Miller, Diane M. (CDC/NIOSH/EID)

From: Laura Perovich <perovich@silentspring.org>
Sent: Friday, December 30, 2011 1:15 PM
To: NIOSH Docket Office (CDC)
Cc: Julia Brody; Ruthann Rudel
Subject: Docket # NIOSH-240
Attachments: response to NIOSH request for comments on carcinogens dec 2011v1.doc

Please accept attached comments on NIOSH carcinogen assessment.

Let me know if you need additional information.

Thanks,
Ruthann

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Re: Docket # NIOSH-240, Request for Information: Announcement of Carcinogen and Recommended Exposure Limit (REL) Policy Assessment

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Dear Dr. John Howard,

Thank you for the opportunity to offer input as NIOSH revises its carcinogen and associated RELs policies to reflect new understandings of cancer and exposure science. Silent Spring Institute is a scientific research organization dedicated to innovative, multidisciplinary studies of environmental factors and women's health. In response to your RFI, we are highlighting our key research findings related to chemicals that may be associated with breast cancer and other health concerns. Consideration of our findings as NIOSH conducts these assessments has the potential to improve health of women exposed to chemicals in the workplace, and also to improve surveillance and compensation programs for occupationally exposed women. We hope these are useful as you consider modifications in your current approaches.

Our research primarily addresses the second of NIOSH's five specific questions, which asks what evidence should form the basis for determining that substances are carcinogens. However some of our points address other topics in your questions, including #1 (should there explicitly be a carcinogen policy), #2 (is 1 in 1000 an appropriate risk level), and #5 (how to handle uncertainties and missing information, including mixtures).

1. Occupational exposures are typically much higher than in the general population, so exposures are more likely to lead to disease and exposure disease relationships can be easier to discern. At the same time, many chemicals have major data gaps about health effects because of inadequate chemicals testing. In light of these two facts, vigilant monitoring of workers for health effects or biomarkers of early effects is a responsible course of action. New technologies such as metabolomics and in vitro chemical activity screening can suggest novel effect markers and lead to better information on chemical health effects. Without this focused attention, most exposure disease relationships will remain undiscovered. We recommend a substantial increase in NIOSH exposure monitoring, in addition to new research programs that will identify early effect markers in occupationally exposed populations. These studies can help identify and prevent chemical-related illness in exposed workers and are a form of surveillance for the general population.

2. Human carcinogens have largely been identified in occupational studies, which provide little information concerning women's cancers because most of the studied populations have been male. Furthermore, occupational surveillance studies – for example surveys of standardized mortality ratios (SMRs) by job category – have not been useful for identifying occupations associated with higher breast cancer because demographic factors that differ among women working in various occupations influence breast cancer rates and these influences mask workplace-related risks (Brody 2007). Thus, more aggressive approaches to identifying potential chemical risks of breast cancer in occupationally exposed populations are needed. These could include the approaches described in #1, above.

3. In light of the lack of occupational studies of chemicals and breast cancer, data from animal cancer bioassays provides important and relevant information for risk evaluation. We have compiled a list of 216 chemicals that cause mammary gland tumors in rodents because these are priorities for study in humans (Rudel 2007). This paper also reviews strengths and weaknesses in the interpretation of these studies, and discusses use of these data in risk assessment. Two key findings of potential interest to NIOSH are highlighted below. Note also that a publicly-available database of these rodent mammary carcinogens on our web site also reports estimates of number of occupationally-exposed women in an attempt to prioritize these cohorts for study and risk reduction (http://sciencereview.silentspring.org/mamm_about.cfm).

    a. We found that information about chemicals' ability to induce mammary gland tumors and the potential impact on breast cancer was not carried into risk assessment and regulatory documents or into resources and reference materials used by worker health and safety officers or occupational medicine physicians. For example, risk assessment and regulatory documents have not been developed for many of the 216 rodent mammary gland carcinogens, and those that exist typically focus on other target organs, often not discussing the mammary gland tumors or potential for breast cancer. NIOSH has developed standardized reference information on 651 potential workplace chemical hazards and just 41 of the 216 mammary carcinogens appear in this guidebook – the "NIOSH Pocket Guide to Chemical Hazards." NIOSH identifies 31 of these as potential occupational carcinogens (based on animal studies) but mammary gland tumors are identified as a target site in animals *for only 9 of these*. Since NIOSH is often the primary source of information regarding potential exposure-related health effects for workers, their health and safety officers, and their physicians, it is a major oversight that these materials don't provide complete information, including identification of mammary gland as a potential target organ.

    b. Similarly, OSHA requires medical surveillance focused on chemical-specific anticipated adverse health effects for workers exposed to 11 of the chemicals on our list of 216 mammary gland carcinogens, but none of these requirements include breast cancer screening (NIOSH 1990). In fact in its landmark 1997 regulation to lower allowable workplace exposure limits for the mammary gland

carcinogen methylene chloride, OSHA proposed that medical surveillance for exposed workers would include breast cancer screening; however, this requirement was dropped in response to objections from Eli Lilly and others. Ethylene oxide is another mammary gland carcinogen with a large number of women potentially exposed at work because it is used to sterilize medical equipment, foods, and spices. Medical surveillance is required for highly exposed workers, but this regulation does not mention breast cancer or mammary gland tumors and the required surveillance does not include breast cancer screening. The recent Institute of Medicine report on environmental factors and breast cancer highlights ethylene oxide as having probable connection to breast cancer. Thus, much of the existing toxicological data relevant to occupational exposures and breast cancer is not fully utilized in chemical risk assessment or regulation.

c. Without complete information regarding the types of health effects that might be associated with chemical exposure in the workplace, for example, physicians and workers have limited ability to make connections between exposures and breast cancer that might otherwise be noticed.

4. While traditional cancer bioassays have identified many common pollutants that increase mammary gland tumors, including common air pollutants, drinking water disinfection byproducts, and chlorinated solvents (Rudel et al. 2007), new research about the role of endocrine disrupting chemicals (EDCs) in breast cancer and other hormonal cancers indicates that traditional cancer bioassays that neglect developmental effects may be missing many more. MG development can be affected after early exposure to EDCs in rodents, and this altered development has been shown to increase susceptibility to subsequent carcinogen exposure. This topic is extensively reviewed in Rudel et al., (2011), which examines whether MG developmental alterations are plausibly related to increased tumor susceptibility, whether by epigenetic imprinting of tissue, alteration of stem cell populations, or increased number or ontological duration of TEBs or other structures known to be more vulnerable to carcinogens. Some experts suggest that such agents should themselves be considered carcinogens. Indeed, the International Agency for Research on Cancer deems an agent carcinogenic if it is "capable of increasing the incidence of malignant neoplasms, reducing their latency, or increasing their severity or multiplicity" (IARC 2006). EPA defines an effect as adverse if it "...reduces the organism's ability to respond to an additional environmental challenge" (US EPA 2010). Applying these definitions, compounds that cause cancer, alone or in combination with other factors at a variety of points in a biological chain of events leading to tumor formation, may reasonably be considered carcinogens; this includes chemicals that increase susceptibility to cancer. Even if such agents are not designated as "carcinogens," their profound impacts should encourage the risk assessment community to consider the increase in cancer susceptibility an adverse effect, and therefore to characterize doses required to elicit the effect. The question of whether a chemical that alters susceptibility to a carcinogen is considered a carcinogen is also reported in Inside EPA's Risk Policy Report (June 28, 2011, page 1).

5. The newest source of information on potential health effects is coming from in vitro screening programs such as US EPA's ToxCast. Even though these assays are still being validated in terms of their ability to predict results of animal or human studies, they provide important data on potential health effects for many chemicals where we have little data. In conjunction with structural activity analysis, these data should be used to facilitate proactive selection of safest materials without waiting for definitive "proof" that a chemical poses unacceptable risk and should be replaced. It is time to move away from acceptable/unacceptable risk-based decision making and towards an approach that utilizes in vitro and in vivo toxicity data as part of alternatives assessment with a goal of selecting safer materials and reducing worker illness.

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Sincerely,

Julia G Brody

Julia Brody, Executive Director

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