonardo Trasande (GSolomon)
- International Antimony Association (i2a)
- John E. Heinze on behalf of the PET Resin Association (PETRA)
- Mitzi Ng Clark on behalf of Keller and Heckman LLP (KH)

The comments are summarized and responded to below. Some comments did not constitute an objection or recommendation directed at the regulatory proposal for which comments were solicited or the procedures followed in this rulemaking process. Consistent with the Administrative Procedure Act, OEHHA is not required to respond to such comments in the FSOR. The absence of responses to such comments should not be construed to mean that OEHHA in any way agrees with or disagrees with them.

Choice of study

Comment 9 (i2a, CEH, GSolomon): Three commenters find that the NTP studies are the most appropriate studies to derive the NSRL.

Response: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Methods of calculating the NSRL

Comment 10 (CEH, GSolomon): Two commenters find that the methods used to calculate the NSRL are appropriate and the proposed NSRL is correctly calculated.

Response: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Combining tumors

Comment 11 (i2a): "Lymphoma incidence in female mice was summed with lung tumor induction even though the lymphomas observed were a seeming reactionary response to lung tumors and hypoxia. The induced lymphomas were of a B cell origin whereas chemically induced lymphomas usually exhibit a T cell origin. (Ward et al.,). Pooling of lung cancer and lymphoma data to generate a dose response function for tumor development is thus of questionable validity but benefits NSRL derivation since dose dependence for lung tumor induction is less than robust and the pooling of lesions at different sites confers dose dependence that facilitates derivation of a NSRL. If there is an etiological linkage assumed between lymphoma and lung tumor formation it should be stated. In the absence of such a linkage, NSRL derivation should be indexed to lung tumor formation only since it is the primary lesion for which a plausible mode of action can be proposed."

Response: The incidences of lung tumors and lymphomas were not summed. Rather, OEHHA conducted a multisite analysis of two types of treatment-related tumors which are not etiologically linked to one another. US EPA's Benchmark Dose Software[16] has a multi-site module that is used to estimate a cumulative risk of carcinogen treatment-related tumors by summing the maximum likelihood estimates for the individual multistage models for the different cancer sites within a given study. It is OEHHA's longstanding practice to conduct multisite analyses when tumors are induced at multiple sites. Combining different tumor types within the same tissue is done where appropriate based on considerations of pathology and/or cellular origin.[17]

In these multisite analyses, each tumor site is treated as independent of one another to calculate composite risk ("i.e., the risk of developing any combination of tumors at any site, not the risk of developing tumors at every site considered"[18]). This is now the standard of practice in risk assessment. US EPA's benchmark dose training module for cancer models explains, "Basing unit risk estimates on only one tumor type may underestimate the carcinogenic potential of a chemical that is observed to induce neoplasia at multiple sites in a bioassay (NRC, 1994)."[19] The National Research Council states, "In the analysis of animal bioassay data on the occurrence of multiple tumor

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[16] US EPA Benchmark Dose Software (BMDS). National Center for Environmental Assessment, US EPA. Available at: https://www.epa.gov/bmds.
[17] OEHHA (2009). Air Toxics Hot Spots Risk Assessment Guidelines Part II: Technical Support Document for Cancer Potency Factors" (May 2009), Office of Environmental Health Hazard Assessment. Available at: http://www.oehha.ca.gov/air/hot_spots/tsd052909.html.
[18] US EPA (2014). Benchmark Dose Modeling – Cancer Models. Benchmark Dose Software Training Webinars. Available at: https://clu-in.org/conf/tio/bmds/slides/BMDS_Cancer_Models.pdf.
[19] *Ibid.*

types, the cancer potencies should be estimated for each relevant tumor type that is related to exposure, and the individual potencies should be summed for those tumors."[20] Therefore, since multiple treatment-related tumor types were observed, OEHHA appropriately conducted a multisite analysis for the female mouse study of antimony trioxide.

Regarding the comment that the NSRL should be based only on lung tumors since it is the only tumor type for which "a plausible mode of action can be proposed," it is not a requirement for a mode or mechanism of action to be established in order to conduct dose-response assessment.

No changes to the proposed regulation were made based on this comment.

Mechanistic issues

Comment 12 (CEH, GSolomon): Two commenters state that antimony trioxide acts through multiple carcinogenic mechanisms, including both genotoxic and non-genotoxic pathways, that are relevant to human carcinogenesis. "The clear presence of genotoxicity as one of the mechanisms of action makes OEHHAs choice of a low dose linear assumption both appropriate and necessary." (GSolomon)

Response: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 13 (i2a): "The i2a further acknowledges that the method of NSRL derivation employed is potentially appropriate for a direct-acting genotoxic carcinogen. However, i2a submits that the procedures used to derive the NSRL are predicated upon mode of action assumptions that are not applicable to ATO which has usually been judged to act via indirect mechanisms."

Response: Antimony trioxide likely acts through several mechanisms. The NTP Report on Carcinogens Monograph on Antimony Trioxide concludes, "antimony (III) trioxide is electrophilic, can cause oxidative stress, likely inhibits DNA repair, can cause oxidative damage, and is likely to decrease cell differentiation."[21] For cancer risk assessment, the default approach used by OEHHA[22] and US EPA[23] is that, in the absence of compelling

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[20] National Research Council (1994). Science and Judgment in Risk Assessment. Washington, DC: The National Academies Press. Available at: http://www.nap.edu/catalog/2125.html.
[21] NTP (2018), full citation provided in footnote 6.
[22] Initial Statement of Reasons – Amendment to Section 25705: No Significant Risk Level for Antimony Trioxide. Available at: https://oehha.ca.gov/media/downloads/crnr/antimonytrioxidensrlisor082622.pdf. OEHHA (2009), full citation provided in footnote 17. OEHHA (1989). Final Statement of Reasons – No Significant Risk Levels and No Observable Effect Levels. Available at: https://oehha.ca.gov/proposition-65/crnr/final-statement-reasons-no-significant-risk-levels-and-no-observable-effect.
[23] US EPA (2012), full citation provided in footnote 14.

information indicating the existence of a threshold, the linear extrapolation method will be used. In particular, it is not necessary to establish that a chemical is a direct-acting genotoxic carcinogen before using the linear extrapolation method. The approach used in the calculation of the NSRL – a non-threshold assumption using the multistage cancer model – is consistent with Section 25703, current quantitative assessment practices for carcinogens by OEHHA, as well as current US EPA practices.[24] The evidence provided by the commenter does not support a departure from the default approach is scientifically more appropriate.

No changes to the proposed regulation were made based on this comment.

Comment 14 (i2a): "Genotoxicity and carcinogenicity studies of antimony compounds, including ATO, were recently reviewed (Boreiko and Rossman, 2020) and it was noted that antimony compounds are weak in vitro genotoxins that do not exert genotoxicity in vivo and lack the ability to undergo covalent interactions with DNA."

Response: As reported in the ISOR, NTP concluded that antimony trioxide is not mutagenic in bacterial or mammalian cells *in vitro*, but can cause DNA damage in mouse lung *in vivo*, micronucleus formation *in vivo*, and chromosomal aberrations and sister chromatid exchange *in vitro*.[25] Specifically, increased micronucleus formation was observed in the red blood cells of mice exposed to antimony trioxide.[26]

Regarding the statement by i2a that antimony trioxide lacks the ability to undergo covalent reactions with DNA, citing Boreiko and Rossman (2020),[27] this paper does not review data specifically for antimony trioxide on endpoints such as covalent interactions with DNA, formation of DNA adducts, or other electrophilic interactions.

NTP summarizes the issue of electrophilicity as follows:

"Although electrophilicity of antimony(III) trioxide has not been reported, antimony compounds are electrophilic and might interact directly with nucleic acids and proteins. Trivalent antimony is highly reactive with sulfhydryl groups and, in particular, vicinal thiol groups. Proteins containing vicinal thiol groups include GSH and enzymes that bind to DNA."[28]

And as noted in the previous response, NTP concluded that "antimony (III) trioxide is electrophilic."[29]

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[24] US EPA (2012), full citation provided in footnote 14.
[25] NTP (2018), full citation provided in footnote 6.
[26] NTP (2017), full citation provided in footnote 6.
[27] Boreiko and Rossman (2020), full citation provided in footnote 4.
[28] NTP (2018), full citation provided in footnote 6.
[29] *Ibid*.

Regardless, evidence of genotoxicity is not a prerequisite for use of a linear extrapolation method in the derivation of an NSRL. As explained in the previous response, the default method of using the multistage cancer model is the most scientifically appropriate, and no alternative methods were proposed that would be more suitable for modeling the antimony trioxide data.

No changes to the proposed regulation were made based on these comments.

Comment 15 (i2a): "Although NTP asserts they conducted genotoxicity studies that indicated induction of genotoxic impacts *in vivo* is a probable mode of action for carcinogenesis, the NTP studies were not conducted in compliance with OECD guidelines for genotoxicity testing. For example, The NTP Comet assay studies neglected to include controls for cytotoxicity, apoptosis or terminal differentiation even thought it was plainly evident that ATO inhalation produced pulmonary toxicity sufficient to induce systemic hypoxia. Failure to control for factors known to be the source of false positive test results removes biological significance from the weak positive assay responses observed by NTP."

Response: The genotoxicity studies were conducted in accordance with the NTP testing protocols.[30] In fact, the OECD guidelines for the comet assay were based on the protocol developed by the formal validation trial conducted by several international organizations, including the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)[31] (see the third point of the introduction to the OECD Guideline for the Testing of Chemicals: *In Vivo* Mammalian Alkaline Comet Assay[32]). Appendix E of the antimony trioxide NTP technical report[33] provides a general overview of the comet assay protocol, but detailed methods describing how the comet assay was conducted are in publications cited by the technical report (Burlinson et al. 2007; Ghanayem et al. 2005; Recio et al. 2010; Tice et al. 2000).[34]

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[30] NTP (2023). Genetic Toxicology Study Overview. Available from: https://ntp.niehs.nih.gov/whatwestudy/testpgm/genetic/index.html#study-protocols Webpage last updated on May 1, 2023. First accessed on April 9, 2023.
[31] Hobbs CA, Recio L, Streicker M, Boyle MH, Tanaka J, Shiga A, Witt KL (2015). Comet assay evaluation of six chemicals of known genotoxic potential in rats. Mutat Res Genet Toxicol Environ Mutagen. 786-788:172-81.
[32] OECD (2016). Test No. 489: In Vivo Mammalian Alkaline Comet Assay, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris. Available at: https://doi.org/10.1787/9789264264885-en.
[33] NTP (2017), full citation provided in footnote 6.
[34] Burlinson B, Tice RR, Speit G, Agurell E, Brendler-Schwaab SY, Collins AR, et al. (2007). Fourth International Working Group on Genotoxicity Testing: Results of the *in vivo* Comet assay workgroup. Mutat. Res. 627, 31-35. Ghanayem BI, Witt KL, Kissling GE, Tice RR, Recio L (2005). Absence of acrylamide-induced genotoxicity in CYP2E1-null mice: Evidence consistent with a glycidamide-mediated

The issue of hypoxia as an explanation for the results of the *in vivo* genotoxicity assays was addressed in the NTP technical report on antimony trioxide:

"In order to assess the potential for genotoxicity in rats and mice following exposure to antimony trioxide, the erythrocyte micronucleus assay, measuring chromosomal damage, was performed in blood, and the comet assay was performed to assess DNA damage in lung tissue and blood leukocytes. Significant increases in micronucleated mature erythrocytes (NCEs) and DNA damage in lung cells were observed in male and female mice. The increases in micronucleated NCEs were supported by a trend toward increased frequencies of micronucleated immature erythrocytes (reticulocytes; PCEs). The increases in micronucleated erythrocytes occurred concomitantly with increases in percent reticulocytes in peripheral blood. The latter observation suggests a stimulation of erythropoiesis as a consequence of exposure to antimony trioxide, and increased cell turnover cannot be discounted as a factor in the small, but exposure concentration-related, increases in micro-nucleated NCEs observed in the mice. The increases in percent reticulocytes may have been a consequence of hypoxia that resulted from exposure to the higher concentrations of antimony trioxide, although hypoxia occurred in the rats as well (as indicated by the cyanosis), with no accompanying increases in percent reticulocytes or micronuclei. Results from the comet assay indicated that DNA damage occurred in lung cells of exposed male and female mice, as evidenced by increases in DNA migration measured as percent tail DNA."[35]

Thus, NTP clearly explains the biological significance of these results, which demonstrate the induction of DNA damage.

No changes to the proposed regulation were made based on this comment.

Comment 16 (i2a): "Finally, the document appears to misunderstand and/or misquote aspects of EPA's Cancer Risk Assessment Guidelines. For example, an electrophilic nature is a characteristic of organic compounds that are carcinogens since it is [sic] can be indicative of an ability to establish covalent interactions with DNA or other critical cell macromolecules. The application of principles of organic chemistry to inorganic substances should be undertaken with caution. In the specific case of metals and metalloid elements, many will be electrophilic (i.e. they will form cations in aqueous environments) but most lack an ability to form stable covalent linkages with organic molecules. Simple methylation is generally the most complex interaction that occurs.

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effect. Mutat. Res. 578, 284-297. Recio L, Hobbs C, Caspary W, Witt KL (2010). Dose-response assessment of four genotoxic chemicals in a combined mouse and rat micronucleus (MN) and Comet assay protocol. J. Toxicol. Sci. 35, 149-162. Tice RR, Agurell E, Anderson D, Burlinson B, Hartmann A, Kobayashi H, et al. (2000). Single cell gel/Comet assay: Guidelines for *in vitro* and *in vivo* genetic toxicology testing. Environ. Mol. Mutagen. 35, 206-221.

[35] NTP (2017), full citation provided in footnote 6.

While it is true that there may be multiple mechanisms of action for ATO-induced lung tumor formation, the mechanism assumed in the OEHHA risk assessment (direct genotoxicity) is the one for which supportive data is the least compelling."

Response: As discussed previously in the responses to Comments 13 and 14, antimony trioxide and other antimony trivalent compounds have been found to be electrophilic and may possibly interact with DNA, RNA, and proteins directly.[36] In its trivalent form, antimony is highly reactive with sulfhydryl groups and thiol groups.[37] The conclusion that antimony trioxide can be genotoxic is not based on theoretical predictions using its chemical structure, but from genotoxicity studies in mice *in vivo,* and chromosomal aberration and sister chromatid exchange studies *in vitro*.

No changes to the proposed regulation were made based on this comment.

Comment 17 (i2a): "The i2a respectfully submits that ATO carcinogenicity is most likely mediated by a mode of action that entails effects such as the induction of reactive oxygen species, inhibition of DNA repair and/or alter cell differential. Such modes of action either entail nongenotoxic impacts or lead to genotoxicity via indirect mechanisms that that have a strong non-linear dose response that approximates a threshold. The mechanistic inferences normally made regarding ATO's mode of action are inconsistent with the mechanistic assumptions made by OEHHA in their cancer risk assessment modeling."

"If the derivation of an NSRL is to be conducted assuming low dose linearity and other features characteristic of direct-acting genotoxic carcinogen it should at least be acknowledged that the risk assessment is very conservative and assumes a mode of action that yields the lowest levels of permissible Safe Harbor exposure. The process of risk assessment is best served when the critical mechanistic assumptions being made are clearly stated, a rationale given for conservative assumptions made and acknowledgement given to alternative modes of action commonly discussed in the peer-reviewed literature that would lead to different quantitative estimates of risk. Justifying risk assessment modeling decisions by mischaracterization or misunderstanding of the available peer-reviewed scientific literature results in a process lacking in scientific transparency and technical rigor."

Response: The scientific assumptions and decisions that went into the derivation of the NSRL are clearly described in the ISOR. A Proposition 65 regulation (Section 25703(a)) states: "In the absence of principles or assumptions scientifically more appropriate, based upon the available data, the following default principles and assumptions shall

[36] NTP (2018), full citation provided in footnote 6.
[37] *Ibid*.

apply in any such assessment:"…"(5) The absence of a carcinogenic threshold dose shall be assumed and no-threshold models shall be utilized."[38] The approach used in the calculation of the NSRL – a non-threshold assumption using the multistage cancer model – is consistent with Section 25703, current quantitative assessment practices for carcinogens by OEHHA,[39] and current US EPA practices.[40]

As quoted from US EPA's cancer risk assessment guidelines, "Nonlinear approaches generally should not be used in cases where the mode of action has not been ascertained."[41] Overall, the information the commenters provided does not include substantial evidence that leads OEHHA to find that a departure from the default approach is scientifically more appropriate.

No changes to the proposed regulation were made based on this comment.

Weight of evidence

Comment 18 (NAFRA): "Any NSRL for ATO developed by OEHHA should be based on the weight of scientific evidence."

Response: In developing the NSRL for antimony trioxide, OEHHA followed the criteria, principles and assumptions specified in Section 25703. The proposed NSRL is based on the most sensitive scientific studies of sufficient quality to meet the criterion in Section 25703. As described in the ISOR, OEHHA carefully considered all relevant streams of data to determine the most scientifically appropriate methods for conducting dose-response analysis for this chemical. The assumptions used in calculating the NSRL are scientifically appropriate.

No changes to the proposed regulation were made based on this comment.

Particle disposition in the lungs

Comment 19 (i2a): "Although there have been significant advances in the development of such predictive models, neither the computer models nor the basic aerodynamic factors that govern particle deposition have been used by OEHHA to estimate the ATO lung burdens associated with carcinogenic impacts."

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[38] Section 25703(a)(5).
[39] OEHHA (2009), full citation provided in footnote 17; see for example: OEHHA (2019). No Significant Risk Level for *p*-chloro-α,α,α-trifluorotoluene. Reproductive and Cancer Hazard Assessment Branch, OEHHA, California Environmental Protection Agency. Available at: https://oehha.ca.gov/media/pcbtfisor101719.pdf.
[40] US EPA (2012), full citation provided in footnote 14.
[41] US EPA (2005), full citation provided in footnote 6.

"The deposition pattern of ATO in the lung determines the alterations that may occur as a result of the direct "local exposure" of pulmonary tissues as opposed to deep tissue systemic exposures mediated by blood borne Sb. The ATO exposure experienced by lung tissues will vary as a function of aerosol properties that dictate particle deposition patterns and the surface area of the lung tissues that will be impacted by inhaled materials. Expression of an NSRL based upon a dose that is indexed to animal body weight will provide at best be an imprecise surrogate for the intensity of pulmonary exposure that yields carcinogenic effects. Moreover, the inhalation studies of ATO conducted by NTP utilized experimentally generated aerosols with a respirable size distribution (1.1 +/- 1.8 mm) that yields deep lung penetration to the alveolar tissues that give rise to tumors. Clearance mechanisms for such particles are limited to processes such as macrophage mediated clearance or particle dissolution. As a result, the inhaled dose that gives rise to tumors is not the daily deposition rate but rather the cumulative lung burden that develops over the course of months or years. Upper airway deposition will also occur, particles so deposited being rapidly cleared to the gastrointestinal tract via mucociliary clearance. This translocated material will be available for uptake and systemic distribution with an uptake efficiency of 1% or less (ATSDR, 2019). The methodology used in the NSRL derivation provides no information on the patterns of particle deposition within the lung which are key to predicting effects. Nor is there consideration given to the differential rates of uptake that will result from deposition in different regions of the respiratory tract. As a result, the exposure estimates used in NSRL derivation are unlikely to have any relationship to the exposure pathways and exposure levels that yield effects.… Accordingly, dosimetric extrapolation from mice to humans should include comparative estimates of the particle deposition and clearance rates in the lungs of mice and humans."

Response: The European Commission (2008)[42] discussed comparisons in particle deposition and clearance between humans and animals:

"The controlled exposure used for animal exposure typically consists of a rather uniform particle size distribution in the region of respirable particle sizes, while also coarser particles are part of occupational exposure, typically measured as total or inhalable dust. Since particles of respirable size are to a larger extent deposited in the lung, and subject to pulmonary absorption, than larger particles, assuming that the human inhalable exposure is indeed respirable would tend to overestimate the human pulmonary exposure and consequently the risk with respect to pulmonary toxicity. However, it must also be kept in mind that a considerably higher lung deposition of respirable particles occur in humans compared to rats (Winter-Sorkina de and Cassee,

[42] European Commission (2008), full citation provided in footnote 4.

2002). This aspect would then cause an underestimation of the risk to humans when extrapolating from inhalational toxicity studies in rats. In addition, clearance of particles from the lung is faster in rats compared to humans (Hofmann and Asgharian, 2003) and this aspect also needs to be considered as it is the retained dose rather than the deposited dose that cause lung effects."

"Altogether, the uncertainties in the different parameters (particle size distribution, particle deposition and particle clearance) influencing the retained dose are considered too large in order to be considered in a quantitative risk characterisation. Higher lung deposition and slower lung clearance in humans compared to rats counteract the possible lower ratio of respirable particles at work places compared to those used in the animal experiment. Industry has used the MPPD (multiple-path particle deposition) model to calculate the lung deposition ratios in rats (IAOIA-EBRC, 2008) using the particle size distribution from the chronic Newton study (Newton et al., 1994), compared to humans, using particle size distributions from the Production industry (Hughson, 2005), described in section 4.1.1.2.2. These calculations indicate that even though the particle size distribution in the working environment indicates larger and more diverse particle sizes (eg. MMAD [mass median aerodynamic diameter] =11.1 µm with GSD [geometric standard deviation] = 3.6 in packaging during Production) compared to the animal experiments (eg. MMAD= 3.8 µm with GSD= 1.8 in the Newton study), the percentage of the airborne diantimony trioxide that is deposited in the alveoli differs with a factor less than 2 (5.1% in the rat versus 3.7% in humans when using the particle size distributions shown above)."[43]

Thus, particle deposition can be predicted to be similar between humans and rodents. Although the European Commission (2008) document discusses rats, similar conclusions can be drawn for comparisons to mice, although particle inhalability is predicted to be slightly lower in mice than rats.[44]

No changes to the proposed regulation were made based on this comment.

Route of exposure

Comment 20 (CEH, GSolomon, i2a, KH, PETRA): Two commenters (CEH, GSolomon) state the NSRL should apply to all routes of exposure, while three commenters (i2a, KH, PETRA) state the NSRL should be limited to exposure by inhalation.

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[43] European Commission (2008), full citation provided in footnote 4.
[44] Asgharian B, Price OT, Oldham M, Chen LC, Saunders EL, Gordon T, et al. (2014). Computational modeling of nanoscale and microscale particle deposition, retention and dosimetry in the mouse respiratory tract. Inhal Toxicol 26(14):829-42.

“While the focus of previous studies (drawing on animal test subjects, as well as assessments of workers in environments with chronic and/or elevated antimony trioxide exposure), has been on inhalation as a carcinogenicity pathway, it is currently standard and best practice to assume the NSRL applies to all pathways of entry into human systems when dealing with a systemic carcinogen such as antimony trioxide.” (CEH)

“Antimony trioxide increased the incidences of malignant tumors or combined malignant and benign tumors at two tissue sites in rats (lung and adrenal gland) and three sites in mice (lung, skin, and lymphoid system). It is important to note that cancer sites outside the lung were identified in both species. OEHHA’s use of tumors in female B6C3F1/N mice is appropriate for derivation of the CSF, especially because these female mice developed tumors in multiple sites, including lung alveolar/bronchiolar adenoma or carcinoma and malignant lymphoma. It is standard practice to extrapolate across various portals of entry to derive the NSRL, especially for substances such as antimony trioxide that have clear systemic evidence of carcinogenicity.” (GSolomon)

“The promulgation of an NSRL limit based upon pulmonary impacts will also be misleading if applied independent of specification the route of exposure for ATO. Whereas the deposition in the deep lung may be followed by high rates of uptake, oral exposures to Sb compounds yields rates of uptake on the order of 1% or less (ATSDR, 2019). Estimates of cancer risk from inhalation, as opposed to oral exposure, will be exaggerated on the simple basis of bioavailability. Moreover, carcinogenic and genotoxic impacts are not seen in most studies of oral ATO administration. Oral cancer bioassays have not been conducted with ATO or other Sb compounds – the conduct of cancer bioassays via oral exposure routes has not been feasible due to the gastrointestinal impacts associated with the emetic and laxative properties of Sb compounds.” (i2a)

“Antimony trioxide is recognized as a suspected carcinogen by the inhalation route only. Early occupational monitoring showed workers in the industry had higher rates of pulmonary cancers compared to control populations. Cancers related to other routes of exposure such as dermal or incidental ingestion have not been associated with occupational exposure to antimony trioxide.” (KH)

“[T]he quantification of the carcinogenicity of antimony trioxide must be considered specifically and exclusively with regard to the exposure of pulmonary tissues from respirable particulate through the route of inhalation.” (KH)

“There is no evidence that the application of an NSRL of 0.13 µg/day for *ingestion* of antimony trioxide would result in an increased cancer rate of 1:100,000. This calls into question whether the proposed NSRL is compliant with 27 CCR §25703(b).” (KH)

"The same is true of dermal exposure. In 2003, the World Health Organization (WHO) considered the carcinogenicity of antimony compounds. In this assessment, WHO concluded that carcinogenicity of the compounds was related to the inhalation route and that there was a lack of appropriate data to evaluate the cancer risks associated with oral antimony exposure. In addition, WHO reported that therapeutic doses of an antimony(V) compound, meglumine antimoniate, does not represent any mutagenic or carcinogenic risks to humans." (KH)

"The proposed specific regulatory levels posing a no significant risk level (NSRL) for antimony trioxide should be limited to exposure by inhalation. The studies cited in support of the NSRL are based on inhalation exposure and extrapolation for ingestion. Consequently, the qualifier "by inhalation" should be added to the NSRL for antimony trioxide." (PETRA)

Response: As stated in the ISOR, the animal carcinogenicity studies that were used to determine the cancer potency exposed the animals to aerosols of antimony trioxide (particles) via the inhalation route. The carcinogenicity of antimony trioxide in inhalation studies reflects effects from both the inhaled particles and, subsequent to inhalation, the dissolved form. After careful review of public comments and available scientific literature reviews such as those by the European Commission (2008), ATSDR (2019), WHO (2003), IARC (1989), and Boreiko and Rossman (2020) and toxicokinetic data from studies such as Gross et al. (1955), Groth et al. (1986), Hiraoka (1986), Newton et al. (1994), Sunagawa (1981), and Westrick (1953),[45] OEHHA determined there are not enough data to assess the relative contributions of particulate and dissolved forms of antimony trioxide to the carcinogenic effects observed in the inhalation studies to confidently inform quantitative route-to-route extrapolation. With this uncertainty, and the apparent differences in absorption between the oral and inhalation routes (explained in the previous response), OEHHA issued a notice of modification on July 12, 2023, to limit the NSRL to the inhalation route. This does not preclude the possibility of the development of an NSRL for the oral route in the future, if more information becomes available.

OEHHA acknowledges that NTP determined there was some evidence of carcinogenic activity in male and female rats based on lung and adrenal medulla tumors.[46] Pursuant to Section 25703(a)(3),[47] OEHHA based its analysis on the most sensitive study, namely the female mouse, which was the species and sex for which NTP found clear evidence of carcinogenic activity based on lung tumors and malignant lymphoma.

[45] Full citations provided in footnotes 4–5.
[46] NTP (2017), full citation provided in footnote 6.
[47] "Risk analysis shall be based on the most sensitive study deemed to be of sufficient quality."

Regarding the statement by KH that "antimony trioxide is recognized as a suspected carcinogen by the inhalation route only," the listing of antimony trioxide as a carcinogen under Proposition 65 is not limited to the inhalation route. The identification of antimony trioxide as a carcinogen by IARC[48] and by the NTP[49] is also not limited by exposure route.

We note the availability of new studies and other relevant information on antimony trioxide and other antimony compounds[50] since the publication of the 2003 WHO document mentioned in the comments, titled "Antimony in drinking-water. Background document for development of WHO Guidelines for Drinking-water Quality."[51]

The comment regarding a different antimony compound, meglumine antimoniate (antimony(V)), is not relevant to this NSRL for antimony trioxide.

Comment 21 (PETRA): "PET [polyethylene terephthalate] is widely used around the globe to package foods and beverages, especially soft drinks and water, as well as other foodstuffs, personal care items and pharmaceuticals. The use of antimony and antimony compounds in food-contact and medical applications (such as PET) is evaluated and regulated for safety by the U.S. Food and Drug Administration, as well as the European Food Safety Authority in Europe, Health Canada, and sister agencies around the world. Given the safety assessments and regulation of antimony compounds for food and medical applications by other regulatory agencies, and the limited data supporting the application of the NSRL for exposure by ingestion, the proposed NSRL for antimony trioxide should be limited to exposure by inhalation."

Response: Since this comment was received, the proposed NSRL has been limited to the inhalation route. See response to Comment 20, above.

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[48] International Agency for Research on Cancer (IARC 2023a). List of Classifications, Agents Classified by the IARC Monographs, Volumes 1-133. IARC, World Health Organization, Lyon, France. Available at: https://monographs.iarc.who.int/list-of-classifications: Antimony trioxide, see 'trivalent antimony", classified as Group 2A (Probably carcinogenic to humans).

[49] NTP (2021). Substances Listed in the Fifteenth Report on Carcinogens. Research Triangle Park, NC: US Department of Health and Human Services, Public Health Service. Available at: https://ntp.niehs.nih.gov/go/roc15: "Antimony(III) trioxide is *reasonably anticipated to be a human carcinogen".*

[50] NTP (2017), full citation provided in footnote 6. NTP (2018), full citation provided in footnote 6. NTP (2021), full citation provided in footnote 49. International Agency for Research on Cancer (IARC 2023b). IARC Monographs on the Evaluation of Carcinogenic Hazards to Humans, Volume 131, Cobalt, antimony compounds, and weapons-grade tungsten alloy. IARC, World Health Organization, Lyon, France. Available at: https://publications.iarc.fr/618.

[51] WHO (2003), full citation provided in footnote 4.

Particle size

Comment 22 (KH, i2a): The commenter states that the multistage cancer model does not account for the size of the particle and the NSRL should be qualified for the specific type of antimony trioxide particle. “In other words, the safe harbor level for antimony trioxide should only be applied where exposure to antimony trioxide is as a respirable particulate defined by the US Environmental Protection Agency as having an aerodynamic diameter equal to or less than 2.5 µm.” (KH)

“Real world exposures to ATO have further been characterized with respect to the particle size distribution of aerosols in the occupational environment (Vetter, et. al., 2018). The mean MMAD of aerosols in ATO production facilities is well within an inhalable size range and lacking a significant respirable fraction capable of deep lung penetration and deposition. An NSRL that is based upon the effects of experimentally generated respirable aerosols will inflate estimates of carcinogenic effects due to the study of particle aerosols that are not representative of those encountered in real world exposure scenarios. The question asked should be ‘what is the concentration of real-world aerosols that will yield a respirable fraction that is quantitatively similar to that which produces effects in mice from experimentally generated respirable aerosols?’ This dose estimate would be the more appropriate starting point for NSRL derivation.” (i2a)

Response: OEHHA disagrees that the NSRL should be limited to a particular particle size. The comment states that the NSRL is based on the effects of experimentally generated respirable aerosols that are not representative of those encountered in “real world exposure scenarios.” However, real world exposures contain a range of particle sizes that are both smaller and larger than the particle sizes used in the rodent studies.

In the NTP studies conducted in rodents, the mass median aerodynamic particle diameter (MMAD) “ranged from 0.9 to 1.5 µm and GSD [geometric standard deviation] from 1.7 to 2.2 across exposure concentration and time in the 2-year studies.”[52] Several sources report human exposure to particles of similar sizes. For example, NTP (2018) reports:

“The only U.S. data on indoor air antimony levels are from an elementary school in Arizona (Majestic *et al.* 2012), where the particles less than 1 µm in diameter (PM_1) fraction of air samples averaged 0.017 µg antimony/m^3. Antimony in air was most likely resuspended from flame-retardant-treated carpet by foot traffic. … ATSDR summarized these data from various U.S. cities for 2014, reporting daily mean concentrations as total antimony ranging from 0.00037 to 0.002 µg/m^3 for total suspended particulate,

[52] NTP (2017), full citation provided in footnote 6.

0.0013 to 0.0206 µg/m^3 for particles less than 10 µm in diameter (PM_{10}), and 0.0019 to 0.022 µg/m^3 for particles less than 2.5 µm in diameter ($PM_{2.5}$).[53]

ATSDR also reported a study of workers exposed to antimony trioxide dust at an antimony smelter where "investigators noted that most of the antimony trioxide dust was <1 µm in diameter."[54] Thus, human exposure to antimony trioxide in any given setting contains a range of particle sizes, many of which are within the range that was tested in the NTP studies.

Furthermore, NTP (2018) mentions that older studies in rats reported induction of lung tumors following exposure to larger particles of antimony trioxide.

"The aerosol size used in the Newton *et al.* (1994) study was large, ranging from 3.76 to 4.55 µm (depending on the instrument used) and included less respirable aerosols than if they had been < 4.0 µm (EPA 1988, OECD 2017). However, the Watt (1983) study used aerosols that were even larger, averaging 5.06 µm, and Watt reported significant increases in lung tumor incidences."[55]

No changes to the proposed regulation were made based on this comment.

Other

Comment 23 (i2a): "The major uses of ATO are in flame retardant polymers and textiles, where ATO acts as a synergist, or as a catalyst for polyethylene terephthalate (PET) manufacture. When used as a flame retardant synergist ATO is bound and remains in products as part of a polymer matrix, thus precluding any exposure of any toxicological significance."

"In industrial settings ATO exposure is controlled. This is either via standard workplace hygiene measures such as closed system bulk transfer, the use of wetter powder suppressing dust generation, engineering controls such as local exhaust ventilation, or the use of masterbatches. Masterbatches are when the flame retardant components, including ATO, are provided to manufacturers already dispersed in a polymer matrix, allowing addition to be controlled and dust-free, thus removing the inhalation pathway – the only realistic pathway for ATO exposure in an industrial setting."

"The principal source of consumer exposure to ATO is from exposure to flame retardant-treated textiles, including upholstery, carpeting, and mattresses, and degradation of polyester textiles (NTP, 2018)."

[53] NTP (2018), full citation provided in footnote 6.
[54] ATSDR (2019), full citation provided in footnote 4.
[55] NTP (2018), full citation provided in footnote 6.

“In consumer use settings ATO remains bound in the polymer matrix, however, there is very low exposure potential via the is [sic] the addition of antimony, particularly to household dust, that occurs as the polymers, such as those found in polyester textiles and flame-retardant fabrics and upholsteries, break down into particulates.”

“In 2020 Intertox, on behalf of i2a, produced a human health risk assessment for typical household dust with the focus on ATO. The findings of the modelled risk assessment showed that ATO does not represent a real and attributable risk to consumers by any toxicological endpoints that have been attributed to antimony / ATO exposure.”

Response: The proposed NSRL is calculated based on a defined level of cancer risk (10^{-5}) and the intrinsic cancer potency of antimony trioxide. The source of consumer exposure does not influence the calculation of the NSRL for the inhalation route. Under Proposition 65 regulations, a warning for antimony trioxide would not be required for inhalation exposures below the NSRL. Section 25721(d) describes the assumptions that shall be used to calculate the reasonably anticipated rate of exposure to a chemical for workplace exposure and exposures to consumer products.

Additionally, for a particular well-defined use of a listed chemical, interested parties may request that OEHHA issue a “safe use determination,” as described in Section 25204. A safe use determination is issued by OEHHA for a carcinogen when the specified use is found to pose no significant risk of cancer. A safe use determination is advisory only, and is specific to the requester and the facts presented in the request.

No changes to the proposed regulation were made based on this comment.

Comment 24 (NAFRA): “Flame retardant systems are a critical tool for product safety and performance.”

“Electronic and electrical equipment utilizing flame retardant systems [antimony trioxide in combination with organohalogen flame retardants] is not a significant source of exposure.”

“Moreover, OEHHA should not reach conclusions regarding the potential for exposure to ATO that relies on overly broad assumptions. NAFRA and its member companies remain committed to the use of flame retardant systems that utilize ATO to ensure the safety of products when used as intended.”

Response: Proposition 65 does not ban chemicals, and adopting an NSRL for antimony trioxide does not preclude antimony trioxide’s use in flame retardant systems. The NSRL merely assists businesses in determining whether they must provide a warning for exposures to the chemical their products or activities may cause. The implementing regulations also provide guidance for businesses to calculate their own NSRL.

OEHHA acknowledges the importance of considering the use of antimony trioxide for product safety. As discussed in the previous response, the proposed NSRL is calculated based on a defined level of cancer risk (10^{-5}) and the intrinsic cancer potency of antimony trioxide. Neither considerations regarding the potential for exposure nor considerations regarding possible benefits attributable to a particular use of a chemical factor into the calculation of the NSRL.

For a particular well-defined use of a listed chemical, interested parties may request that OEHHA issue a "safe use determination," as described in Section 25204. A safe use determination is issued by OEHHA for a carcinogen when the specified use is found to pose no significant risk of cancer. A safe use determination is advisory only, and is specific to the requester and the facts presented in the request.

No changes to the proposed regulation were made based on this comment.

Comment 25 (KH): "Further, the proposed NSRL represents exposure that is much lower than antimony trioxide that is naturally occurring."

Response: Since this comment was received, the proposed NSRL has been limited to inhalation exposure. See response to comment 20 above. The commenter did not provide any data or information on concentrations of naturally occurring antimony trioxide present in the environment or in other possible sources of exposure, such as consumer products. If inhalation exposure levels to antimony trioxide (naturally occurring or otherwise) from the use of a product falls below the NSRL, a Proposition 65 warning is not required.

No changes to the proposed regulation were made based on this comment.

Comment 26 (Claigan): "In response to the potential new No Significant Risk level of 0.13 ug/day, Claigan Environmental Inc. (Claigan) tested a small number of common electronic components containing antimony trioxide." Claigan tested for exposure due to ingestion through hand-to-mouth activity using standard NIOSH 9100 wipe tests and reported that that the estimated daily exposure would be above the proposed NSRL.

Response: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 27 (CEH): "All trivalent antimony compounds should be listed under Proposition 65 as known to the State of California to cause cancer."

Response: This comment is outside the scope of the proposed regulation. For information on how chemicals are added to the Proposition 65 list, see https://oehha.ca.gov/proposition-65/how-chemicals-are-added-proposition-65-list.

The comment may have been prompted by OEHHA's September 30, 2022 publication of a notice of intent to list antimony (trivalent compounds) via the Labor Code mechanism.[56] However, OEHHA subsequently announced that it will not proceed at this time with the Proposition 65 listing of antimony (trivalent compounds) under that mechanism.[57]

No changes to the proposed regulation were made based on this comment.

[56] OEHHA (2022). Notice of intent to list chemical by the labor code mechanism: Antimony (trivalent compounds), available at: https://oehha.ca.gov/media/downloads/crnr/noiltrivalentantimony093022.pdf.
[57] OEHHA (2023). Antimony (Trivalent Compounds) Found Not to Meet Labor Code Listing Criteria, available at: https://oehha.ca.gov/proposition-65/crnr/antimony-trivalent-compounds-found-not-meet-labor-code-listing-criteria.

Summary of and Response to Public Comments to the Modification and Addition of Documents – July 2023

A public comment period on the modification and addition of documents to the rulemaking file was provided from July 12, 2023 to July 27, 2023. OEHHA received written public comments on the modification to the proposed rulemaking from the following organizations:

- International Antimony Association (i2a)
- Roopa Krithivasan, Defend Our Health (DOH)

The comments are summarized and responded to below. Some comments did not constitute an objection or a recommendation directed at the modified regulatory proposal or documents added to the record for which comments were solicited or the procedures followed in this rulemaking process. Consistent with the Administrative Procedure Act, OEHHA is not required to respond to such comments in the FSOR. The absence of responses to such comments should not be construed to mean that OEHHA in any way agrees with or disagrees with them.

Comment 28 (i2a): "The i2a concurs that the No Significant Risk Level for antimony trioxide should be limited to inhalation exposures. The i2a further agrees that the scientific literature being added to the record is appropriate for a more balanced summary of the available information on the carcinogenic potential of antimony trioxide."

Response: OEHHA acknowledges the comment. No changes to the proposed regulation were made based on this comment.

Comment 29 (i2a): "I2a agrees that there is insufficient information to support route-to-route extrapolation from inhalation cancer bioassays. It should be further noted that there have been no suggestions of carcinogenic impacts by any exposure route except inhalation. There are no oral cancer bioassay data available (a reflection of the difficulty inherent in chronic administration of emetic substances that disrupt gastrointestinal function) but oral administration of antimony (III) compounds has not been associated with preneoplastic changes that could signal oral carcinogenic potential. This includes a lack of genotoxic responses in the higher quality studies of genotoxicity (Boreiko and Rossman, 2020). NSRL specificity for inhalation is thus not based solely upon a difference in uptake rates by different exposure routes. It should be noted that oral cancer bioassay data are lacking and that shorter term (e.g. 90 day) administration of antimony (III) compounds has not been associated with preneoplastic changes that could signal carcinogenic potential."

Response: The modification to limit the NSRL to the inhalation route should not be viewed as a determination that antimony trioxide lacks carcinogenicity via other routes.

Antimony trioxide is listed as a carcinogen on Proposition 65 without any limitation on exposure route. The fact that no long-term studies in animals exposed via the oral route were identified, or that less-than-lifetime studies may not have exposed or observed the animals long enough to detect preneoplastic effects, is not evidence that antimony trioxide cannot cause cancer via the oral route.

Regarding genotoxicity, few studies tested for genotoxicity endpoints in animals *in vivo* via the oral route. Of these, most were considered inadequate to assess genotoxicity due to design and methodology flaws.[58] In the review article cited by the commenter, Boreiko and Rossman (2020),[59] only one study was identified as "higher quality" (Kirkland et al. 2007),[60] which did not find treatment-related increases in chromosomal aberrations or micronuclei. NTP (2018) notes that Kirkland et al. (2007) scored 2,000 polychromatic erythrocytes per rat for micronuclei, but the current OECD recommendation is to score 4,000 immature erythrocytes per animal.[61] Similar to carcinogenicity, the absence of adequate tests does not provide evidence of lack of genotoxicity via the oral route, and the genotoxicity of antimony trioxide applies to all routes. Genotoxicity is not the basis for limiting the NRSL to the inhalation route.

No changes to the proposed regulation were made based on this comment.

Comment 30 (i2a): "The case for inhalation specificity for the NSRL for antimony trioxide would be enhanced if it were noted that available inhalation carcinogenicity data were generated using respirable aerosols capable of penetration to, and deposition in, the alveolar tissues of the deep lung. Studies using respirable particles have been associated with lung tumors in rodents (e.g. Groth et al). In contrast, studies using antimony trioxide aerosols with a larger MMAD yield only limited deep lung deposition (e.g. Newton et al) and are not associated with lung tumors. A notation that lung tumors are associated with the inhalation of respirable (as opposed to inhalable) particles would strengthen the technical foundation for an NSRL specific to inhalation."

Response: OEHHA agrees that the particles tested in bioassays were of respirable size.[62] OEHHA notes that although the aerosol size in Newton et al. (1994)[63] was

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[58] NTP (2018), full citation provided in footnote 6. Elliott BM, Mackay JM, Clay P, Ashby J (1998). An assessment of the genetic toxicology of antimony trioxide. Mutat Res 415(1-2):109-17. Gurnani N, Sharma A, Talukder G (1992a). Comparison of the clastogenic effects of antimony trioxide on mice in vivo following acute and chronic exposure. Biometals 5(1):47-50. Gurnani N, Sharma A, Talukder G (1992b). Cytotoxic effects of antimony trichloride on mice in vivo. Cytobios 70(281):131-6.
[59] Boreiko and Rossman (2020), full citation provided in footnote 4.
[60] Kirkland D, Whitwell J, Deyo J, Serex T (2007). Failure of antimony trioxide to induce micronuclei or chromosomal aberrations in rat bone-marrow after sub-chronic oral dosing. Mutat Res 627(2):119-28.
[61] NTP (2018), full citation provided in footnote 6.
[62] See the description regarding particles of respirable size in OEHHA (2003), Listing notice for carbon black (available from https://oehha.ca.gov/media/downloads/proposition-65/chemicals/22103not.pdf).
[63] Newton et al. (1994), full citation provided in footnote 5.

relatively large (MMAD 3.76 ± 0.84 µm), a study by Watt (1983)[64] used larger particles (MMAD 5.06 µm) and reported significant increases in lung tumor incidences.[65] Both studies though used respirable particles.

No changes to the proposed regulation were made based on this comment.

Comment 31 (i2a): "The NSRL documentation states that "the carcinogenicity of antimony trioxide in inhalation studies reflects effects from both the inhaled particles and, subsequent to inhalation, the dissolved form." The hypothesized role of a dissolved form of antimony in lung tumor induction is just one of several mechanisms that could result in neoplastic alterations. As noted in multiple documents being added to the record (e.g. ATSDR, 2019; Boreiko and Rossman, 2020; European Commission, 2008; Groth et al, 1986; Newton et al., 1994) the induction of lung tumors in rats has been proposed to be related to overload of the mechanisms for removal of insoluble particles from the lung. The more correct rationale would note that the form of antimony responsible for carcinogenic impacts has not been identified, thereby precluding route to route extrapolation. Acknowledgement of the potential role of poorly soluble low toxicity (PSLT) particles in lung carcinogenesis could be included. A recent review of PSLTs could be cited to acknowledge alternate pathways for lung cancer induction (Driscoll and Borm, Inhal. Toxicol. 32:53-62)."

Response: Antimony trioxide particles dissolve in biological fluids and can exert intrinsic toxicity at the site of deposition. NTP explains that lung overload did not occur in the low dose group, where lung tumors were observed.[66] Thus, lung tumors could not be explained only by the high lung burdens. These points are explained in detail in the following paragraphs.

Inhaled antimony trioxide particles dissolve in biological fluids to a greater extent than in water. NTP (2018) reports the solubility of antimony trioxide in artificial fluids estimated using synthetic equivalents after 24 hours of exposure: "[a]ntimony(III) trioxide had the highest percent solubility [81.7%] in artificial alveolar lysosomal fluid (pH = 4.5), which may be representative of the lung tissue contacted by inhaled antimony(III) trioxide." The bioaccessibility in other fluids was simulated to be 60.8% for artificial sweat, 56.7% for interstitial fluid within the deep lung, 41.5% for human blood serum, and 13.6% for gastric fluid. Thus, regardless of where the antimony trioxide particles deposit, they dissolve in biological fluids and can exert intrinsic toxicity.

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[64] Watt WD (1983), as cited by NTP (2018). Chronic inhalation toxicity of antimony trioxide: Validation of the threshold limit value. Detroit, MI: Wayne State University, PhD Thesis.
[65] NTP (2018), full citation provided in footnote 6.
[66] *Ibid*.

Additionally, the NTP technical report[67] and the RoC monograph[68] explain that lung overload did not occur in mice exposed to the lowest dose of antimony trioxide, where lung tumors were observed. The RoC monograph[69] concluded:

"The NTP also considered the question of lung overload during the 2-year exposure, concluding that lung overload was not reached at the lowest concentration tested (3 mg/m^3), but was reached in both rats and mice at the middle (10 mg/m^3) and high concentrations (30 mg/m^3)." (p. 43)

"In the case of antimony trioxide, evidence of suggested toxicity and increased cancer at concentration below the occurrence of lung clearance overload showed that observed lung cancer was not due to overload." (p. P-2)

The NTP technical report addressed this issue in detail, making several important points. First, the report concluded that lung overload did not occur in the lowest dose group (3 mg/m^3), but did occur in the mid- (10 mg/m^3) and high-dose (30 mg/m^3) groups. The data are consistent with guidance indicating that all groups should be used in interpretation of carcinogenicity data. NTP explains this point as follows:

"Based on the relatively long clearance half-lives at 10 and 30 mg/m^3 and high lung burdens at 30 mg/m^3 in rats, and the unexpectedly high lung burdens at 551 days in mice, which precluded the mouse data from being modeled, it was hypothesized that lung overload occurred in rats and mice (Morrow 1988, 1992; Tran *et al.*, 2000). Calculations were made to determine if volumetric- or surface area-based overload occurred in either species. These calculations yielded generally similar results for the two interpretations of overload. Notably, lung overload did not occur at 3 mg/m^3 in either species using either metric but did occur at 10 and 30 mg/m^3, with the degree of overload increasing with exposure concentration. These data are consistent with available guidance for chronic inhalation study exposure concentration selection and data interpretation for particles, which indicates that both concentrations predicted to induce and those predicted not to induce lung overload should be selected and that all data (both in presence and absence of overload) should be utilized in the interpretation of carcinogenicity data (ILSI Risk Science Institute, 2000)."[70]

Additionally, there were no significant differences in the types or incidences of pertinent mutations (*i.e.*, *Kras* and *Egfr*) in rat and mouse lung tumors from antimony trioxide exposures that did and did not cause pulmonary overload, which suggests that

[67] NTP (2017), full citation provided in footnote 6.
[68] NTP (2018), full citation provided in footnote 6.
[69] *Ibid*.
[70] NTP (2017), full citation provided in footnote 6.

"overload did not alter the mutation spectra of the observed neoplasms."[71] Lastly, NTP explains that genotoxicity was observed not only in the lung, but also in blood, indicating that "antimony trioxide displays at least some intrinsic toxicity, and that the observed lung tumors could not be explained only by the high lung burdens in the study animals."[72]

No changes to the proposed regulation were made based on this comment.

Comment 32 (i2a): "Recent studies (Boreiko et al., Mutat Res. 865:503333) have suggested that indirect mechanisms, such as those entailing the induction of reactive oxygen species, are responsible for the genotoxic and/or carcinogenic impacts of antimony compounds. An indirect mechanistic basis for genotoxicity and carcinogenicity is consistent with PSLT impacts in the induction of rat lung tumors. Indirect mechanisms, especially when indexed to inflammatory responses, also support the need for an NSRL specific to inhalation exposures."

Response: Similar comments were raised on the August 2022 proposal. See responses to comments 13–17. However, these comments are not within the scope of the modification to the proposed rulemaking.

No changes to the proposed regulation were made based on this comment.

Comment 33 (DOH): "The initial proposal was to list an NSRL that does not delineate a limited exposure pathway, and to set a single NSRL for oral and inhalation pathways. As we previously noted in our comment [by CEH] submitted October 11, 2022, we believe this approach was correct and appropriate, and the proposed modification ignores established approaches for safeguarding the health of the public."

"The initial proposal to list a single NSRL is also consistent with the way previously proposed Proposition 65 NSRL values have been treated. Out of 971 chemicals and chemical classes listed for cancer under "type of toxicity", 318 of these have NSRLs listed. Of these, the vast majority (296) do not specify a route of exposure, while only 14 carcinogens have NSRLs that are listed as being limited to either an inhalation and oral exposure pathway [3]. As noted above, previous studies on antimony oxide show clear evidence of systemic toxicity and therefore should be treated in the same way as these 296 chemicals with non-route-specific NSRLs under prop 65."

Response: The commenter has correctly noted that the majority of NSRLs are not limited to a specific exposure pathway.[73] However, in some circumstances there is evidence of a difference in the NSRL, expressed as an external dose in micrograms per

[71] NTP (2017), full citation provided in footnote 6.
[72] *Ibid.*
[73] Section 25703(a)(4).

day, between routes of exposure. For antimony trioxide, there appears to be a difference in the absorption rate by the oral and inhalation routes of exposure. The carcinogenicity of antimony trioxide in inhalation studies reflects effects from both the inhaled particles and, subsequent to inhalation, the dissolved form. OEHHA determined there are not enough data to assess the relative contributions of particulate and dissolved forms of antimony trioxide to the carcinogenic effects observed in the inhalation studies to confidently inform quantitative route-to-route extrapolation.

No changes to the proposed regulation were made based on this comment.

Comment 34 (DOH): "The studies summarized in the NTP 2018 Report[1] on Carcinogens suggest that antimony trioxide shows clear systemic evidence of carcinogenicity. Antimony trioxide exposure increased the incidence of lung and adrenal tumors in rat test subjects, and lung, skin, and lymphoid tumor occurrence in mice. Specifically, antimony trioxide increased the incidences of malignant tumors or combined malignant and benign tumors in rats (lung and adrenal gland) and in mice (lung, skin, and lymphoid system). Cancer sites outside the lungs in both species suggest systemic pathways of carcinogenicity."

"Relatedly, while the focus of previous studies (drawing on animal test subjects, as well as assessments of workers in environments with chronic and/or elevated antimony trioxide exposure), has been on inhalation as a carcinogenicity pathway, it is currently standard and best practice to assume the NSRL applies to all pathways of entry into human systems when dealing with a systemic carcinogen[2] such as antimony trioxide."

Response: OEHHA agrees with the commenter that following the administration of antimony trioxide by the inhalation route systemic tumors were observed in both species. As noted in response to comment 29, the listing of antimony trioxide is not limited to the inhalation route. However, as explained in the responses to comments 20 and 22, and in the July 12, 2023 notice of modification, there are apparent differences in absorption between the oral and inhalation routes and there are not enough data to assess the relative contributions of particulate and dissolved forms of antimony trioxide to the carcinogenic effects observed in the inhalation studies to confidently inform quantitative route-to-route extrapolation. For these reasons, the NSRL has been modified to be limited to the inhalation route.

No changes to the proposed regulation were made based on this comment.

Alternatives Determination

In accordance with Government Code section 11346.9(a)(4), (a)(7), OEHHA has, throughout the adoption process of this regulation, considered available alternatives to determine whether any alternative would be more effective in carrying out the purpose for which the regulation was proposed. OEHHA has also considered whether an alternative existed that would be more cost effective in carrying out the purpose for which the regulation was proposed, or would be as cost effective and less burdensome to affected private persons than the proposed action.

OEHHA has determined that no alternative considered would be more effective, or as effective and less burdensome to affected private persons, than the proposed action. OEHHA considered taking no action but finds that taking no action is inconsistent with the intent of the Act and its implementing regulations and would perpetuate confusion and lack of clarity as articulated in various inquiries by stakeholders. Therefore, OEHHA has determined that no alternative considered would be more cost-effective, or as effective in implementing the statutory policy or other provision of law.

For chemicals listed under the Act as known to cause cancer, the Act exempts discharges to sources of drinking water and exposures of people without provision of a warning if the exposure poses “no significant risk” of cancer (Health and Safety Code, section 25249.10(c)). The Act does not specify numerical levels of exposure that represent no significant risk of cancer.

The purpose of this regulation is to establish a No Significant Risk Level for antimony trioxide. At or below this level, the Act does not require a warning or prohibit discharges of the chemical to sources of drinking water. Thus, adopting this level will allow businesses subject to the Act to determine whether a given discharge to sources of drinking water or a given exposure to this chemical is subject to the warning requirement or discharge prohibition provisions of the Act (Health and Safety Code, section 25249.5 and 25349.6).

Although Section 25703 describes principles and assumptions for conducting risk assessments to derive No Significant Risk Levels, some businesses subject to the Act do not have the resources to perform these assessments. Yet each business with ten or more employees must determine whether its activities or products are subject to the discharge prohibition or warning requirements of the Act. Adopting an NSRL for this chemical provides an efficient way of determining if a business is in compliance with the Act.

Local Mandate Determination

OEHHA has determined this regulatory action will not pose a mandate on local agencies or school districts, nor does it require reimbursement by the State pursuant to Part 7 (commencing with Section 17500) of Division 4 of the Government Code. OEHHA has also determined that no nondiscretionary costs or savings to local agencies or school districts will result from this regulatory action. Proposition 65 provides an express exemption from the warning requirement and discharge prohibition for all state and local agencies. Thus, these regulations do not impose any mandate on local agencies or school districts.