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OFFICE OF THE
SCIENCE ADVISOR

MEMORANDUM

SUBJECT: Implementation of the Cancer Guidelines and Accompanying Supplemental Guidance - Science Policy Council Cancer Guidelines Implementation Workgroup Communication II: Performing Risk Assessments that include Carcinogens Described in the *Supplemental Guidance* as having a Mutagenic Mode of Action

FROM: William H. Farland, Ph.D.
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TO: Science Policy Council
Science Policy Council Steering Committee

The Science Policy Council (SPC) Cancer Guidelines Implementation Workgroup (Workgroup) provides information to facilitate the development of new carcinogenicity risk assessments and to promote consistency with Agency policy, guidance, and guidelines.

The information in the attached communication is intended for Agency risk assessors who are involved in conducting or reviewing risk assessments for carcinogens. The scope of Agency assessments varies widely, from screening level exposure and risk assessments involving hundreds of chemicals, to comprehensive toxicological assessments of single chemicals, such as those in the Agency's Integrated Risk Information System (IRIS). The activities of Agency risk assessors are equally diverse, and so risk assessors will need to consider their specific roles and responsibilities when deciding how best to use the information provided here. Agency risk assessors are strongly urged to become familiar with the sections of the 2005 Guidelines for Carcinogen Risk Assessment *(Cancer Guidelines)* and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens *(Supplemental Guidance)* that are relevant to their particular activities, and to consult these documents for a more complete description of the topics discussed in this communication.

The purpose of the attached communication is to address how to apply the *Supplemental Guidance* to carcinogens that are described in the *Supplemental Guidance* as having a mutagenic mode of action (MOA). This communication focuses on this topic because the 2005 *Cancer Guidelines* emphasize the importance of MOA in assessing

cancer risk, and the MOA determination is critical to the application of the new *Supplemental Guidance*. Additionally, while much of the *Cancer Guidelines* focus on hazard characterization and dose-response assessment, the *Supplemental Guidance* includes guidance for risk assessors who are using slope factors and exposure data to estimate cancer risk for early-life exposures in risk characterization.

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Science Policy Council Cancer Guidelines Implementation Workgroup

Communication II. Performing risk assessments that include carcinogens described in the *Supplemental Guidance* as having a mutagenic mode of action

Section 1. Introduction

The *Supplemental Guidance* (see Tables 4, 6, and 7) describes the following 12 chemicals as having a mutagenic mode of action (MOA) for carcinogenicity[1]:

Chemical	CASRN
benzidine	92-87-5
benzo[a]pyrene (BaP)	50-32-8
dibenz[a,h]anthracene (DBA)	53-70-3
diethylnitrosamine (DEN)	55-18-5
{*aka* diethylnitrosamine (DENA), n-nitrosodiethylamine (NDEA), n-ethyl-n-nitrosoethanamine}	
dimethylbenz[a]anthracene (DMBA)	57-97-6
dimethylnitrosamine (DMN)	62-75-9
{*aka* dimethylnitrosoamine (DMNA), nitrosodimethylamine (NDMA), n-methyl-n-nitrosomethanamine}	
ethylnitrosourea (ENU)	759-73-9
{*aka* n-nitroso-ethylurea}	
3-methylcholanthrene (3-MC)	56-49-5
methylnitrosourea (NMU or MNU)	684-93-5
{*aka* n-nitroso-n-methylurea (NMU)}	
safrole	94-59-7
urethane	51-79-6
{*aka* ethyl carbamate}	
vinyl chloride	75-01-4

The Science Policy Council (SPC) Cancer Guidelines Implementation Workgroup (Workgroup) examined these 12 chemicals to determine if the analyses in the *Supplemental Guidance* could provide information on or insight into a chemical-specific evaluation of cancer potency for early-life exposure. The available data cited in the *Supplemental Guidance* and Barton *et al.* (2005)[1] provide answers to some of the questions posed in a MOA analysis, although they do not necessarily represent formal MOA analyses.

Analyses of toxicological data on early-life, adult, or lifetime exposures were the basis for the calculation of generic age-dependent adjustment factors (ADAFs) recommended

[1] Barton *et al.*, 2005. "Assessing Susceptibility from Early-Life Exposure to Carcinogens." Environmental Health Perspectives 113(9): 1125-1133, available at www.epa.gov/cancerguidelines

in the *Supplemental Guidance*. The *Supplemental Guidance* calculates potency ratios from early-life to adult or to lifetime exposures. These potency ratios were used for the analyses in the *Supplemental Guidance* to derive the generic ADAFs, but they were not designed to be applied to the chemical-specific cancer slope factors previously calculated for the chemicals named above. Although the potency ratios in the *Supplemental Guidance* cannot be directly applied to the existing cancer slope factors, they may inform development of chemical-specific analyses. Thus, pending any new assessments of these chemicals, the following recommendations are provided.

Section 2. Recommendations

Until a reanalysis of the primary data, including the data on early-life exposure, is undertaken for the chemicals listed in Section 1, the Workgroup recommends that, with the exception of vinyl chloride, ADAFs be used for the chemicals with existing IRIS slope factors (benzidine, BaP, DEN, and DMN). No recommendation is made for chemicals for which there are no existing IRIS dose-response assessments. Rather, the available data on early-life susceptibility will be considered when an Agency assessment is undertaken. For vinyl chloride, EPA published a chemical-specific analysis from the primary data. This analysis, available on IRIS, should be used when assessing vinyl chloride.

The Workgroup also recognizes that benzo[*a*]pyrene (BaP) often is used as an index chemical when assessing other carcinogenic PAHs. Such a use is described in the "Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons" (U.S. EPA 1993. EPA/600/R-93/089). When assessing early-life exposure for PAHs using such an approach, the ADAF(s) should be applied to the BaP slope factor before using relative potency factors to estimate risk from exposure to other PAHs.