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NTP Designated Federal Official
Office of Liaison, Policy and Review, DNTP
MD K2–03
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RE: Comments on NIEHS/NTP's "Draft Report on Carcinogens Monograph for Cumene" (Federal Register 78: No. 14, January 22, 2013, p. 4419-4421)

Dear Dr. White,

The American Chemistry Council (ACC) appreciates the opportunity to comment on the National Institute of Environmental Health Sciences (NIEHS) National Toxicology Program's (NTP) Report on Carcinogens (RoC) "Draft Report on Carcinogens Monograph for Cumene." ACC[1] has long maintained that the practice of federal agency hazard and risk assessments can and should reflect the best science and practices, and we support actions to enhance the integration of up to date scientific knowledge, methods and practices in chemical assessment and decision making programs throughout government.

As you know, significant questions have been raised about the scientific integrity, credibility and relevance of the 12th RoC. This concern was reflected by bipartisan Congressional action in 2012 which required the Department of Health and Human Services (HHS) to contract with the National Academy of Sciences (NAS) to conduct a scientific peer review of the 12th RoC determinations related to formaldehyde and styrene. The NAS reviews of styrene and formaldehyde will necessitate examination by the NAS panels of the underlying scientific evaluation policies and practices employed by NIEHS/NTP for data evaluation, for integrating studies to weigh the overall evidence for determining cause and effect, and the criteria for determining the potential for carcinogenic hazards to humans at environmentally relevant levels of exposures. The findings and recommendations of these NAS reviews will be informative not only for styrene and formaldehyde, but importantly, for future RoCs.

Last May, we pointed out that moving forward with developing the 13th RoC before the NAS completes the reviews of the 12th RoC would perpetuate the deficiencies in the scientific rigor of the RoC

[1] The American Chemistry Council (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 $760 billion enterprise and a key element of the nation's economy. It is the largest exporting sector in the U.S., 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.

evaluation methods and review processes.[2] Unfortunately, NIEHS/NTP elected to proceed ahead and now, as predicted, and without the benefit of NAS's reviews, NIEHS/NTP is poised to put forward a 13th RoC assessment that has significant scientific flaws. Once again, NIEHS/NTP has invoked a strength of evidence approach which uses default options over data and over-relies on opaque study integration procedures in lieu of an objective and transparent weight of evidence evaluative framework which uses mode of action as its central organizing principle.

A fundamental problem with NIEHS/NTP's RoC evaluation is that the approach starts not with the data, but rather with the default assumption that essentially all tumors induced in animal studies infer carcinogenic hazard or risk to humans, and then requires that there be unequivocal evidence to refute this assumption. As science can rarely, if ever, unequivocally disprove something, this is a problematic, unworkable and inappropriate "de facto standard." The current RoC approach inappropriately downplays the overall weight of evidence concerning the lack of relevance to humans of many of the modes of action by which tumors are induced in experimental animals.[3] We believe that the approach used by NIEHS/NTP to evaluate scientific evidence for determining cause and effect of carcinogenic hazards to humans needs to be modernized. To properly assess the chemicals for the RoC, NIEHS/NTP needs to adopt a consistent, systematic weight of evidence framework that incorporates transparent and rigorous data evaluation methods and uses 21st century knowledge of toxicological modes of action[4] as the central organizing principle for integrating study results. Adopting these methods and criteria will allow data from laboratory experiments, epidemiological investigations, and cutting-edge mechanistic research from all relevant studies, GLP and non-GLP, from all investigators, regardless of affiliation or funding source, to be comprehensively and systematically reviewed. Once reviewed for quality, relevance and reliability, each study can be given appropriate weight and integrated in a manner that provides a robust understanding of the mode of action and the potential carcinogenic hazards that environmentally relevant levels of exposures could pose to humans.

Carcinogens act by different mechanisms, and there are important dose- and species-specific responses to consider when evaluating potential carcinogenic hazards and risk to humans.[5,6] Today, as a consequence of continued rapid advances in scientific understanding and the application of this understanding to regulatory science policy, decision logic for evaluating the biological events leading to an animal tumor response and consideration of how these events relate to human hazards and risks is possible as a routine matter in cancer risk assessment. Significant progress has been made, both in the U.S. and internationally, in defining rigorous scientific frameworks for evaluating toxicity datasets to determine biologically plausible modes of action and relevance to humans.[7,8,9,10] Unfortunately, the

[2] Letter from Cal Dooley, ACC CEO to HHS Secretary Sebelius dated May 24, 2012.
[3] Cohen SM and Arnold LL. 2011. Chemical Carcinogenesis. Toxicol Sci. 120 Suppl 1:S76-92.
[4] Mode of action information describes key events and processes that would in general explain the overall process of development of a toxic effect. Mode of action is distinguished from "mechanism of action," which implies a more detailed understanding and description of each and every event, often at the molecular level. There are many examples of possible modes of carcinogenic action, such as mutagenicity, mitogenesis, inhibition of cell death, cytotoxicity with reparative cell proliferation, and immune suppression.
[5] *op. cit.* footnote 3.
[6] Slikker Jr W, Andersen ME, Bogdanffy MS, Bus JS, Cohen SD, Conolly RB, David RM, Doerrer NG, Dorman DC, Gaylor DW, Hattis D, Rogers JM, Woodrow SR, Swenberg JA, and Wallace K. 2004. "Dose-Dependent Transitions in Mechanisms of Toxicity." Toxicol Appl Pharmacol. 201(3): 203-25.
[7] Boobis AR, Cohen SM, Dellarco V, McGregor, D, Meek, ME, Vickers C, et al. 2006. IPCS Framework for Analyzing the Relevance of a Cancer Mode of Action for Humans. Crit Rev Toxicol 36: 781-792.

NIEHS/NTP RoC methodology has remained static and has not kept pace with these advances despite significant investments by government, academia and industry into mode of action toxicological research.

For example, in the draft evaluation of cumene for the 13th RoC, NIEHS/NTP proposes that cumene be classified as "reasonably anticipated to be a human carcinogen based on sufficient evidence in experimental animals" even though there is considerable evidence, documented in NIEHS/NTP's own analysis, which shows cumene is likely not genotoxic and that the cumene-induced kidney tumors in male rats and lung tumors in mice likely occur via modes of action that are not relevant to humans.[11,12,13] This proposed conclusion by NIEHS/NTP largely stems from the use of an overly simplistic approach that places defaults as the starting point of the decision making approach, makes the default a de facto standard, and then requires that the default be unequivocally disproven. This is illustrated in draft cumene assessment[14] conclusions where NIEHS/NTP repeatedly uses such phrases as "we cannot rule out," "other mechanisms could not be unequivocally ruled out," "other modes of action could not be unequivocally ruled out and the human relevance of the kidney tumors in male rats was not dismissed" and "no convincing evidence was identified" in justification for continued reliance on assumptions over the weight of the evidence for decision making. This approach undervalues and undermines the considerable amount of scientific data on modes of action which show that many substances which produce tumors in lab animal studies likely pose little or no carcinogenic hazard or risk to humans.[15]

This undervaluation of scientific data can be seen throughout the draft RoC monograph for cumene. For example:

- Essentially no weight is given to the substantial evidence that cumene meets a significant number, albeit not all, of the criteria for "unequivocally" establishing an alpha-2-u-globulin mode of action for rat kidney tumorigenesis. (draft monograph page 50.)

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[8] Julien E, Boobis AR, Olin, SS. 2009. "The Key Events Dose-Response Framework: A cross-disciplinary mode-of-action based approach to examining dose-response and thresholds." Crit Rev Food Sci Nutr. 49(8):682-689.
[9] Rhomberg LR, Bailey LA, Goodman JE. 2010. "Hypothesis-based weight of evidence: A tool for evaluating and communicating uncertainties and inconsistencies in the large body of evidence in proposing a carcinogenic mode of action – Naphthalene as an example." Crit Rev Toxicol. 40:671-696.
[10] Rhomberg LR, Bailey LA, Goodman JE, Hamade A, Mayfield D. 2011. "Is exposure to formaldehyde in air causally associated with leukemia? – A hypothesis-based weight-of-evidence analysis." Crit Rev Toxicol. 41(7):555-621.
[11] NTP/NIEHS Draft Report on Carcinogens Monograph for Cumene, January 18, 2013. http://ntp.niehs.nih.gov/NTP/About_NTP/MonoPeerRvw/2013/March/DraftRoCCumeneMonograph_508.pdf. See, for example, page 55 ("…cumene was not mutagenic or genotoxic in most of the standard in vitro and in vivo assays….") and page 57 ("Although the available data are consistent with an 2u-globulin nephropathy mode of action in renal tumor formation, all of the criteria were not met.")
[12] Cruzan G, Bus J, Banton M, Gingell R, Carlson G. 2009. Mouse specific lung tumors from CYP2F2-mediated cytotoxic metabolism: An endpoint/toxic response where data from multiple chemicals converge to support a mode of action. Regul Toxicol Pharm. 55(2): 205-218.
[13] Cruzan G, Bus J, Hotchkiss J, Harkema J, Banton M, Sarang S. 2012. CYP2F2-generated metabolites, not styrene oxide, are a key event mediating the mode of action of styrene-induced mouse lung tumors. Regul Toxicol Pharmacol. 62(1): 214-220.
[14] *op. cit.* footnote 11.
[15] *op. cit.* footnotes 3, 12 and 13

- Even though "… cumene was not mutagenic or genotoxic in most of the standard in vitro and in vivo assays…." (draft monograph page 55), NIEHS/NTP assert that the differential k-ras and p53 mutation spectra strictly support a genotoxic MoA. However, this assertion falls well short of providing convincing evidence of genotoxicity. As stated in the draft monograph (page 43), "tumors that arise spontaneously or through non-genotoxic or indirect genotoxic mechanisms (indirect DNA damage) may also contain increased frequencies of proto-oncogene mutations (Eastmond 2012, Hong et al. 2008) and many of these molecular changes may be an effect rather than a cause of cell transformation (Stanley 1995)." In addition, the draft RoC monograph also admits that the mutational spectra observed in cumene-induced lung tumors is not convincing evidence of a genotoxic MoA, stating (draft monograph page 44) thus: "… the observed differences in mutation spectra between spontaneous and cumene-exposed tumors are required but not sufficient to determine whether or not cumene is genotoxic in mouse lung at the K-ras and p53 genes."[16]

- Moreover, cumene is structurally related to styrene, and scientific evidence shows that chemicals with such similar structures may induce species-specific lung tumors in mice[17] that are not relevant to humans. Therefore, it is puzzling that NIEHS/NTP has elected to press ahead with the 13th RoC monograph on cumene when, concurrently, the NAS is reviewing the NIEHS/NTP approach used to evaluate the significance of mouse lung tumors associated with styrene exposure and their relevance, or lack thereof, to human health hazards.

In addition to the significant scientific shortcomings detailed above, the current approach employed by NIEHS/NTP for RoC evaluations does not meet HHS's Policies and Principles for Assuring Scientific Integrity.[18] This policy specifies that "HHS shall convey scientific and technological information to the public such that the presentation is accurate, transparent, and informative. To do so, HHS shall communicate scientific and technological findings by including a clear explication of underlying assumptions and, where appropriate, an accurate contextualization of uncertainties and a description of the probabilities associated with both optimistic and pessimistic projections." To comply with this HHS policy, for substances like cumene, where there is significant scientific data showing that the overall weight of the evidence indicates the modes of action in lab animal studies are not relevant to cancer

[16] The predominant codon 12 G>T transversions identified for cumene-induced lung tumors is a well-known mutation that is indicative of exposure to genotoxic and adduct-forming substances (Shiao, 2009). On this basis, the draft RoC monograph suggests that the increased incidence of k-ras and p53 mutations in cumene-induced mouse lung tumors correlates with similar mutational differences observed in human lung cancers following cigarette smoke exposure, including multiple PAHs many of which are genotoxic or mutagenic and are known to cause lung cancer by adduct formation. However, no DNA adducts for cumene or its metabolites have ever been identified and cumene has not been shown to form mutagenic DNA adducts in vitro. Hong et al. (2008) suggested a potential indirect mechanism of mouse lung tumors, speculating that indirect oxidative damage to DNA associated with 8-oxo-deoxyguanosine adduct formation, and based on this, NIEHS/NTP conclude that "…the findings of DNA damage in female mouse lung tissue (as measured by the NTP 2012 comet assay) provides some support that the G to T K-ras mutations may have been caused by cumene via DNA damage." This is mere speculation at best. There is no evidence for 8-oxo-deoxyguanosine adduct formation with cumene, and neither has cumene been shown to cause significant oxidative stress-induced DNA damage. Furthermore, no DNA damage was shown in male mouse lungs (as measured by comet assay) despite the incidence of lung tumors.

[17] *op. cit.* footnotes 12 and 13.

[18] United States Department Of Health And Human Services Policies And Principles For Assuring Scientific Integrity. (Accessed March 7, 2013 from http://www.hhs.gov/open/recordsandreports/index.html at URL: http://www.cdc.gov/od/science/docs/Scientifc_integrity_principles_12-19-11.pdf

induction in humans, NIEHS/NTP should indicate that there is a significant probability that cumene does not meet the RoC criteria because it is not reasonably anticipated to pose a carcinogenic hazard to humans.

In conclusion, when knowledge of mode of action is used as the central organizing element, the weight of evidence shows cumene is not genotoxic, that the induction of rat kidney tumors occurs by accumulation of alpha-2-urinary globulin (a conclusion that the NTP supported in its 2-year carcinogenicity assessment of cumene[19] – NTP TR-542), a species-specific mode of action that does not operate in humans, and that mouse lung tumor induction is also entirely consistent with a species-specific mode of action that does not operate in humans. The species and organ-specific nature of cumene-induced rodent tumors (the modes of action which have been well characterized in published literature) is inconsistent with the RoCs preliminary recommendations that the multi-organ nature of these tumors is "sufficient evidence of carcinogenicity."

There is a pressing need for NIEHS/NTP to address the fundamental scientific shortcomings within the RoC process. NIEHS/NTP should adopt a consistent, systematic weight of evidence framework that incorporates transparent and rigorous data evaluation methods and uses 21st century knowledge of toxicological modes of action as the central organizing principle for integrating study results. We reiterate our request that the NIEHS/NTP pause development of the 13th RoC at this time, improve their practices for data integration and await the completion of the NAS reviews and then, once improvements have been incorporated into the RoC evaluation methods and review processes, move ahead with development of the 13th RoC.

ACC appreciates your thoughtful consideration of these comments and recommendations. In order to enhance the transparency and understanding of the RoC processes, ACC requests that NIEHS/NTP provide a written response to public comments it receives on both the RoC process and specific monographs. If you or NIEHS/NTP staff have questions related to these comments, please contact us by phone at 202-249-7000 or directly by e-mail at Jon_Busch@americanchemistry.com or Rick_Becker@americanchemistry.com.

Sincerely,

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[19] NTP Technical Report on the Toxicology and Carcinogenesis Studies of Cumene (CAS NO. 98-82-8) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). February 2009. http://ntp.niehs.nih.gov/files/542_final_web.pdf