



October 18, 2013

Dr. Ruth Lunn
Director, ORoC, DNTP, NIEHS
P.O. Box 12233, MD K2-14
Research Triangle Park, NC 27709
Via: <http://ntp.niehs.nih.gov/go/rocnom>

RE: Nominations to the Report on Carcinogens; Request for Information; Federal Register, Vol. 78, No. 183; Friday, September 20, 2013

Dear Dr. Lunn:

Thank you for the opportunity to comment on the nomination of 2-Butoxyethanol (EGBE) for consideration to be included in a future National Toxicology Program (NTP) Report on Carcinogens (RoC). The Glycol Ethers Panel (Panel)¹ of the American Chemistry Council (ACC)² believes that a review of carcinogenicity for EGBE is not necessary at this time because numerous regulatory bodies including the US Environmental Protection Agency (EPA), the International Agency for Research on Cancer (IARC) and the European Union (EU) have already reviewed EGBE. The EPA has classified EGBE as "Not likely to be carcinogenic to humans" as cited in the IRIS database.³ IARC found inadequate human evidence and limited animal evidence for the carcinogenicity of EGBE and concluded that EGBE is "not classifiable as to its carcinogenicity to humans."⁴ A subsequent European Union Risk Assessment Report proposed "No classification" for carcinogenicity.⁵ Considering the EPA, IARC, and EU assessments of EGBE, it is unnecessary to include EGBE in the NTP RoC at this time.

¹ Glycol Ethers Panel members are Eastman Chemical Company, LyondellBasell Industries and The Dow Chemical Company.

² 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.

³ EPA IRIS database link: http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showQuickView&substance_nمبر=0500

⁴ IARC. 2006. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans; Volume 88: Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxy-2-propanol. International Agency for Research on Cancer; Lyon, France. December 2006. Summary: <http://monographs.iarc.fr/ENG/Monographs/vol88/volume88.pdf>.

⁵ European Union Risk Assessment Report, 2-Butoxyethanol, - Volume 68 Part I Environment (Publication: EUR 22501 EN) – pages 2-97 - Part II Human Health (Final approved version awaiting for publication) – pages 98-419.



Information Requested by NTP:

In response to NTP's request for exposure and use data on current production, use patterns, and human exposure, the Panel refers NTP to the 2012 Chemical Data Reporting (CDR) information on the production and use of chemicals manufactured or imported into the United States, which is available online in the EPA Chemical Data Access Tool (CDAT).⁶ Regarding the NTP request for information about published, ongoing, or planned studies related to evaluating carcinogenicity, we have attached a list of studies sponsored by the Panel (Attachment 1). The Panel is currently preparing an EGBE exposure analysis and risk characterization report and this will be available for NTP to review as soon as it becomes publically available. The Panel has also conducted a literature search for recent EGBE studies and attached the references and abstracts (Attachment 2).

NTP has also requested information on scientific issues important for assessing carcinogenicity of the substance. The EPA reviewed the risk and hazards associated with EGBE which resulted in delisting the substance from Clean Air Act hazardous air pollutant (HAP) reporting requirements. As part of the review, EPA's panel found that "it is reasonable to expect that a lack of hemolytic effects in humans would preclude the formation of liver tumors in humans and that a lack of hyperplastic effects in the region of the gastroesophageal junction in humans would preclude the formation of gastrointestinal tumors in humans."⁷ Furthermore, the EU risk assessment states "In conclusion, given the species and sex specificity of the neoplastic responses and the current evidence supporting the hypothesis that the more likely mechanism of action is based on haematotoxicity, then EGBE is unlikely to be a human carcinogen."⁸ These factors should preclude EGBE from the RoC evaluation.

NTP has also requested names of scientists with expertise or knowledge about the substance. The Panel offers the following scientists as potential contacts for further information on EGBE:

- James Klaunig, Ph.D. at Indiana State University
- Richard Corley, Ph.D. at Battelle Northwest National Laboratories
- Mark Udden, M.D. at Baylor School of Medicine
- Rodney Boatman Ph.D. of Boatman Toxicology Consulting LLC

⁶ EPA CDAT Link http://java.epa.gov/oppt_chemical_search/

⁷ EPA 2005. An Evaluation of the Human Carcinogenic Potential of Ethylene Glycol Butyl Ether. U.S. Environmental Protection Agency, EPA 600/R-04/123, February 2005. Available at: http://hero.epa.gov/index.cfm?action=reference.details&reference_id=594432

⁸ *Id.* 5



- Tipton Tyler Ph.D.
- Jeff Gift, Ph.D. of US EPA

In addition to the opinions and information provided on EGBE, the ACC urges NTP not to develop any future RoCs until after the National Academy of Sciences (NAS) has issued its recommendations, at the conclusion of the ongoing NAS review of formaldehyde and styrene, and the NAS recommendations are fully considered and incorporated into the RoC evaluation methods and review processes.

The Panel appreciates the opportunity to provide this information. Please contact Jon Busch at Jon_Busch@americanchemistry.com or (202) 249-6725 for any additional assistance.

[Redacted]

Seth Barna
Director, Chemical Products and Technology
American Chemistry Council

Attachments:

- 1: List of Panel studies
- 2: Literature search results



Attachment 1: List of Panel studies

2006. Investigations on the Characteristics of EGBE and DGBE induced hemolysis of rat, human, & sensitive sub-population red blood cells
2005. Mechanisms of 2-Butoxyethanol Carcinogenesis: In Vitro Studies
2004. In Vivo Metabolism and Kinetics of Ethylene Glycol Monobutyle Ether and its Metabolites 2-Butoxyacetaldehyde (BAL) and 2-butoxyacetic Acid (BAA) as Measured in Blood and in Liver and
2002. In Vivo Kinetic Studies with 2-Butoxyethanol Part 1: Target Tissue Dosimetry
1999. Potential Mechanisms of Rodent Liver Toxicity by 2-Butoxyethanol: Oxidative Stress Studies
1999. Short-Term Studies to Evaluate the Dosimetry and Modes of Action of 2-Butoxyethanol in B6C 3F1 Mice
1999. Species, Gender, and Age Related Differences in the Pharmacokinetics of 2-Butoxyacetic Acid. I. In Vitro Metabolism of 2-butoxyethanol
1999. Species, Gender and Age Related Differences in the Pharmacokinetics of 2-Butoxyethanol and 2-Butoxyacetic Acid. II. In Vitro Renal Active Transport of 2-Butoxyacetic Acid
1998. Preliminary Evaluation of 2 year Mouse and Rat Data for Ethylene Glycol Monobutyl Ether (NTP-1998) to support a Benchmark Concentration
1998. Memorialization of the ethylene glycol monobutyl ether (EGBE) petition data
1997. Assessment of Background Ambient Concentrations and Area Source Impacts for a Petition to Delist Ethylene Glycol Monobutyl Ether from Section 112(b) of the Clean Air Act
1996. Mutagenicity Test with Ethylene Glycol Monobutyl Ether (EGBE) in the Salmonella-Escherichia Coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmation Assay
1996. Ethylene Glycol Ethers: An Environmental Risk Assessment
1995. Evaluation of EGBE Toxicity Data and Reference Concentration (RfC)
1994. Analysis of 2-Butoxyethanol and butoxyacetic Acid in Rat and Human Blood by Gas Chromatography/Mass Spectrometry
1994. Ethylene Glycol Monobutyl Ether Acute Oral Toxicity Study in the Guinea Pig Forestomach Homogenates from Mice
1993. Ethylene Glycol Monobutyl Ether: Development of a Physiologically-Based Pharmacokinetic Model for Human Health Risk Assessment
1992. Critique of "Ethylene Glycol Monobutyl Ether Alters the Flow properties of Red Blood Cells in the Rat



1990. Studies on the Hematologic Toxicity of Ethylene Glycol Monobutyle Ether (EGBE)
1985. Assessment of Hematologic Toxicity of Ethylene glycol Monobutyl Ether (EGBE)
1985. Assessment of Hematologic Toxicity of Ethylene Glycol Monobutyl Ether (EGBE)
1984. 2-Methoxyethanol, 2-(2-Methoxyethoxy) Ethanol, 2-(2-Ethoxyethoxy), Ethnanol, 2-(2-butoxyethanol) Ethanol: Absorption Through Human Skin In Vitro
1985. Assessment of Hematologic Toxicity of Ethylene Glycol Monobutyl Ether (EGBE)
1983. 90 Day Subchronic Dermal Toxicity Study in Rabbits with Ethylene Glycol Monobutyl Ether

