Dragon, Karen E. (CDC/NIOSH/EID)

From: Jake Vandevort [jvandevort@lawbc.com]
Sent: Thursday, September 22, 2011 5:23 PM
To: NIOSH Docket Office (CDC)
Subject: Docket Number NIOSH-240 -- Titanium Dioxide Stewardship Council
Attachments: 00083148.PDF

Dear Sir or Madam:

Appended for your consideration are comments submitted on behalf of the Titanium Dioxide Stewardship Council (TDSC). TDSC appreciates this opportunity to submit comments, and commends NIOSH for requesting views on its Recommended Exposure Limit Policy (76 Fed. Reg. 52664-52665 (Aug. 23, 2011)). If you have any questions, please do not hesitate to contact me.

Regards,

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Titanium Dioxide Stewardship Council

September 22, 2011

Via E-Mail

NIOSH Docket Office
Robert A. Taft Laboratories, MS-C34
4676 Columbia Parkway
Cincinnati, OH 45226

Re: Comments of the Titanium Dioxide Stewardship Council on "Request for Information: Announcement of Carcinogen and Recommended Exposure Limit Policy Assessment"; Docket Number NIOSH-240

Dear Sir or Madam:

The Titanium Dioxide Stewardship Council (TDSC)[1] submits these comments in response to a request for information on five key issues related to the current National Institute for Occupational Safety and Health (NIOSH) Cancer Classification and Recommended Exposure Limit (REL) policies (76 Fed. Reg. 52664-52665 (Aug. 23, 2011)). The Council appreciates this opportunity to comment, and commends NIOSH for requesting views on its REL policy.

Background

The NIOSH REL policy the Institute currently follows is that stated in 1995. Under this policy, a single category of carcinogen -- "potential occupational carcinogen" -- is applied to all recognized animal and/or human carcinogens. Such a single carcinogen classification fails to address a number of important, but related issues such as potency, species specific mode(s) of carcinogenic activity, and the adequacy of available scientific information. The following comments address these and other issues related to the five key issues that NIOSH proposed for comment.

[1] The Titanium Dioxide Stewardship Council represents the interests of U.S. producers of titanium dioxide, and was formed to promote the safe use of titanium dioxide and titanium tetrachloride through research, product stewardship, advocacy, and outreach efforts within the framework of responsible chemical management.

(1) Should there explicitly be a carcinogen policy as opposed to a broader policy on toxicant identification and classification (*e.g.*, carcinogens, reproductive hazards, neurotoxic agents)?

The Cancer Policy the Occupational Safety and Health Administration (OSHA) is to follow was originally described under the Occupational Safety and Health Act (*see* 29 C.F.R. §§ 1990.111 and 1990.112). In particular, this regulation identifies two categories of potential occupational carcinogens: Category I carcinogens are those meeting the definition based on studies in humans and/or a study in a single mammalian species in a long-term bioassay for which there is concordance of the findings with other scientifically evaluated evidence of a potential carcinogenic hazard; and Category II carcinogens are those which, after scientific evaluation, the evidence is found to be only "suggestive" or for which data from a single mammalian species exists, but without evidence of concordance.

NIOSH originally adapted a more stringent and restrictive carcinogen policy recognizing only a single category of "potential occupational carcinogen." Prior to 1995 and under this policy, NIOSH did not recommend exposure limits for potential occupational carcinogens, but instead recommended "lowest feasible" or "no detectable" exposure levels. This policy was replaced in 1995 with what is currently in force, which allows NIOSH to formulate REL values that may include both a consideration of a no-effect level, but also exposure levels at which there may be residual risk.[2].

NIOSH should continue to maintain a separate and explicit carcinogen policy that recognizes more specifically the OSHA Category II classification (or other classification system as discussed below) and that allows for less restrictive risk characterizations for certain classifications of potential occupational carcinogens. Such a revised policy would be in greater harmony with other such internationally recognized rating systems and represent a more exacting approach to cancer classification of chemicals.

(2) What evidence should form the basis for determining that substances are carcinogens? How should these criteria correspond to nomenclature and categorizations (*e.g.*, known, reasonably anticipated, etc.)?

Most authoritative bodies and agencies charged with assigning carcinogen ratings use generally similar graduated scales that recognize a spectrum of carcinogen hazard potential and possible human relevance. Illustrative of these schemes are the most recent guidelines

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2 Rosenstock, Linda, NIOSH Recommended Exposure Limit Policy (1995), available at http://www.cdc.gov/niosh/topics/cancer/pdfs/1995_NIOSHRELpolicy.pdf.

published by the U.S. Environmental Protection Agency (EPA) in 2005 (EPA/630/P-03/0018). Under EPA's system, a number of carcinogen classifications are recognized:

- *Carcinogenic to humans* -- based primarily on strong and convincing evidence in humans with supporting information from animal studies or suggestive causal data for humans with convincing animal data;

- *Likely to be carcinogenic* -- based on a spectrum of adequate data ranging from human data showing an association of exposure with increased tumor incidence to less convincing or absent human data, but with convincing data from experimental animals;

- *Suggestive evidence of carcinogenicity, but not sufficient to assess human carcinogenic potential* -- a category assigned in cases for which there is suggestive human or animal data, but judged to be less adequate than that required for a higher hazard classification;

- *Data are inadequate for assessment of human carcinogenic potential* -- including the situation in which information suggestive of carcinogenicity is generally inadequate, lacking, or conflicting; and

- *Not likely to be carcinogenic in humans* -- a category assigned in cases for which convincing data indicate a lack of carcinogenic potential or for which carcinogenic effects observed in animals are judged not relevant to humans.

Regarding the "Carcinogenic to humans" classification, it is highly suggested that for classification criteria, well-conducted, peer-reviewed epidemiological evidence should clearly outweigh animal toxicology data, particularly if the animal studies were conducted at high doses or exposure concentrations. This is an important criterion for NIOSH to develop carcinogenic ratings. Unlike the International Agency for Research on Cancer (IARC) system, which is a hazard-based system, it would be preferable for NIOSH to develop a risk-based system, particularly when considering the criteria for assessing a classification for "Carcinogenic to humans." An example of this discrepancy in the IARC system is the particle overload issue, wherein the results of two-year rat inhalation toxicity studies at excessive (particle overload) concentrations appear to have equal weight to peer-reviewed, well-conducted epidemiological studies of workers exposed to the highest concentrations at the workplace.

A common feature of current carcinogen classification systems is the use of a weight-of-evidence approach to the assessment of available data, including both human and

animal data, as well as information on the mode(s) of carcinogenic action. Such weight-of-evidence approaches are common to the methods used by IARC[3] and EPA (EPA/630/P-03/001B) and have been adapted under the recent European Union (EU) regulation on classification, labeling, and packaging (CLP) of substances and mixtures (Regulation (EC) 1272/2008).

As discussed above, the most appropriate basis for the determination of the carcinogenic potential of a chemical to humans must come from a complete assessment of all available and relevant animal and human data, as well as mechanistic data relevant to the determination of a mode(s) of carcinogenic action, if possible. As is often the case, the lack of definitive data from human studies showing an association of increased tumors with exposure requires the appropriate weighting of both animal and human data for the final assessment. As part of the weighting of relevant data, the relevance, adequacy, and reliability of the data must be evaluated. A system such as that proposed by *Klimisch et al.*[4] has gained widespread acceptance and provides a method for evaluating the quality and adequacy of data used for risk assessment.

(3) Should 1 in 1,000 working lifetime risk (for persons occupationally exposed) be the target level or an REL for carcinogens or should lower targets be considered?

NIOSH should consider the methodological limits and drawbacks of the excess cancer risk approach in deriving limit values. The following points can make such excess risk calculations via attributable fractions (AF) uninterpretable:

- The use of Levin's 1953 formula in case of adjusted relative risks;
- The use of broad definitions (*e.g.*, binary exposure) in calculations of AFs;
- The non-additivity of AFs across exposures and co-variables; and

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3 IARC, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans: Preamble, (World Health Organization, International Agency for Research on Cancer, Lyon, France)(Jan. 2006).

4 Klimisch, H.J., Andreae, Mand, & Tillman, U., *A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data*, Reg. Toxicol Pharmacol, 25: 1-5 (1997).

- Deaths may occur advanced or may be postponed, but there are neither extra nor avoided deaths. For the terminology and problems involved *see Rothman et al.*[5]

All relevant data concerning the potency, species specificity, mode(s) of carcinogenic activity, and human relevance should be taken into account to determine what acceptable risk level should be used. An acceptable risk level for a working lifetime should not include a prescribed minimum target value. Thus, for an active and known animal and human carcinogen, an acceptable risk level above 1 in 1,000 may be appropriate. For less active or potent carcinogens, however, with no evidence of human activity or for which less conclusive human evidence exits, a 1 in 1,000 risk may be appropriate. In certain cases, it may not be appropriate to assign a risk value.

The recognition of a spectrum of carcinogenic potential implies that risk assessment procedures applicable to highly active and potent known human carcinogens may not be appropriate for the assessment of a less potent carcinogen, with tumor formation secondary to an effect such as tissue irritation with persistent compensatory hyperplasia. Specifically, a weight-of-evidence assessment may also suggest a mode(s) of carcinogenic action more appropriately modeled as a threshold effect, for which exposures below a certain level would be expected to have little or no residual risk of carcinogenicity. In this latter case, a conservative linear or "low-dose-linear" model, as often applied in non-threshold carcinogen assessments, would not be appropriate.

It should also be recognized that the determination of a true threshold versus a non-threshold effect may be problematic, in which case a more qualitative assessment of the available data may support a threshold assessment versus the more conservative non-threshold assessment. In particular, such a more qualitative threshold assessment may be appropriate for chemicals rated as carcinogens based on only limited or suggestive data. Assignment of risk or risk categorization would be handled on a case-by-case basis.

(4) In establishing NIOSH RELs, how should the phrase "to the extent feasible" (defined in the 1995 NIOSH REL Policy) be interpreted and applied?

The term "to the extent feasible" refers to the REL setting process of NIOSH and recognizes that in certain cases, exposure levels may be proposed at which residual risk may exist, particularly regarding the risk of cancer. Included in this policy is the statement that REL values "will be based on risk evaluations using human and animal health effects data, and on an

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[5] Rothman K.J., Greenland, S., & Lash T.L., Modern Epidemiology, (Philadelphia: Lippincott Williams & Wilkins)(3d ed. 2008).

assessment of what levels can be feasibly achieved by engineering controls and measured by analytical techniques." Implicit in this definition is the availability of appropriate analytical techniques and readily available analytical equipment for the subject chemical.

The recommended 1995 NIOSH REL Policy indicates that NIOSH intended to recommend the "lowest feasible" or "no detectable" exposure to carcinogenic hazards. Moreover, the policy stated that "To the extent feasible, NIOSH will project not only a no-effect exposure, but also exposure levels at which there may be residual risks. This policy applies to all workplace hazards, including carcinogens…."

It is, however, unclear what criteria NIOSH would utilize to assess the REL Policy. The methodology for implementing this policy should have transparency, and the process should be clear to the public observer. For instance, does "to the extent feasible" refer to the assessment of relevant human data, relevant doses, and routes of administration when evaluating animal toxicity data? The question as defined above clearly is open-ended and requires greater defined processes to evaluate the methodology for developing RELs.

(5) In the absence of data, what uncertainties or assumptions are appropriate for use in the development of RELs? What is the utility of a standard "action level" (*i.e.*, an exposure limit set below the REL typically used to trigger risk management actions) and how should it be set? How should NIOSH address worker exposure to complex mixtures?

There are a number of systems that attempt to address situations where there is simply an absence of data. For example, the precautionary principle is used in Europe and presumes adverse chemical effects. This often imposes impractical use limitations and huge burdens on society. Rather than adopting or developing another such system, in the absence of data, do not develop RELs. If a chemical warrants carcinogenicity evaluation, develop a schedule and initiate the appropriate testing.

Thank you for your time and consideration of these comments. If you have any questions, please contact Jake Vandevort at 410-255-2773 or at jvandevort@bc-cm.com.

Respectfully Submitted

Brian R. Coleman

Brian R. Coleman
Chairman
Titanium Dioxide Stewardship Council