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Paul Schulte, PhD, Director
National Institute for Occupational Safety and Health (NIOSH)
NIOSH Docket Office
Robert A. Taft Laboratories
4676 Columbia Parkway
MS C–34
Cincinnati, Ohio 45226

Submitted via the Federal eRulemaking Portal: http://www.regulations.gov

RE: Draft Current Intelligence Bulletin ''Update of NIOSH Carcinogen Classification and Target Risk Level Policy for Chemical Hazards in the Workplace;'' [CDC–2013–0023; Docket Number NIOSH 240–A]

Dear Dr. Schulte:

The American Chemistry Council's (ACC)[1] Center for Advancing Risk Assessment Science and Policy (ARASP)[2] welcomes the opportunity to provide comments in response to the National Institute for Occupational Safety and Health (NIOSH) notice indicating the availability of the draft document titled "Update to NIOSH Carcinogen Classification and Target Risk Level Policy for Chemical Hazards in the Workplace" (herein referred to as Revised Policy)[3]. ARASP fosters activities to promote the adoption of policies and practices that assure the best available and most relevant science is used as the foundation for assessing potential risks from chemical exposures. ARASP submitted comments[4] in December 2011 when NIOSH issued a request for public input on its approach to classifying carcinogens and establishing recommended exposure limits for occupational exposures to hazards associated with cancer.

[1] ACC represents the leading companies engaged in the business of chemistry. ACC members apply the science of chemistry to make innovative products and services that make people's lives better, healthier and safer. ACC is committed to improved environmental, health and safety performance through Responsible Care®, common sense advocacy designed to address major public policy issues, and health and environmental research and product testing. The business of chemistry is a $770 billion enterprise and a key element of the nation's economy. It is one of the nation's largest exporters, accounting for 12 percent of U.S. exports. Chemistry companies are among the largest investors in research and development. Safety and security have always been primary concerns of ACC members, and they have intensified their efforts, working closely with government agencies to improve security and to defend against any threat to the nation's critical infrastructure.

[2] ARASP is a coalition of nineteen organizations focused on promoting the development and application of up-to-date, scientifically sound methods for conducting chemical assessments. ARASP members include: Acrylonitrile Group, ACC's Chlorine Chemistry Division, Ethylene Oxide Panel, Formaldehyde Panel, Hexavalent Chromium Panel, High Phthalates Panel, Hydrocarbon Solvents Panel, Olefins Panel, Oxo Process Panel, Propylene Oxide/Propylene Glycol Panel, Public Health and Science Policy Team, Silicones Environmental, Health and Safety Center of North America and Vinyl Chloride Health Committee, American Cleaning Institute, American Petroleum Institute, CropLife America, Halogenated Solvents Industry Alliance, Nickel Producers Environmental Research Association and Styrene Information and Research Center.

[3] 78 FR 68849; http://www.cdc.gov/niosh/docket/review/docket240A/pdf/FRN-2013-273.PDF

[4] ACC ARASP December 2011 Comments on NIOSH Cancer Policy and RELs; Attachment 1

We recognize the important role that NIOSH plays in evaluating potential workplace hazards and developing recommended exposure limits that are supported by the available scientific information. NIOSH considers the Revised Policy a "highly influential scientific assessment" and therefore it should adhere to a rigorous standard of quality and peer review as set forth in the Office of Management and Budget (OMB) "Final Information Quality Bulletin for Peer Review[5]." The OMB Bulletin notes that "In general, an agency conducting a peer review of a highly influential scientific assessment must ensure that the peer review process is transparent by making available to the public the written charge to the peer reviewers, the peer reviewers' names, the peer reviewers' report(s), and the agency's response to the peer reviewers' report(s)." While NIOSH has plans to conduct a peer review of the Revised Policy it is not clear if there will be a public peer review meeting where the peer review committee will discuss the Revised Policy. As well it is unclear if the peer review committee contains a balance of expertise and perspectives or if the public will be afforded an opportunity to recommend experts for inclusion on the peer review committee.

Recommendation – NIOSH should ensure that its peer review includes: (1) the release of the names of the peer reviewers and their identified areas of expertise, (2) the conduct of a public peer review meeting that would allow discussion among the peer reviewers and afford the public an opportunity to interact with the peer reviewers and provide oral comments, (3) sufficient time for the peer review committee to review and consider public comments during their review of the Revised Policy, and (4) a NIOSH response to peer review comments prior to finalizing the Revised Policy. ARASP would also like the opportunity to present our comments orally to the peer review panel.

NIOSH has posted on its website a charge to peer reviewers that includes eight questions[6]. The comments included below have been organized to be responsive those questions.

A. Input on NIOSH Questions 1 – 4

Question 1 – Are the proposed carcinogen policies consistent with the current scientific knowledge of toxicology, risk assessment, industrial hygiene, and occupational cancer? If not, provide specific information and references that should be considered.

Question 2 – Is there additional scientific information related to the issues of the proposed NIOSH carcinogen policies that should be considered for inclusion? If so, provide information and specify references for consideration. Is there any discussion in the document that should be omitted?

Question 3 – Is the proposed carcinogen classification policy explained in a clear and transparent manner? Is the basis for the proposed policy adequately explained? If not, specify (section, page, and line number) where clarification is needed.

[5]OMB's "Final Information Quality Bulletin for Peer Review".
http://www.whitehouse.gov/sites/default/files/omb/assets/omb/memoranda/fy2005/m05-03.pdf
[6] NIOSH Charge to Peer Reviewers – http://www.cdc.gov/niosh/review/peer/HISA/carcinogen-pr.html

> Question 4 – Are there issues relevant to the classification of occupational carcinogens that have not been adequately addressed in this proposed policy? If so, provide information and specify references for consideration.

As the topics covered in these four questions are related, ARASP is providing a combined response to them.

The Revised Policy outlines NIOSH's process to assess potential chemical hazards in the workplace that may increase cancer risk. The approach plans to utilize carcinogen classifications from other organizations along with the information on associated workplace exposures. If NIOSH finds the scientific basis for the cancer classification relevant to occupational exposure then it will list that chemical as an occupational carcinogen. ARASP supports a process that utilizes up-to-date scientific knowledge about human health impacts and occupational exposure in an objective and systematic way to evaluate carcinogenic risk.

Recommendation – NIOSH should ensure that its process allows for the utilization of all available scientific evidence when evaluating risk and relies on mode of action information to determine the relevance and biological plausibility for occupational exposure that could result in a cancer risk.

NIOSH has indicated that it plans to utilize the hazard assessments and classifications developed by the Environmental Protection Agency (EPA), National Toxicology Program (NTP) and the International Agency for Research on Cancer (IARC) and assess their relevance to the occupational setting. ARASP does not find this approach consistent with ensuring the consideration of all high quality scientific evidence. The NIOSH evaluation process must incorporate the best available and most relevant information utilizing a weight of evidence (WOE) approach that considers positive, negative and null study results when reaching conclusions. Many stakeholders and independent reviews have raised concerns about the approaches used by these programs. For instance, concerns have been raised by the National Research Council (NRC)[7,8] and the Governmental Accountability Office[9] regarding the EPA's Integrated Risk Information System (IRIS) including out of date information and significant concerns with the Agency's WOE evaluations. Additionally, the NRC[10] is conducting a review of some NTP Report on Carcinogens (RoC) cancer classifications to ensure that the criteria used for classification is appropriate.

[7] National Research Council, Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde (2011). Available at https://download.nap.edu/catalog.php?record_id=13142. In particular, see chapter 7 of this report which applies to all IRIS assessments.
[8] A committee of the NRC will assess the scientific, technical, and process changes being implemented by EPA for its IRIS Program. Because several reviews of IRIS assessments have expressed concerns about EPA's weight-of-evidence analyses, the committee will review current methods for evidence-based reviews and recommend approaches for weighing scientific evidence for chemical hazard and dose-response assessments.
[9] GAO High Risk Series (February 2013). http://www.gao.gov/assets/660/652133.pdf Found that EPA has not fully addressed recurring issues concerning the clarity and transparency of its development and presentation of draft IRIS assessments. In addition, EPA has not addressed other long-standing issues regarding the availability and accuracy of current information to users of IRIS.
[10] The NRC at the request of the Department of Health and Human Services will undertake a scientific peer review of the determinations concerning formaldehyde and styrene in the NTP's 12th Report on Carcinogens (RoC).

Recommendation – NIOSH should fully evaluate the scientific basis and quality of the individual scientific assessments that underlie the classifications developed by EPA, NTP, and IARC prior to utilizing the classifications as a basis for the NIOSH classification. This will ensure that the scientific evidence is the most current and supports the assigned classification.

B. Input on NIOSH Question 5

> Question 5 – NIOSH adapted the OSHA Hazard Communication Table Relating Approximate Equivalences among IARC, NTP RoC, and GHS Carcinogenicity Classifications to provide a simple, systematic method of determining GHS cancer hazard categories. However, NIOSH has further considered the GHS carcinogen categories 1B and 2 because NTP classification reasonably anticipated to be a human carcinogen and IARC classification 2B have criteria that overlap the two GHS categories. NIOSH is requesting comments on the validity of the NIOSH Correspondence table (Table 2) and its usefulness as a guide to determine GHS hazard categories.

ARASP supports an approach to utilize GHS carcinogen classifications when relevant and applicable to identify occupational hazards, as it will allow a means of developing common positions and consistency in the evaluation of chemical risks. The Revised Policy plans to assign a GHS carcinogen category of 1A (known to have carcinogenic potential for humans) whenever the NTP, EPA or IARC have made a corresponding classification. However, for other categories, assigning classifications is not as straightforward. For example, NIOSH's approach allows the possibility of a GHS classification of 1B (presumed to have carcinogenic potential for humans) for substances that have been classified by NTP as "reasonably anticipated." It is possible that a substance classified by NTP as "reasonably anticipated" could have been classified based on less than sufficient evidence of carcinogenicity in humans or laboratory animals and as such this type of substance would be more accurately assigned a GHS classification of Category 2 (suspected carcinogen) based on evidence which is not sufficiently convincing. While this is partially addressed in the text on page 27, it is not accurately captured in Table 1 or 2 which appear to imply that all NTP RoC classifications of "reasonably anticipated" are equivalent to a GHS classification of 1B. It is unclear in the Revised Policy whether NIOSH will utilize a default approach of assigning a GHS classification of 1B to chemicals classified by NTP as "reasonably anticipated." Using the NTP classification without sufficient review of the underlying data could lead to misleading or inaccurate NIOSH classifications. It is also important to note that an NTP classification does not necessarily consider important mechanistic and mode of action information that may impact a final classification reached by NIOSH.

Recommendation – In order to ensure the consideration of current scientific knowledge, NIOSH should evaluate each cancer classification on a substance by substance basis. The evaluation should explicitly review all available data, including information that may not have been considered or available during the time NTP, EPA or IARC derived its classifications. A thorough systematic review of the available data will be necessary

to ensure that the appropriate classification is scientifically supported and assigned by NIOSH.

C. Input on NIOSH Question 6

Question 6 – Is the proposed target risk level policy explained in a clear and transparent manner? Is the basis for the proposed policy adequately explained? If not, specify (section, page, and line number) where clarification is needed.

Resolving Conflicts Between NTP, EPA and IARC Classifications

In the Revised Policy it is unclear whether NIOSH will consider a hierarchy when utilizing the classifications derived from other agencies. Page 24 of the Revised Policy notes that when differences arise NIOSH will consider the totality of the data and the relevance of the data to the workplace and the review will be based on how recently the data were evaluated, how complete the data set was, and whether the routes of exposure, modes of action, and other considerations were relevant to workplace exposures.

Recommendation – The Revised Policy should include greater discussion regarding if NIOSH will utilize a hierarchy when relying on other agencies classifications to reach conclusions.

Recommendation – NIOSH should include information about the WOE framework it will plan to employ to ensure that all relevant information is considered. There are several approaches that NIOSH should consider related to the evaluation of risk from less-than-lifetime exposures,[11] combining toxicological and epidemiological evidence to establish causal inference,[12] utilization of mode of action information in evaluations[13] and best practices for conducting systematic review[14].

Approach to Exposure-Response

The Revised Policy states that NIOSH will treat exposure-response as low-dose linear unless a non-linear mode of action has been clearly established (page 30 of the Revised Policy). As the scientific understanding relating to mode of action is rarely, if ever, 'clearly established,' any default approach should consistently consider the current understanding of modes of action and dose response relationships relevant to the exposure levels of concern. Unfortunately, the NIOSH proposed approach does not appear to readily allow for the consideration of mode of action information. Consequently, the NIOSH default approach of

[11] Felter, Susan P., et al. "A proposed framework for assessing risk from less-than-lifetime exposures to carcinogens." Critical reviews in toxicology 41.6 (2011): 507-544.
[12] Adami, Hans-Olov, et al. "Toxicology and epidemiology: improving the science with a framework for combining toxicological and epidemiological evidence to establish causal inference." Toxicological Sciences 122.2 (2011): 223-234.
[13] Meek, M. E., et al. "New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis." Journal of Applied Toxicology 34.1 (2014): 1-18.
[14] Rhomberg, Lorenz R., et al. "A survey of frameworks for best practices in weight-of-evidence analyses." Critical reviews in toxicology 43.9 (2013): 753-784.

low-dose linearity can potentially over estimate risk. As noted in the EPA's 2005 Guidelines for Carcinogen Risk Assessment[15]:

> "The linear approach is used when: (1) there is an absence of sufficient information on modes of action or (2) the mode of action information indicates that the dose-response curve at low dose is or is expected to be linear. Where alternative approaches have significant biological support, and no scientific consensus favors a single approach, an assessment may present results using alternative approaches. A nonlinear approach can be used to develop a reference dose or a reference concentration (see Section 3.3.4)."

Recommendation – NIOSH should revise its current approach to allow for the use of mode of action information in determining whether low-dose linearity is warranted. In the event that the available data could support either a linear or non-linear dose-response, both approaches should be presented and utilized to develop RELs.

Utilizing Best Available Chemical Assessment Practices

In section 5.0 of the Revised Policy, NIOSH describes its process for the development of candidate RELs. It states that "NIOSH conducts quantitative risk assessment by using mathematical models to describe the exposure-response and to estimate low-dose risk." NIOSH in turn uses those estimates to set RELs. However, the Revised Policy does not describe the types of modeling that NIOSH intends to utilize when developing RELs. Additionally, the Revised Policy states that as NIOSH uses epidemiology data to develop RELs it "…will project both the central estimate and a 95% lower confidence limit, and the REL will typically be based on the 95% lower confidence limit. While we support the presentation of both the central estimate and the 95% lower confidence limit, NIOSH should not have a default approach to deriving RELs based on the 95% lower confidence limit.

Recommendation – Some discussion should be added to the Revised Policy to reflect available modeling approaches that may be employed by NIOSH.

Recommendation – When deriving a REL that is based primarily on animal data, NIOSH should develop a human equivalency concentration (HEC) to adequately incorporate available toxicokinetic information in the REL calculation. EPA's 2005 Guidelines on Carcinogenic Risk Assessment provides additional detail on the derivation and utility of HECs.

Recommendation – An objective and transparent REL derivation process should rely on the best available dose-response data to determine the best estimate for calculating a REL. NIOSH should determine whether to use the central estimate or the 95% lower confidence limit based on the data available and not have a default policy of utilizing the 95% lower confidence limit.

[15] EPA Guidelines for Carcinogen Risk Assessment (March 2005). http://www.epa.gov/raf/publications/pdfs/CANCER_GUIDELINES_FINAL_3-25-05.PDF

D. Input on NIOSH Questions 7 - 8

Question 7 – An analytical feasibility (AF) notation will be used to identify those RELs that are established to reflect the limitations of the sampling and analytical method (i.e., AF) and not the target risk level of 1 in 1,000. Is this notation adequately explained?

Question 8 – Is the proposed analytical feasibility and technical achievability policy explained in a clear and transparent manner? Is the basis for the proposed policy adequately explained? If not, specify (section, page, and line number) where clarification is needed.

As the topics covered in these two questions are related, ARASP is providing a combined response to them.

The proposed feasibility policy and the analytical feasibility notation are adequately explained in the Revised Policy. Employers and employees benefit from health protective RELs which are based on the most relevant scientific information for evaluating occupation exposures and that can be measured using available analytical technologies.

Recommendation – ARASP supports a policy that allows for the establishment of RELs at a level where exposure can be accurately measured and quantified.

Conclusion

ARASP supports NIOSH's efforts to revise its carcinogen classification and target risk level policy. We recommend that NIOSH subject the Revised Policy to a comprehensive peer review and adequately address peer review and public comments, including all the comments included above, prior to finalizing the policy. Additionally, each individual substance that is evaluated using this policy should be subject to peer review and a call for information to ensure that NIOSH has the most up to date scientific data to reach conclusions. ARASP would also like the opportunity to present our comments orally to the peer review panel. If you have any questions or require additional information please feel free to contact me by phone (202-249-7000) or by email Kimberly_wise@americanchemistry.com with any questions.

Respectfully,

Kimberly Wise
Senior Director
Chemical Products & Technology Division
American Chemistry Council