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Dr. David Michaels
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U.S. Department of Labor
200 Constitution Avenue NW
Washington, DC 20210

RE: Occupational Safety and Health Administration (OSHA) Draft Weight of Evidence Guidance Document (OSHA-2016-0004)

Dear Dr. Michaels:

Thank you for the opportunity to provide comments to OSHA on its **Draft Weight of Evidence Guidance Document (OSHA-2016-0004).** We wholeheartedly support the stated intention in the OSHA Draft Weight of Evidence Guidance document, ***"to ensure that the hazards of all chemicals produced or imported are evaluated and that information concerning their potential hazards is transmitted to employers and workers."*** However, as detailed below, we believe that, in practice, this guidance document likely would reduce the information given to employers, workers, and health professionals who counsel patients about their exposure to toxic chemicals.

Therefore, we strongly recommend that the OSHA guidance document be withdrawn and that OSHA ensure timely and effective notification of chemical hazards through a compliance directive in which:

1. OSHA should consider an existing classification by an authoritative body as sufficient and required grounds for classification;
2. In the absence of an existing classification by an authoritative body, OSHA should explicitly state that it considers one scientifically-valid human or non-human study to be grounds for classification and disclosure of the chemical on the Safety Data Sheet (SDS);
3. OSHA should set a high burden of proof for classifiers wanting to discount a single positive well-conducted human or non-human study. Specifically, if a classifier determines a single positive well-conducted study does not warrant classification, the burden of proof should be on the classifier to demonstrate to OSHA why workers, employers, and health professionals should not be alerted to that potential "early warning signal" of the single well-conducted positive study. Moreover, OSHA should **not** consider uncertainties about a chemical's mechanism of action, uncertainties about the relevance of non-human model systems to human health, or whether or not a study was conducted under Good Laboratory Practices (GLP), as compelling evidence to discount a single well-conducted positive study; and
4. OSHA should explicitly specify use of robust and transparent systematic review methods for the purpose of evidence integration when such methods are needed, i.e., the use of

the National Toxicology Program (NTP) Office of Health Assessment and Translation (OHAT) method or methods that mirror the OHAT methods components.

By way of background, beginning in 2009 the University of California, San Francisco Program on Reproductive Health and the Environment has organized the collaboration of scientists, clinicians, and other stakeholders to develop and demonstrate proof of concept of the *Navigation Guide*, a novel systematic review method specifically designed to transparently establish the strength of evidence of the toxicity of environmental chemicals. Over the past 7 years we have conducted substantive outreach and education about the methodology, including 12 publications.[1-12]. In 2014 the NTP published a method for systematic reviews [13] that mirrors the *Navigation Guide*, and the National Academy of Sciences has released two reports that cited the *Navigation Guide* and the NTP OHAT methods as exemplary of the type of methodologies the US Environmental Protection Agency (USEPA) should use in its chemical hazard assessments [14, 15]. The results of our first case study of applying the *Navigation Guide* have been cited in a regulatory rulemaking proposal by the European Chemicals Agency which would restrict exposure to PFOA [16].

Thus, our comments on the OSHA Guidance document reflects many years of scholarship and deliberations about robust methods to integrate the science about what we know about chemical hazards into timely action to prevent harm from hazards at work, at home, and in the community.

In addition, our research focuses on preventing pre-conception, prenatal, and childhood exposures to environmental chemicals. During these periods, exposure to environmental chemicals can have a profound and lasting impact on health across the individual's life course and may even be passed to subsequent generations, continuing to impact multiple individuals within a family.

Thus, we are deeply invested in ensuring that women and men of reproductive age exposed to toxic chemicals at work have a timely and effective way to be warned of potential reproductive, developmental, and other health hazards [17, 18].

Our rationale for our recommendations is as follows:

- **We wholeheartedly support the stated intention in the OSHA *Draft Weight of Evidence Guidance* document**, **"*to ensure that the hazards of all chemicals produced or imported are evaluated and that information concerning their potential hazards is transmitted to employers and workers.*"**

Communicating information about potential hazards to employers, workers, and the health professionals who counsel patients about their exposures is crucial to preventing harm. Dozens of examples of the adverse health impacts of ignoring early warning signals of potential health hazards have been compiled by the European Environmental Agency [19], and this history should inform and buttress OSHA's approach to the Hazard Communications Standard (HCS).

- **We believe that, in practice, this guidance document likely will reduce the information given to employers, workers, and health professionals who counsel patients about their exposure to toxic chemicals**.

We believe the guidance document opens the door to debates about scientific uncertainty within the hazard communication process --- a proven recipe for undermining timely notification of potential hazards. Such scientific debates belong in the setting of permissible exposure limits and risk assessment, not hazard communication. OSHA's guidance document reflects on this difference between hazard communication and risk assessment goals in the introduction, where OSHA states on page 2, "*Under the HCS, OSHA has*

established a lower threshold for dissemination of hazard information than would be used for a rule that implements specific, risk-based controls for individual substances regulated by the Agency."

Despite this laudable goal, the guidance document belies this difference, presenting a range of approaches to weight of evidence (WoE). Notably, not all are equally valid scientifically, and they include a potentially wide range of thresholds for scientific certainty to classify a chemical hazard.

Generally, OSHA's guidance document appears to permit use of less robust "expert based narrative review" methods with undefined thresholds for "sufficient" evidence to classify a hazard at the same time that it clearly favors "systematic reviews" with pre-defined definitions of the level of evidence needed for classification.

In the clinical sciences, we know that expert-based narrative reviews of the evidence are less effective than systematic and transparent reviews for clinical decision-making. For example, a landmark study about treatment of myocardial infarction published in *JAMA* in 1992 showed that some expert reviews did not mention effective therapies for myocardial infarction, while others recommended therapies proven to be ineffective or even dangerous [20]. This led to the development and uptake of rigorous, transparent, and systematic methodologies to evaluate clearly-formulated questions now embodied in prominent empirically demonstrated methods such as the Cochrane Collaboration, [21] and Grading of Recommendations Assessment, Development and Evaluation (GRADE) [22].

In comparison to the rules of systematic review embodied in Cochrane and GRADE, the OSHA guidelines are a confusing and contradictory collection of possible methods. For example in the discussion on pages 6-7 of methods that can be used to conduct WoE:

- OSHA describes "packets of information" and assigning "weight to each packet of information … in terms of how strongly each supports classification or supports no classification;" this is confusing terminology, "packets of information" is not defined in the document, nor is this term used in systematic review terminology;
- OSHA discusses the "degree of confidence that the outcome is *causally* associated with the substance in question" (*emphasis added*), which is too high of a threshold for evidence in occupational or environmental health which generally precludes experimental human evidence for ethical reasons;
- OSHA directs the classifier to look for a "unified picture of the effects of the material in the body [of evidence] or whether there are discrepancies within the collected assembly of data," opening up the possibility of tallying positive and negative studies, rather than a more scientifically robust risk of bias evaluation of each included study; this language is also vague and will lead to inconsistent evaluation of studies;
- OSHA states "another tool that some evaluators have used in the evaluation of a particular set of experimental data involves criteria developed by Klimisch et al … [S]cores for reliability of the data can be assigned using these criteria and then used to help judge the relative weight to give to various studies on the same substance or its analogs in the overall weight of evidence. However this method must be used judiciously." OSHA also rightly states, "The [Klimisch] assessment is subjective and only oriented to an evaluation of the quality of the study-it does not assess bias or validity of the study. In addition, its criteria have an inherent preference for standardized studies, which is not employed under the HCS WoE approach." Yet OSHA goes on to state "Other methods for judging the acceptability of studies *may be used together with or separate from those in these publications" (emphasis added).* So that Agency appears to permit the use of inadequate methods of WoE, such as scoring and Klimish;

- Steps 4 and 5 on the table on page 7 permit a classifier to decide on the sufficiency of an authoritative body as a basis of classification, but OSHA does not define the level of evidence needed to overrule an authoritative body's decision;
- Further, OSHA states on pages 10 - 11, … "decision-making process must also take into account any other available data … and that conduct of that [positive] study must be first evaluated carefully … and that studies done in accordance with internationally accepted test guidelines, such as those from the OECD and USEPA, are generally acceptable … and that classification can be made based on information from one study, but the approach must be performed while taking into account the validity of that study, the scientific strength of the results from the study, and all other available data on the chemical … in some cases, a single positive study might be chosen as the basis for classification, but other studies do not demonstrate a similar effect. In such instances, the discrepancy must be reasonably resolved before the decision on classification is finalized …" This statement is quite broad and requires more specifics. For instance, there are no criteria provided for what constitutes "reasonably resolving" such discrepancies, yet this is a critical point that needs explicit criteria.

At the same time, we commend OSHA's guidance document for endorsing the use of scientifically robust and empirically demonstrated methods, for example:

- OSHA states on the table on page 7 that the "search strategy and protocol should be documented;"
- OSHA recommends the "Krauth et. al tool for risk of bias;"
- OSHA states on page 9 that "The OHAT Approach for Systematic Review and Evidence Integration is compatible with the GHS guiding scientific principles to hazard evaluation and *can* serve as a model for the WoE discussed in the present guidance" (*emphasis added*).

We strongly agree that the OHAT method is an excellent example of how to conduct a systematic review, but the endorsement of the OHAT method in the OSHA guidance document is inconsistent with other statements in the guidance document compiled above. Depending on which part of the guidance document one follows, one might get a very different decision on whether or not to classify a chemical as a hazard.

By providing this range of inconsistent and potentially contradictory guidance about WoE, the document unfortunately allows far too much discretion on the part of the classifier about which method to use. Thus, it opens the door to prolonged discussions of the strengths and limitations of various methods and critically to what levels of "proof" will be needed to classify a hazard. In practice, these issues could be debated by legions of scientists for decades to come. This lack of specificity and clarity seems inconsistent with the stated goals of the HCS to provide health-protective information in a truly timely way.

A good example of how the goal of timely, health protective classifications could be undermined can be seen in Page 8 (first paragraph) of the document. There it says OSHA could request the evidence for the basis of the classifier's decision and question or challenge it during a compliance inspection. That would place OSHA a position of deciding -- after the fact -- about the rigor of the classifier's review and the classifier's "expert opinion."

We have serious concerns that this mechanism for challenging a classification will be too time consuming and constitute ineffective policy in practice. Instead, we believe that it would be much clearer and efficient to specify in a compliance directive what OSHA will consider to be an appropriate method for a WoE review, and that for the reasons already stated by OSHA, the OHAT or comparable method ***should be*** *the explicit* model for WoE. Our recommendation is based on the experience over the past 40 years in the clinical sciences with systematic reviews and our demonstration through case studies of the *Navigation Guide*

method that the application of systematic review methods in environmental health sciences is feasible and more scientifically robust than expert based narrative reviews [5].

- **We strongly recommend that the OSHA Guidance document be withdrawn and that OSHA ensure timely and effective notification of chemical hazards with a compliance directive in which:**

1. **OSHA should consider an existing classification by an authoritative body as sufficient and required grounds for classification.**

Section 2.2 (Preparing an Evaluation) Paragraph 3 states, **"**… in some cases appropriate reviews have been done previously by independent or government authoritative bodies, and the conclusions of such reviews *can* be used for purposes of the hazard communication under the HCS …" (*emphasis added*). We recommend authoritative body listings *should* be required to used for classification.

Moreover, if there are discrepancies between authoritative bodies, OSHA should require that the most health protective listing is used for the purpose of hazard communication. We believe that specifying that authoritative lists (such as those compiled in the Pharos database, see: https://www.pharosproject.net and by the California Department of Toxic Substances' Green Chemistry Initiative, see https://www.dtsc.ca.gov/SCP/SourceLists.cfm) are grounds for classification in a compliance directive, and are the most effective way for OSHA to accomplish its stated goals for hazard communication. These lists often represent the results of years of debate and deliberation among scientists, the regulated industry, and the public about the strength of the available science.

Not requiring use of these lists means that workers, employers, and health professionals are not appropriately informed that at least some qualified and independent scientists have deemed a chemical to have a potential hazard. In addition, not requiring the use of authoritative lists allows the regulated industry to "overrule" the decisions of authoritative and independent agencies based on their classifier's "expert" interpretation of the science, and obscure this extremely relevant information from those who are directly impacted. Giving classifiers -- and their employers -- the discretion to disregard these authoritative lists based on their "expert judgment" is a recipe for undermining the right-to-know.

Furthermore, the document states:

> *If a classifier reaches a final WoE conclusion that differs from that of the NTP or IARC, OSHA would look in the event of a compliance inspection, for a clear justification for the different classification. (See Section 3.2.3.3). If OSHA disagrees with the classifier's classification after evaluating the classifier's justification, OSHA may issue a citation.*

As above, we strongly disagree with the wording because it appears to allow a classifier the discretion to not disclose the fact that IARC or NTP has issued a hazard statement about a chemical. While OSHA could subsequently challenge such a decision in a compliance inspection, the default position should be letting employers, workers, and health professionals know up front what NTP and IARC (and other authoritative bodies) concluded, even if the regulated community does not agree with those conclusions. That's an effective "early warning system.

Additionally, the explicit use of authoritative lists offers many benefits, including consistent classification, less time and resources conducting weight of evidence classifications, simplified compliance, reduced potential liability for manufacturers and importers required to consider the full range of available scientific literature and other evidence concerning potential hazards, and increased transparency.

In short, enforcement would be simpler, and more transparent and consistent, if the classifications are

based on authoritative lists as opposed to individually determined, criteria---based weight of evidence determinations. In practice, leaving it up to OSHA to serve as referee between the classifier and an authoritative body's decision can foster long delays while potentially harmful workplace exposures mount. This provision of the OSHA guidance opens a pathway for classifiers to obscure relevant information from the impacted community and thus, as above, we strongly recommend that OSHA ensure the use of the findings of independent or government authoritative bodies by specifying that OSHA will cite excursions from such listings in an OSHA compliance directive, or through regulation if needed.

2. OSHA should explicitly state that it considers one scientifically valid study to be grounds for classification and disclosure of the chemical on the Safety Data Sheet (SDS).

OSHA'S compliance document should explicitly state that it considers one scientifically valid human or non-human positive study to be grounds for classification and disclosure of the chemical on the SDS. As written, the guidance document does not clearly ensure classification based on a single study.

- OSHA states in Section 2.1:
  However, as discussed in Section 2.4, a single positive test that is performed according to good scientific principles, and with statistically and biologically significant positive results, may justify classification (emphasis added). (See also A.0.3.5 of the HCS.).
- Section 2.4 and subsection 3.2.2 provide circumstances where a single positive study could be discounted, for example,
  … a decision based on either one positive epidemiological study or one positive laboratory study must also address information that supports or conflicts with the decision on classification… in such instances [when there are other studies which do not demonstrate a similar effect of the single positive study chosen], the discrepancy must be reasonably resolved before the decision on classification is finalized … .

Thus, the OSHA guidance opens the door to dismissing the results of a single positive well-conducted study because of uncertainties in the body of evidence. This is inconsistent with agency's goal of erring on the side of providing a timely warning. Classifying a chemical hazard based on a single positive study is consistent with:

a. The OSHA regulation pertaining to carcinogens;
b. EPA risk assessment guidelines for neurotoxicants, carcinogens, reproductive toxicants, and developmental toxicants; and
c. IARC's classification of carcinogens.

Authoritative organizations have classified chemicals as health hazards based on evidence from a single study, for example, ethylene oxide and diesel exhaust (NIOSH), hydrogen cyanide (USEPA), and toluene (Cal-EPA).

3. OSHA should set a high burden of proof for classifiers wanting to discount a single positive well-conducted study. Specifically, if a classifier determines a single positive well-conducted study does not warrant classification, the burden of proof should be on the classifier to demonstrate to OSHA why workers, employers, and health professionals should not be alerted to that potential "early warning signal" of the single well-conducted positive study. Moreover, OSHA should not consider uncertainties about a chemical's mechanism of action, uncertainties about the relevance of non-human model systems to

human health, or whether or not a study was conducted under Good Laboratory Practices (GLP), as compelling evidence to discount a single well-conducted positive study.

OSHA has clearly articulated its intention to ensure that the HCS serves as an early warning system for employers and workers of potential hazards:

- In Section 2.4 Classification Based on a Single Positive Study Page 11 OSHA states,
  "The purpose of the HCS is to ensure that all employers receive the information they need to design and implement worker protection programs and properly train their workers in the hazards of chemicals that are used in the workplace. Therefore, it is important to avoid a false negative or under classification of a chemical where an employee may believe that a chemical is safe when it is not. In such cases, the worker may have a false sense of security."

- The guidance document also states,
  "Under the HCS, OSHA has established a lower threshold for dissemination of hazard information than would be used for a rule that implements specific risk-based controls for an individual substance regulated by the Agency. The HCS is intended to be conservative in nature to ensure that employers are informed about the potential hazards of the products they use and that workers are alerted to and protected against these potential hazards. In other words, where there is uncertainty, OSHA expects that documents produced to meet the requirements of the HCS will err on the side if providing warnings and categorization into more hazardous categories."

We strongly concur with OSHA's stated intention and believe that to realize this critical goal, an OSHA compliance directive should be very specific about the burden of proof needed to discount a single positive study.

OSHA's Guidance document makes numerous statements related to situations in which a classifier may downgrade a classification given apparent evidence that the mode of action in animals is not relevant to humans. This guidance is inconsistent with erring on the side of warning as chemicals may induce toxicity through several modes of action as well as different modes of action in different species [23]. The National Academy of Sciences has recommended scientists move from a "common mechanisms of action" approach to a "common adverse outcome" focus, because there may be not just one but many pathways to the same adverse health outcome [23].

More generally, in hazard classification one can expect to encounter uncertainties about a chemical's mechanism of action, uncertainties about the relevance of non-human model systems to human health, and uncertainties related to the limitations of study design. In fact, the main direction of error for scientific studies relevant to chemical hazard assessment (i.e., epidemiology, toxicology, statistics) are biased towards generating false negatives [24]. In occupational health studies relatively small errors in classifying worker exposures can bias relative risks substantially towards the null (i.e., false negatives) [25].

While these uncertainties are valid topics of discussion, scientific discovery, and risk assessment, bringing them into the hazard classification process effectively permits classifiers to judge whether or not there is "too much uncertainty" to let employers and workers know there may be a hazard.

Consistent with OSHA's stated goal to "err on the side of providing warnings and categorization into more hazardous categories," the burden of proof about a hazard should not be linked to the degree to which we know a chemical's mechanism of action, whether or not the model system for the study is relevant to human health, or to whether or not a study was conducted under GLP or was an academic study in the peer-reviewed literature.

Under the Bradford Hill Considerations cited in the OSHA document, the strengths of evidence needed to act should be linked to the purpose of the action to be taken [24]. For example, a very low bar of evidence, such as a case report of illness, should be sufficient evidence to communicate a potential hazard if the health harm was extremely serious, i.e., death or severe disability. Similarly, studies done under Good Laboratory Practices (GLP) are not inherently less biased than peer-reviewed academic studies, and as such, GLP studies should not be deemed to be compelling evidence for discounting a single positive study.

In sum, workers and employers should not be deprived of information about a potential chemical hazard because there is uncertainty in the evidence. All science is uncertain, and hazard communication should err on the side of letting employers and workers know the earliest warning signal of potential harm.

4. **OSHA should explicitly specify use of robust and transparent systematic review methods for the purpose of evidence integration when such methods are needed, (i.e., the use of the NTP Office of Health Assessment and Translation (OHAT) method) or methods that mirror the OHAT methods components, including a written protocol, a specified study question, a comprehensive search strategy, explicit inclusion/exclusion criteria, rating the quality and strength of the evidence according to predefined criteria.**

As noted above, Section 2.3 (*Approaches related to weight of evidence used by other authoritative bodies*) describes approaches to weight of evidence. On page 9, it states "the NTP's OHAT Approach for Systematic Review and Evidence Integration is compatible with the GHS guiding scientific principles to hazard evaluation and can serve as a model for the WoE process discussed in the present guidance."

We strongly endorse the use of the OHAT method when a systematic review is warranted. The OHAT method mirrors the *Navigation Guide* systematic review method that we have developed and demonstrated to be an effective tool for conducting systematic reviews in environmental health. We recommend that OSHA ensure the use of the OHAT or similar method such as the *Navigation Guide* in the absence of an authoritative listing in a compliance directive.

In conclusion, we sincerely appreciate that OSHA's Draft Guidance document clearly articulates a very strong commitment to providing employers and workers and the health professionals who counsel them with early warnings of potential hazards. At the same time we find that the OSHA document will not support this goal in practice.

Thus, we strongly recommend that the OSHA guidance document be withdrawn and that OSHA ensure timely and effective notification of chemical hazards through a compliance directive which specifies the use of decisions by authoritative bodies, classification based on a single human or non-human positive study, a high burden of proof for classifiers who discount a single positive study, and the use of only robust methods of systematic review for evidence integration, i.e., the OHAT or comparable method. Thank you in advance for your consideration of our comments.

Sincerely,

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