NTP Response to the NTP Board of Scientific Counselors (BSC) Peer Review Comments on the Draft Substances Profiles for the *12th Report on Carcinogens*

June 21–22, 2010

BSC Meeting

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Introduction

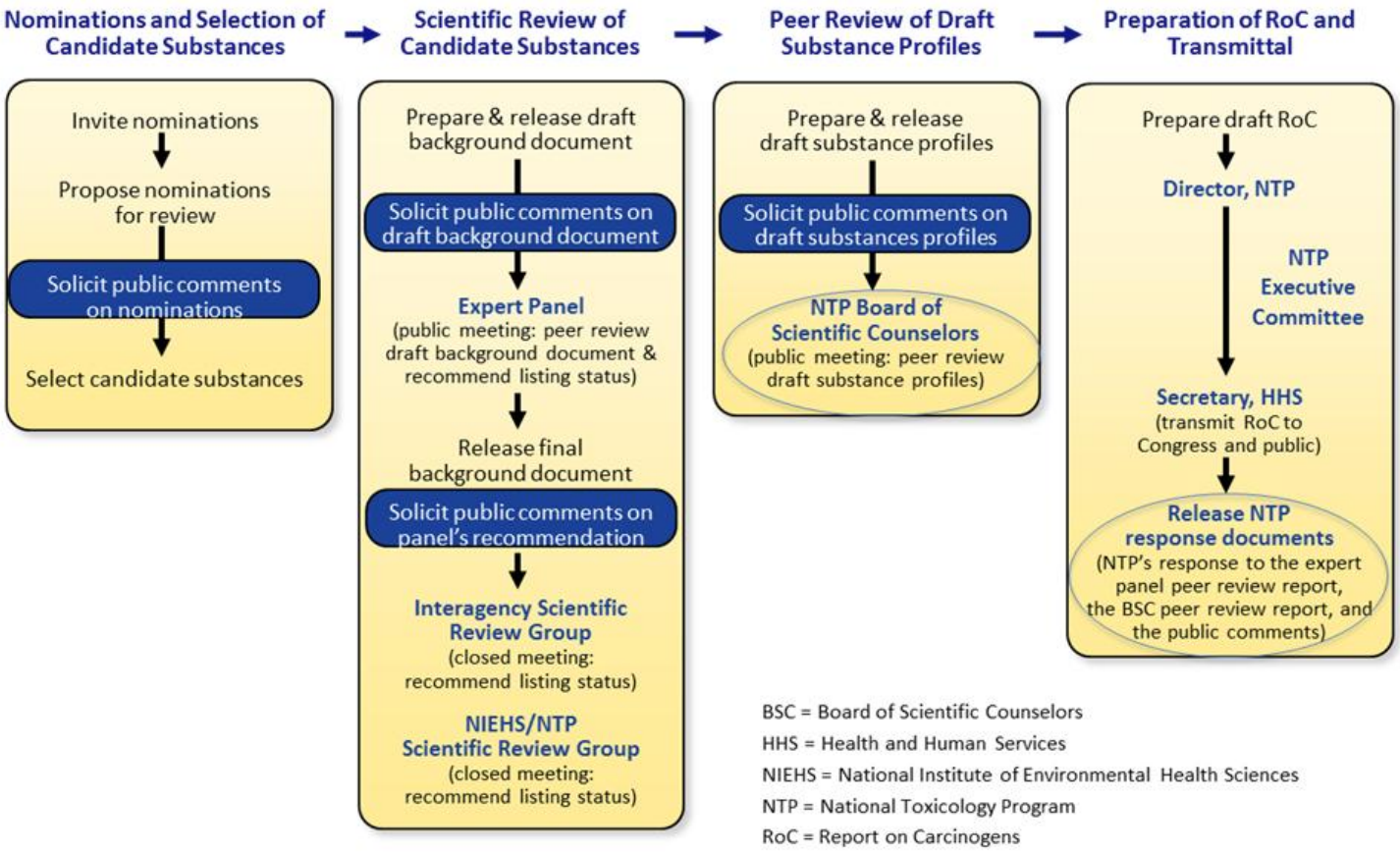
The National Toxicology Program (NTP) followed a formal process for the review of candidate substances for the *Twelfth Report on Carcinogens* (*12th RoC*) (see page 2 for a schematic of the review process) that included the peer review of the draft substance profiles for each candidate substance by the Board of Scientific Counselors (BSC) and opportunity for public comment (see part 3 of the review process). The peer review for three candidate substances took place at a public meeting on June 21–22, 2010 (see page 3 for the attending BSC members). Five other candidate substances were reviewed at an earlier meeting on February 24, 2009.

A draft substance profile provides the preliminary listing recommendation for a substance in the *12th RoC* (i.e., *known to be a human carcinogen* or *reasonably anticipated to be a human carcinogen*, or not to list); the carcinogenicity studies that support the recommendation; information on human exposure including data on use, production and occupational and environmental exposure; and current Federal regulations to limit exposure. The charge to the BSC was to determine whether the scientific information cited in the draft substance profile for a candidate substance is technically correct, clearly stated, and supports the NTP's preliminary policy decision regarding its listing in the *12th RoC*. The BSC's peer-review comments on the draft substance profiles are captured in the minutes for these meetings.[1]

The NTP carefully reviewed and considered the BSC peer-review comments in revising and finalizing the substance profiles, which were approved by the Secretary of the Department of Health and Human Services and are now part of the *12th RoC*.[2] As noted in the RoC review process (see part 4 of the review process), the NTP releases a report responding to the BSC peer-review comments at the time the *12th RoC* is published. The BSC's major scientific and technical comments and the NTP's response to those comments are provided in this report for each candidate substance.

[1] http://ntp.niehs.nih.gov/go/9741, choose meeting date and select meeting minutes.
[2] http://ntp.niehs.nih.gov/go/roc12

NTP Report on Carcinogens Review Process



BSC = Board of Scientific Counselors
HHS = Health and Human Services
NIEHS = National Institute of Environmental Health Sciences
NTP = National Toxicology Program
RoC = Report on Carcinogens

NTP Board of Counselors Meetings: Roster of Attending Members

June 21–22, 2010 Meeting

Draft substance profiles for the following candidate substances were reviewed: cobalt–tungsten carbide: powders and hard metals, formaldehyde, and glass wool fibers.

Members

Tracie E. Bunton, D.V.M., Ph.D., DACVP, Eicarte LLC
Russell C. Cattley, V.M.D., Ph.D., Amgen
David A. Eastmond, Ph.D., University of California, Riverside
Elaine M. Faustman, Ph.D., University of Washington
Stephen W. Looney, Ph.D., Medical College of Georgia
Mitzi Nagarkatti, Ph.D., University of South Carolina School of Medicine
Raymond F. Novak, Ph.D. (Chair), Wayne State University School of Medicine
Ruthann A. Rudel, M.S., Silent Spring Institute
James L. Sherley, M.D., Ph.D., Boston Biomedical Research Institute
Gina M. Solomon, M.D., M.P.H., Natural Resources Defense Council
Justin G. Teeguarden, Ph.D., Pacific Northwest National Laboratory

Pending Members

Miguel Fernández, M.D., University of Texas Health Science Center at San Antonio
Dana Loomis, Ph.D., University of Nevada, Reno [present only on June 22, 2010]
Melissa A. McDiarmid, M.D., M.P.H., University of Maryland School of Medicine
Richard Miller, D.V.M., Ph.D., GlaxoSmithKline
Judith Zelikoff, Ph.D., New York University School of Medicine

Ad Hoc *Members*

Joseph R. Landolph, Ph.D., University of Southern California
Andrew Olshan, Ph.D., University of North Carolina at Chapel Hill
Margaret M. Quinn, Sc.D., CIH, University of Massachusetts, Lowell

Cobalt–Tungsten Carbide: Powders and Hard Metals

The draft substance profile on cobalt–tungsten carbide: powders and hard metals was peer-reviewed by the BSC at the meeting held June 21–22, 2010[3] (see page 3 for a roster of attending members). The NTP's preliminary policy decision was that cobalt–tungsten carbide: powders and hard metals should be listed in the *12th RoC* as *reasonably anticipated to be human carcinogens* based on limited evidence of carcinogenicity from studies in humans and supporting evidence from studies on mechanisms of carcinogenesis. The NTP reviewed the BSC comments, revised the substance profile, and finalized its listing recommendation for cobalt–tungsten carbide: powders and hard metals in the *12th RoC*, which was approved by the Secretary of the Department of Health and Human Services. Cobalt–tungsten carbide: powders and hard metals are listed as *reasonably anticipated to be human carcinogens* in the *12th RoC*.

BSC Comments and NTP Responses: Scientific and Technical Issues

BSC Comments:

1. Add information on the crystalline structure of cobalt–tungsten carbide.
2. Add information on the size of the cobalt–tungsten carbide particles to which workers are exposed.
3. Add language to indicate that the effect-estimates in the epidemiological studies were imprecise.
4. Add information (if available) on phagocytosis of cobalt–tungsten carbide.
5. Discuss the negative genotoxicity data.

NTP Response: The NTP concurs with these suggestions and incorporated the requested information into the appropriate sections of the final substance profile for cobalt–tungsten carbide: powders and hard metals. Information was added as recommended including comment 1 to the "Properties" section, comment 2 to the "Exposure" section, and comments 3 to 5 to the "Carcinogenicity" section.

6. Add a more balanced discussion of the exposure study in Fallon, Nevada, since there is controversy regarding this study.

NTP Response: A detailed discussion of the strengths and limitations of the series of exposure studies, and critiques of these studies are outside the scope of the substance profile, but are reported in the final background document (NTP 2009). The substance profile notes the controversy and refers the reader to the final background document.

References

NTP. 2009. *Report on Carcinogens Background Document for Cobalt–Tungsten Carbide: Powders and Hard Metals*. Research Triangle Park, NC: National Toxicology Program, 180 pp. http://ntp.niehs.nih.gov/NTP/roc/twelfth/2010/FinalBDs/HardMetalsBD20100408.pdf

[3] For the complete minutes from the NTP BSC meeting, see http://ntp.niehs.nih.gov/go/9741, June 21–22, 2010 meeting, and select meeting minutes.

Formaldehyde

The draft substance profile on formaldehyde was peer-reviewed by the BSC at the meeting held June 21–22, 2010[4] (see page 3 for a roster of attending members). The NTP's preliminary policy decision was that formaldehyde should be listed in the *12th RoC* as *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans and supporting evidence from studies on mechanisms of carcinogenesis. The NTP reviewed the BSC comments, revised the substance profile, and finalized its listing recommendation for formaldehyde, which was approved by the Secretary of the Department of Health and Human Services. Formaldehyde is listed as *known to be a human carcinogen* in the *12th RoC*.

BSC Comments and NTP Responses: Scientific and Technical Issues

BSC Comments:

1. The draft substance profile is unclear regarding food and drinking water as major sources of exposure to formaldehyde. Please clarify. Discuss potential absorption through the gastrointestinal tract and the skin. Although skin may not be a primary route, 20% of cosmetics reportedly contain formaldehyde.
2. Correct the levels reported for formaldehyde in the Federal Emergency Management Agency (FEMA) trailers; the levels reported in the draft substance profiles were measured two years after construction and during the winter and thus the levels were underestimated.
3. Use consistent units of exposure throughout the profile (ppm or mg).
4. Add information on the limitations of the use of mortality data (vs. incidence) in the epidemiological studies of leukemia.
5. Change the heading of this section from Myeloid Leukemia to 'Lymphohematopoietic Cancer' (LHC) and provide more information about studies showing an association between formaldehyde exposure and LHCs, for example, include data from the NCI cohort on Hodgkin's lymphoma.
6. Discuss how studies of myeloid leukemia provide the strongest evidence of an association to formaldehyde exposure.
7. Change latency to "time since first exposure" for the NIOSH study.
8. Amend the statement about latency related to leukemia in the NCI study to "This pattern is consistent with a follow-up lasting longer than a peak or optimal latency period, as has been seen with other leukemia-inducing agents," referencing Silver *et al.* 2002 instead of Triebig 2010.
9. Reword the sentence in the introduction paragraph discussing the mechanisms for myeloid leukemia, which states, "The mechanisms by which formaldehyde causes myeloid leukemia in humans are not known; nevertheless, the available evidence taken together does not indicate that such mechanisms are implausible" to be something similar to, "While the mechanisms by which formaldehyde causes

[4] For the complete minutes from the NTP BSC meeting, see http://ntp.niehs.nih.gov/go/9741, June 21–22, 2010 meeting, and select meeting minutes.

myeloid leukemia in humans are not known, a number of plausible mechanisms have been advanced."

10. Reword the description of the Murrell *et al.* (2005) study to "Murrell *et al.* (2005) found that the olfactory epithelium of the nasal passages of rats contained multipotent stem/progenitor cells that were able to repopulate the hematopoietic tissues of irradiated rats and to form progenitor cells of multiple lineages."

NTP Response: The NTP concurs with these suggestions and incorporated the requested information into the appropriate sections of the final substance profile for formaldehyde. The profile was amended as suggested for comments 1 to 3 in the "Exposure" section and comments 4 to 10 in the "Carcinogenicity" section.

11. Some reviewers stated that the evidence for myeloid leukemia in humans was strongly suggestive, but not sufficient, whereas other reviewers thought that the draft substance profile supported the NTP's preliminary listing recommendation.

NTP Response: The NTP believes that formaldehyde is a *known human carcinogen* based on findings of increased risks of myeloid leukemia in addition to nasopharyngeal and sinonasal cancer. As discussed in the draft substance profile, the findings of increased risks of myeloid cancer are consistent across the major studies (meaning large and most informative studies) that specifically looked at this subtype of leukemia (Hauptmann *et al*. 2009, Pinkerton *et al.* 2004, and Beane Freeman *et al.* 2009). In addition a recent meta-analysis, published after the review of the draft substance profile, found a relative risk of 2.47 (95% Confidence Interval = 1.57 to 3.86) for myeloid leukemia among individuals with the highest exposure (Schwilk *et al.* 2010). This meta-analysis includes the most recent case-control study of embalmers (Hauptmann *et al.* 2009), which was not included in previous meta-analyses.

12. In the "Carcinogenicity" section, add more detail information on animal data, particularly for oral exposure, and on the study of the combined *in utero* and oral exposure to formaldehyde.

NTP Response: The substance profile is a concise summary of the scientific evidence that supports the listing and is not intended to be a comprehensive review. The draft substance profile contains the relevant information from these studies typically captured in a substance profile. Detailed information for these topics is available in the background document for formaldehyde (NTP 2010).

13. It was noted that formaldehyde is one of the few chemicals for which there is quantitative dose-response information and dosimetry in animal studies that actually support location-specific tumors and tumor types. The BSC felt that point should be more distinct in the profile.

NTP Response: The substance profile briefly discusses some data that support this issue, for example, it states, "In rats, regional formaldehyde flux (as estimated by computational fluid dynamic models) was correlated with the anatomical distribution of formaldehyde-induced lesions (squamous metaplasia)." The purpose of the RoC is to identify hazards, thus a detailed discussion of quantitative dose-response data is outside the scope of a substance profile.

References

Beane Freeman LE, Blair A, Lubin JH, Stewart PA, Hayes RB, Hoover RN, Hauptmann M. 2009. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute Cohort. *J Natl Cancer Inst* 101(10): 751-761.

Hauptmann M, Stewart PA, Lubin JH, Beane Freeman LE, Hornung RW, Herrick RF, *et al.* 2009. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. *J Natl Cancer Inst* 101(24): 1696-708

Murrell W, Feron F, Wetzig A, Cameron N, Splatt K, Bellette B, *et al.* 2005. Multipotent stem cells from adult olfactory mucosa. *Dev Dyn* 233(2): 496-515.

NTP. 2010. *Report on Carcinogens Background Document for Formaldehyde*. Research Triangle Park, NC: National Toxicology Program, 552 pp. http://ntp.niehs.nih.gov/ntp/roc/twelfth/2009/November/Formaldehyde_BD_Final.pdf

Pinkerton LE, Hein MJ, Stayner LT. 2004. Mortality among a cohort of garment workers exposed to formaldehyde: an update. *Occup Environ Med* 61(3): 193-200.

Schwilk E, Zhang L, Smith MT, Smith AH, Steinmaus C. 2010. Formaldehyde and leukemia: an updated meta-analysis and evaluation of bias. *J Occup Environ Med.* 52(9): 878-86

Silver SR, Rinsky RA, Cooper SP, Hornung RW, Lai D. 2002. Effect of follow-up time on risk estimates: a longitudinal examination of the relative risks of leukemia and multiple myeloma in a rubber hydrochloride cohort. *Am J Ind Med* 42(6): 481-489.

Triebig G. 2010. Implications of latency period between benzene exposure and development of leukemia--a synopsis of literature. *Chem Biol Interact* 184(1-2): 26-29.

Certain Glass Wool Fibers (Inhalable)

The draft substance profile on glass wool fibers (respirable) as a class was peer-reviewed by the BSC at the meeting held June 21–22, 2010[5] (see page 3 for a roster of attending members). The NTP preliminary policy decision was that glass wool fibers (respirable) as a class should be listed in the *12th RoC* as *reasonably anticipated to be human carcinogens* based on sufficient evidence of carcinogenicity from studies in experimental animals and supporting evidence from studies on mechanisms of carcinogenesis. The NTP reviewed the BSC comments and revised the substance profile. The NTP changed the scope of the listing to be certain glass wool fibers (inhalable) and finalized its listing recommendation, which were approved by the Secretary of Department of Health and Human Services. Certain glass wool fibers (inhalable) are listed as *reasonably anticipated to be human carcinogens* in the *12th RoC.*

BSC Comments and NTP Response: NTP's Preliminary Listing Recommendation

The draft substance profile recommended listing glass wool fibers (respirable) as a class, but noted that carcinogenicity within the class of respirable glass wool fibers varies, and not all fibers within this class cause cancer.

BSC Comments:

1. One reviewer supported listing glass wool fibers as a class because the association of factors such as $K_{dis,}$ biopersistence, and fiber dimensions (diameter and length) with cancer outcomes in animals is not yet fully established or has not been fully characterized in studies in humans and experimental animals.
2. One reviewer disagreed with the listing as a class and recommended that biopersistence was a factor that seems to correlate with *in vivo* responses. Another member suggested that "biopersistent" should be added to the document's title to point out the importance of this property, but left ambiguous and without details.
3. A comment was made that mechanistic data suggest differences between glass wool and special purpose fibers with respect to biosolubility and biopersistence, and that those are likely critical factors when comparing the carcinogenicity of the different fibers. Therefore, the relationship of those factors to carcinogenicity should be addressed more explicitly in the profile.

NTP response: The NTP concurs that biopersistence is an important factor in predicting carcinogenicity, and agrees that the term should be left ambiguous because the physical-chemical properties that predict fiber biopersistence and carcinogenicity are not fully established. Thus, fibers need to be evaluated on a case-by-case basis. The NTP revised the title of the listing to *certain* glass wool fibers (inhalable), and the profile states that "evidence from studies of fiber properties which indicates that only certain fibers within this class — specifically, fibers that are biopersistent in the lung or tracheobronchial region — are *reasonably anticipated to be human carcinogens."* The NTP also expanded the discussion of studies evaluating

[5] For the complete minutes from the NTP BSC meeting, see http://ntp.niehs.nih.gov/go/9741, June 21–22, 2010 meeting, and select meeting minutes.

biopersistence and biodurability in the "Fiber Properties Related to Carcinogenicity" section of the substance profile. The substance profiles states, "In general, special-purpose fibers are more durable than insulation glass wool fibers; these findings thus suggest that durability is an important factor in predicting the potential carcinogenicity of glass wool fibers." in the "Cancer Studies in Experimental Animals" section, under "Summary".

4. One reviewer disagreed with the NTP's conclusion that the evidence from studies in humans was inadequate and thought instead that it was limited because (1) there was consistency across studies in that nearly all studies reported a modest elevation in lung or respiratory cancer risk, and (2) exposure assessments were generally of limited quality, likely resulting in substantial misclassification of the study populations by exposure status, which would bias the relative risks toward the null.

NTP Response: The NTP would like to clarify that inadequate evidence in human studies does not mean the findings are negative. The NTP agrees that there were consistent findings across studies and that in general, exposure misclassification would bias the relative risks towards the null. However, the NTP does not believe that the human evidence is limited because the magnitude of the relative risks was small and in the range found for confounding from smoking, and because there was no evidence of increasing risk with different types of exposure measurements (such as duration of exposure and level of exposure). The NTP changed the text in the "Cancer Studies in Humans" section from, "there was no convincing evidence that the excess lung cancer was due to exposure specifically to glass wool fibers" to "it is unclear that the excess lung cancer was due to exposure specifically to glass wool fibers" and provided a discussion of the limitations of the exposure assessment.

BSC Comments and NTP Responses: Scientific and Technical Issues

BSC Comments:

1. Estimates for the number of workers exposed to special-purpose fibers and upper limits for airborne fiber levels should be added to the profile.
2. The exposure section of the substance profile should include a description of indices of exposures that have been considered to be biologically active including fiber length, diameter, and biopersistence.
3. Extend the description of physical distinctions of the fibers to the summary section of the substance profile.
4. Add a short mode of action statement in the mechanistic section to discuss how mesotheliomas develop.

NTP Response: The NTP concurs with these suggestions and incorporated the requested information into the appropriate sections of the final substance profile for certain glass wool fibers (inhalable). Additional information was added as recommended including comments 1 and 2 to the "Exposure," section, comment 3 to the "Studies in Experimental Animals, Summary," section, and comment 4 to the "Mechanisms of Carcinogenicity" section.

5. Add information to the profile to clarify why the mononuclear cell leukemia (MCL) findings in rats were considered significant.

NTP Response: The NTP expanded its discussion in "Studies in Experimental Animals" to explain why the MCL findings in rats were considered important. The discussion states (1) that the incidence of MCL exceeded the historical controls and (2) that granulomatous pleural and subpleural plaques and glass-laden macrophages where found in adjoining lymph nodes, indicating exposure to glass fibers.

6. One reviewer stated that the *in vitro* dissolution constant (K_{dis}) should be more recognized in the document, whereas other reviewers were not convinced of the correlative value of K_{dis} with carcinogenicity or stated that there were other factors besides K_{dis} related to carcinogenicity.

NTP Response: The discussion of K_{dis} was expanded in the "Fiber Properties Related to Carcinogenicity" section of the substance profile to include information on the modeling studies comparing K_{dis} to fibrosis. The final profile, similar to the draft profile, notes some of the limitations for predicting tumorigenicity using K_{dis}.

7. Dose should have been considered in the discussion of the Miller *et al*. 1999 study of mesothelioma (Miller *et al*. 1999).

NTP Response: The NTP concurs with this comment. The statement "…the incidence of mesothelioma in rats exposed by intraperitoneal injection was higher for the insulation fiber (59%) than for the special-purpose fiber (33%) (Miller *et al*. 1999)" has been removed from the profile because there was a large difference between the doses used for insulation and special-purpose fibers.

References

Miller BG, Searl A, Davis JM, Donaldson K, Cullen RT, Bolton RE, Buchanan D, Soutar CA. 1999. Influence of fibre length, dissolution and biopersistence on the production of mesothelioma in the rat peritoneal cavity. *Ann Occup Hyg* 43(3): 155-166.