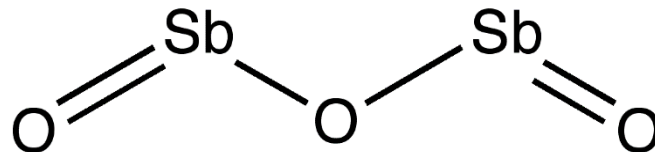


# Report on the Peer Review of the Report on Carcinogens (RoC) Draft Monograph on Antimony Trioxide



Amy Wang, PhD

Office of the Report on Carcinogens, Division of National Toxicology Program  
National Institute of Environmental Health Sciences

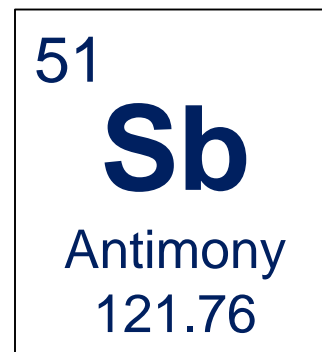
NTP Board of Scientific Counselors Meeting  
October 9, 2018



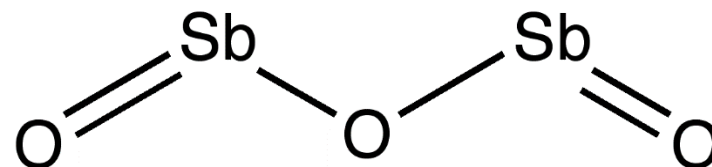


## Antimony trioxide

- Antimony is a metalloid found in nature

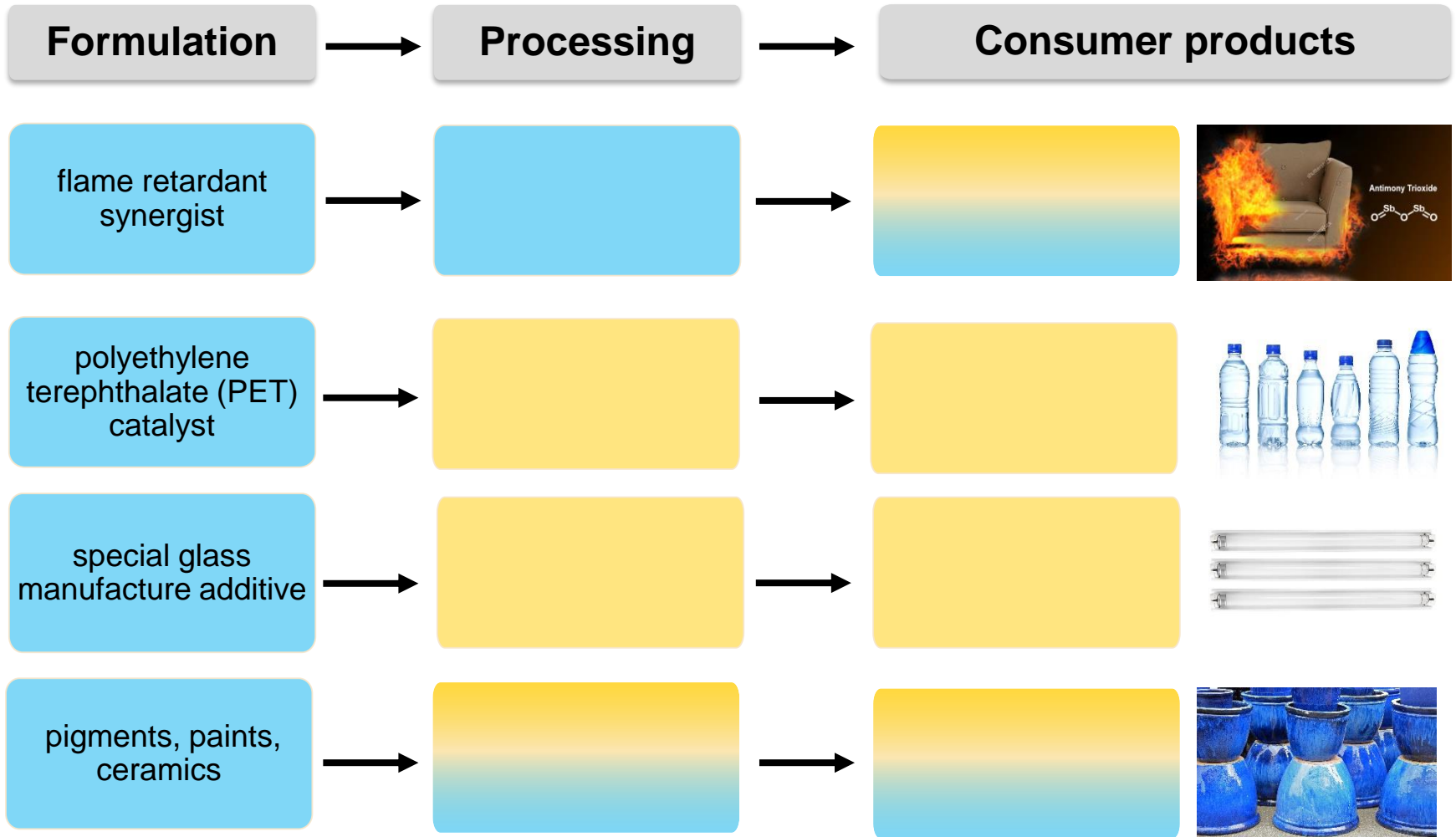





- Antimony(III) trioxide is the most commercially significant form of processed antimony





# Uses of Antimony(III) Trioxide



 =  $Sb_2O_3$      = no longer  $Sb_2O_3$      = depends on circumstance

Slide courtesy of Sandy Garner, ILS



## Peer Review Panel Members

Name	Affiliation
Rebecca Fry, PhD	University of North Carolina at Chapel Hill
Hao Zhu, PhD	Rutgers University-Camden
Elaine Symanski, PhD	The University of Texas Health Science Center at Houston
Elizabeth Ward, PhD	American Cancer Society (retired)
John Wise, Sr., PhD	University of Louisville
Michael Waalkes, PhD	NIEHS (retired)
Richard Peterson II, DVM, PhD, DACVP	AbbVie

## NTP BSC liaison

Kenneth McMartin, PhD Louisiana State University



## Public comments

- Public comments, including published and unpublished information, were received in several phases of the process
- ORoC staff considered technical and scientific issues at all phases
- Public comments on draft monograph were provided to the peer review panel



# NTP Draft Recommendation: Exposure

## A significant number of people in the United States are exposed to antimony(III) trioxide

- Highest levels of exposure occur in the workplace
- The general population is exposed
  - Primary releases (i.e., pollutant is antimony(III) trioxide) from industrial uses to air: Estimated 11,365 lb to air in year 2010
  - Secondary (i.e., pollutant is transformed from other antimony species into antimony(III) trioxide) releases to the environment
  - House dust from some consumer products
  - Antimony detected in urine (The National Health and Nutrition Examination Survey, or NHANES)

**Panel: Concurred**



# NTP Draft Recommendation: Human Studies

## **Inadequate** human evidence for determining carcinogenicity

- **Limited by:**
  - Few studies with small sample sizes for stomach and lung cancers
  - Potential confounding due to smoking and occupational co-exposures

**Panel: Agreed unanimously**



## Key issues discussed at the peer review panel meeting

- Male rat lung tumors
  - Overload alone does not explain the observed carcinogenicity in rats
    - Increased lung tumors in mice at  $\text{Sb}_2\text{O}_3$  concentrations below overload threshold
    - Genotoxicity in exposed mice, indicating  $\text{Sb}_2\text{O}_3$  has intrinsic toxicity
  - Incidences of alveolar/bronchiolar adenoma exceed current and historical controls
  - Adenoma can progress to carcinoma
  - Rat lung tumors are evidence of carcinogenicity (i.e., agree with NTP 2017)





# NTP Draft Recommendation: Animal Studies

## Sufficient animal evidence for antimony trioxide carcinogenicity

Increased incidences of malignant tumors and combined incidences of malignant and benign tumors at multiple tissue sites in multiple species

**lung tumors**

Benign	Alveolar/bronchiolar adenoma (F)
Malignant	Alveolar/bronchiolar carcinoma (M and F)
Combined	Alveolar/bronchiolar adenoma or carcinoma (F)

Mouse study: NTP 2017

**skin tumors**

Benign	Fibrous histiocytoma (M)
Combined	Fibrous histiocytoma or fibrosarcoma (M)

**lymphoma**

Malignant	Lymphoma (F)
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**lung tumors**

Benign	Alveolar/bronchiolar adenoma (M* & F)	NTP 2017
Combined	Alveolar/bronchiolar adenoma or carcinoma (M*)	
Benign	Bronchiolar/alveolar adenoma (F)	Groth et al. 1986
Malignant	Squamous-cell carcinoma (F)	
Malignant	Scirrhus carcinoma (F)	
Malignant	Scirrhus carcinoma (F)	Watt 1983

**adrenal gland tumors**

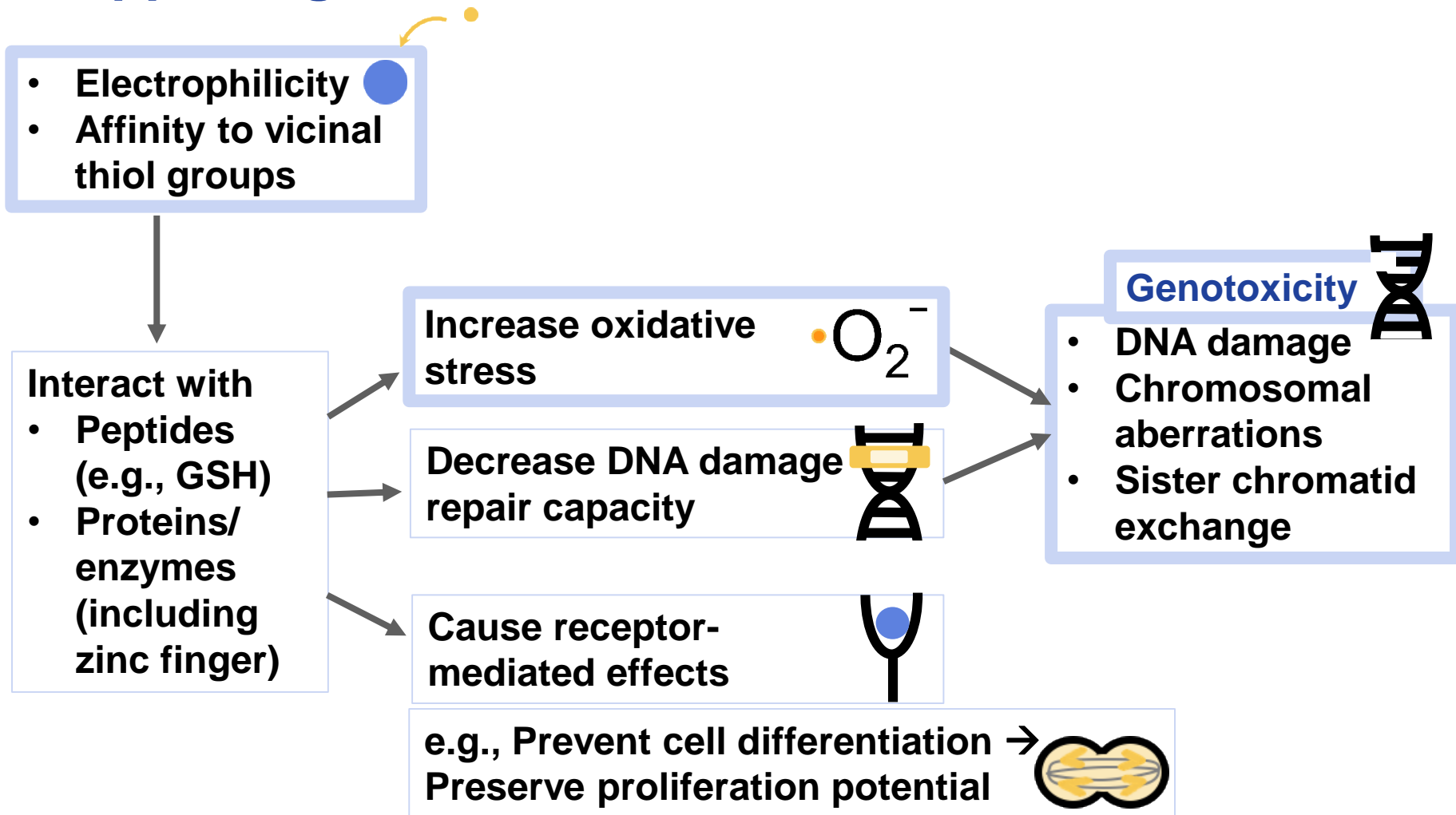
Benign	Pheochromocytoma (M & F)
Combined	Pheochromocytoma (F)
	NTP 2017

Newton et al. 1994 reported no increase in tumors.

**Panel: Agreed unanimously**



# Supporting mechanistic information



= direct evidence from  $\text{Sb}_2\text{O}_3$

= direct evidence from compounds containing  $\text{Sb(III)}$



# NTP Preliminary Listing Recommendation


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Antimony trioxide should be listed in the RoC as ***reasonably anticipated to be a human carcinogen*** based on sufficient evidence from studies in experimental animals and supporting mechanistic data.

**Panel: Agreed unanimously**



# Revised Draft RoC Monograph


 **National Toxicology Program**  
U.S. Department of Health and Human Services

**Revised Draft:  
Report on Carcinogens Monograph on  
Antimony Trioxide**

August 15, 2018

Office of the Report on Carcinogens  
Division of the National Toxicology Program  
National Institute of Environmental Health Sciences  
U.S. Department of Health and Human Services

This revised Report on Carcinogens monograph has not been formally distributed by the National Toxicology Program. It does not represent and should not be construed to represent any final NTP determination or policy.

 **National Toxicology Program**  
U.S. Department of Health and Human Services

**Draft Report on Carcinogens Monograph on  
Antimony Trioxide**


**Revised Draft Substance Profile Proposed for  
the RoC**

August 15, 2018

Office of the Report on Carcinogens  
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**Antimony Trioxide**  
CAS No. 1309-64-44  
Reasonably anticipated to be a human carcinogen<sup>1</sup>



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

**Cancer Studies in Experimental Animals**  
Antimony trioxide administered by inhalation caused lung tumors in rats and mice of both sexes and tumors at several other tissue sites in female rats and in mice of both sexes. No cancer studies in experimental animals with exposure to antimony trioxide by other routes were identified. This conclusion of carcinogenicity was based on three studies in three different strains or stocks of rats and one study in mice. NTP studies (2017) examined all organs and tissues in both sexes of Wistar Han rats and B6C3F1N mice, and three other studies examined primarily the lung in both sexes of Wistar rats (Groth *et al.* 1986) or Fischer 344 rats (Newton *et al.* 1994) or female CDF rats (Watt 1985). The NTP studies were most informative based on the study design and detailed reports, while other studies are also adequate to inform carcinogenicity after critical evaluation of potential bias.

In the lung, exposure of female rats to antimony trioxide significantly increased the incidences of benign lung tumors (alveolar/bronchiolar adenoma) (Groth *et al.* 1986, NTP 2017), which can progress to malignant tumors, and incidences of malignant lung tumors (squamous carcinoma and/or squamous-cell carcinoma) (Watt 1985, Groth *et al.* 1986). In male rats, the combined incidences of benign lung tumors (alveolar/bronchiolar adenoma) and malignant lung tumors (alveolar/bronchiolar carcinoma) were not significantly increased, but both exceeded the historical control ranges for all past studies (NTP 2017). When this is considered together with a positive trend with dose and increased lung tumors in the other sex and species (female rats, both sexes of mice), the increase in combined incidences was deemed to be related to exposure to antimony trioxide (NTP 2017). Another study in male and female rats (Newton *et al.* 1994) found no increase in the frequency of lung tumors, possibly because the highest tested concentration was too low (as indicated by the absence of changes in survival or body weight in the high-dose groups). Newton *et al.* (1994) was the only study that reported no increase in tumors.

Exposure of mice to antimony trioxide caused statistically significant increases in the incidences of benign lung tumors (alveolar/bronchiolar adenoma) in females, malignant lung tumors

<sup>1</sup>NTP preliminary listing recommendation proposed for the RoC.

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+ appendices  
+ supplemental material

B	C	D	E	F	G	H	I	J	K	L	M	N	O
Reference	(additional) References	Data class	Species	Strain		Age at start	Duration	Historical data available?	Transgenic model?	Randomization bias rating	Randomization bias rationale	Concurrent controls bias rating	Concurrent controls bias rationale
NTP 2017		Full carcinogenicity	Rat	Wistar Han [Cr:WI (Han)]	M	6 weeks	105 weeks	TRUE	FALSE	+++	Animals were randomly assigned	+++	Concurrent chamber control was used



# New: Supplemental Material

## Detailed risk of bias information on animal studies

	Adequacy of study duration bias rating	Adequacy of study duration bias rationale	Confounding bias rating	Confounding bias rationale	Reporting and statistics bias rating
groups +++		The study duration was 2 years, with 12 months	+++	Material of high purity. Animal husbandry	+++
not high +++		The study duration was 2 years, with 1 year	++	Animals in high dose group were heavier than	++

## Animal cancer study results ready for further analysis

Non-neoplastic findings	Other comments	Dose	N at start	Incidence
Lung were examined after 12 months and after 24 months.	12 Month results:	0	65	1/52
Lung were examined after 12 months and after 24 months.	12 Month results:	0.06	65	0/52
Lung were examined after 12 months and after 24 months.	12 Month results:	0.51	65	0/53
Lung were examined after 12 months and after 24 months.	12 Month results:	4.5	65	1/52
Lung were examined after 12 months and after 24 months.	12 Month results:	0	50	0/49
Lung were examined after 12 months and after 24 months.	12 Month results:	0.06	50	0/52
Lung were examined after 12 months and after 24 months.	12 Month results:	0.51	50	1/54
Lung were examined after 12 months and after 24 months.	12 Month results:	4.5	50	0/50
Lungs from exposed animals grossly appeared mottled – with	Only the incidence	0		0/13
Lungs from exposed animals grossly appeared mottled – with	Only the incidence	1.6		0/17
Lungs from exposed animals grossly appeared mottled – with	Only the incidence	4.2		9/18
Lungs from exposed animals grossly appeared mottled – with	Only the incidence	0		0/13
Lungs from exposed animals grossly appeared mottled – with	Only the incidence	1.6		0/17



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## Immediate next steps after BSC meeting

- Present to NTP director
- Finalize RoC monograph



# Acknowledgements

## Collaborators

Ruth M. Lunn	NIEHS, DNTP*
Sanford C. Garner	ILS
Joanne Trgovcich	ICF
Suril S. Mehta	NIEHS, DNTP*
Andrew D. Ewens	ILS
Alton F. Peters	ILS
Kristine L. Witt	NIEHS, DNTP

## Contributors

Gloria D. Jahnke	NIEHS, DNTP*
Jui-Hua Hsieh	NIEHS, DNTP
Melanie C. Buser	ATSDR
Kristina M. Hatlelid	CPSC
Linda M. Sargent	CDC
Yin-tak Woo	EPA
Whitney D. Arroyave	ILS
Stephen S. Ferguson	NIEHS, DNTP
Gordon P. Flake†	NIEHS, DNTP
Michelle J. Hooth	NIEHS, DNTP
B. Alex Merrick	NIEHS, DNTP
Daniel L. Morgan	NIEHS, DNTP
Arun K.R. Pandiri	NIEHS, DNTP
Matthew D. Stout	NIEHS, DNTP
Kyla W. Taylor	NIEHS, DNTP

## Acknowledgements

Michael A. Babich	CPSC
Alison H. Harrill	NIEHS, DNTP
Sharon L. Oxendine	EPA
Nisha S. Sipes	NIEHS, DNTP
Stanley T. Atwood	ILS
Mary S. Wolfe	NIEHS, DNTP
Andy J. Shapiro, MS	NIEHS, DNTP (formerly)
Susan Dakin	Independent consultant
Jessica A. Geter	ILS (formerly)
Lara Handler	ILS
Ella J. Darden	ILS
Tracy L. Saunders	ILS
F. Louise Assem	ICF
Susan Blaine	ICF
Camden N. Byrd	ICF
Anna N. Stamatogiannakis	ICF

\*Members of the Office of the Report on Carcinogens (ORoC)

†Deceased July 30, 2018

CPSC = Consumer Product Safety Commission

DNTP = Division of National Toxicology Program

ICF = ICF Incorporated, LLC (Support provided through NIEHS Contract Number GS00Q14OADU417/HHSN273201600015U)

ILS = Integrated Laboratory Systems, Inc. (Support provided through subcontract number 16EDBO0078 with ICF)

NIEHS = National Institute of Environmental Health Sciences