Comments from the Natural Resources Defense Council (NRDC) on the DRAFT External Peer Review Charge Questions for the IRIS Toxicological Review of Formaldehyde—Inhalation (April 2022)

June 13, 2022
Docket EPA-HQ-ORD-2010-0396

We submit these comments on behalf of the Natural Resources Defense Council (NRDC). NRDC combines the power of more than three million members and online activists with the expertise of some 700 scientists, lawyers, and policy advocates to safeguard the earth—its people, its plants and animals, and the natural systems on which all life depends. NRDC has no direct or indirect financial or fiduciary interest in the manufacture or sale of any pesticide or chemical that is the subject of these comments.

Thank you for the opportunity to provide public comments on EPA's draft IRIS formaldehyde inhalation toxicity assessment, released April 2022. Page references in these comments refer to that document:

U.S. EPA. IRIS Toxicological Review of Formaldehyde-Inhalation (External Review Draft, 2022). U.S. Environmental Protection Agency, Washington, DC, EPA/635/R-22/039, 2022. Document ID EPA-HQ-ORD-2010-0396-0032.

More information here: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=248150

We appreciate the public release of interagency comments, which add significantly to the public understanding of the IRIS assessment and it's utility to different government agencies. IRIS assessments are used by all levels of government, including state and local regulators, as well as countries around the world. Thus, comments by those agencies are of interest to the public, workers, and others that are affected by the regulatory and other decisions based on IRIS assessments.

Overall, we appreciate the evaluation. It is a thorough and well-reasoned scientific evaluation of the inhalation risks of formaldehyde, including both cancer and non-cancer health endpoints. Our specific comments in response to the Charge Questions are below.

CHARGE 1. *Assessment Development Methods and Organization. The Toxicological Review describes and applies a systematic review process for identifying, screening, and evaluating pertinent studies, and then for prioritizing the evidence to inform hazard and dose-response decisions.*

NRDC RESPONSE TO CHARGE 1 – Assessment Development Methods and Organization

b. Please comment on whether there is sufficient documentation on methods and criteria for the following:

- *o Identification of epidemiologic, experimental, and mechanistic studies (please identify any additional peer-reviewed studies that the assessment should consider).*
- *o Critical evaluation of individual studies or sets of studies.*
- *o Assessment of the weight of evidence (i.e., evidence integration).*
- *o Selection of studies and data sets for deriving toxicity values.*

It is unclear what EPA used for its study inclusion and exclusion criteria. For example, NIEHS comments expressed concern that EPA's literature search was inadequately broad, and unjustifiably limited. NIEHS noted that, "the limited set of search terms is unlikely to capture all animal studies of hypersensitivity" and may exclude other important studies. Moreover, the public is unable to fully access the Systemic Evidence Maps, which are crucial to convey critical information such as how the study inclusion and exclusion criteria were applied to particular studies, and how that may limit the data set used for the evaluation. NIEHS identified this concern as "Tier 1 – Necessary Revision", which NRDC agrees with.

Comments from NIOSH identified three genotox studies – Chebotarev et al 1986, Vasudeva and Anand 1996, Yager et al 1986 - that are not included in EPA's evaluation, that provide experimental evidence supporting a genotoxic mechanism of toxicity for formaldehyde.[1] While the first is in Russian, an English abstract is available, and for the other two they are available in English. If EPA is excluding all studies that are not in English, this is problematic and deserves some discussion and scrutiny.

NIOSH commenters also noted the failure to include an important published meta-analysis of myeloid leukemia risks in occupationally exposed workers, focused on occupations known to have high formaldehyde exposures by Zhang et al 2009. The study shows a statistically significant 1.5X increase leukemia in 15 studies (RR=1.54, CI 1.18-2.00), and an almost 2-fold higher risk for myeloid leukemia in six studies (RR=1.90, CI 1.31-2.76). Omission of this important paper should be corrected.

Zhang et al 2009 propose a biologically plausible mechanism for leukemia as follows: "formaldehyde may act on bone marrow directly or, alternatively, may cause leukemia by damaging the hematopoietic stem or early progenitor cells that are located in the circulating blood or nasal passages, which then

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[1] Chebotarev AN, Titenko NV, Selezneva TG, Fomenko VN, Katosova LM. Sopostavlenie khromosomnykh aberratsiĭ, sestrinskikh khromatidnykh obmenov i vneplanovogo sinteza DNK pri otsenke mutagennosti vneshnesredovykh faktorov [Comparison of chromosome aberrations, sister chromatid exchanges and unscheduled DNA synthesis in the evaluation of the mutagenicity of environmental factors]. Tsitol Genet. 1986 Mar-Apr;20(2):109-15. Russian. PMID: 3705165.

Vasudeva N, Anand C. Cytogenetic evaluation of medical students exposed to formaldehyde vapor in the gross anatomy dissection laboratory. J Am Coll Health. 1996 Jan;44(4):177-9. doi: 10.1080/07448481.1996.9937526. PMID: 8583043.

Yager JW, Cohn KL, Spear RC, Fisher JM, Morse L. Sister-chromatid exchanges in lymphocytes of anatomy students exposed to formaldehyde-embalming solution. Mutat Res. 1986 Jun;174(2):135-9. doi: 10.1016/0165-7992(86)90104-1. PMID: 3713731.

travel to the bone marrow and become leukemic stem cells."[2] Where the EPA Draft states that, "No MOA has been established to explain how formaldehyde inhalation can cause myeloid leukemia without systemic distribution…" (p. 54) this statement – and sentiment – should be corrected to note the proposed mechanism of Zhang et al 2009.

Using the EPA IRIS evaluation of 150 PFAS substances as a case study (Carleson et al 2022),[3] the problems with setting inappropriate study exclusion criteria were recently demonstrated in an invited commentary and companion analysis (Pelch and Kwiatkowski (2022). [4] Pelch and Kwiatkowski 2002 reported that the EPA IRIS data set excluded all wildlife studies, studies on non-rodent species, and studies by routes of exposure other than oral and inhalation. The IRIS data set included unpublished and non-peer reviewed industry-sponsored guideline studies that are conducted for the purpose of gaining regulatory product approval; most of these have only a study summary available to the public. The result was that EPA ultimately included only 44 published animal studies, 148 published epidemiologic studies, and from the unpublished 'gray' literature, 95 animal studies and 50 epidemiologic studies. By comparison, Pelch and Kwiatkowski included over 1,000 relevant studies, including 505 human epidemiology, 385 published animal studies, and 220 in vitro studies. The studies included in the Pelch and Kwiatkowski SEM are all completely accessible to the public. It is a concern to NRDC that as a general practice, the EPA IRIS program is applying study selection criteria that may bias against published studies and favor non-peer reviewed industry-sponsored studies.

Mechanistic data –

Regarding the assessment of the weight of evidence (i.e., evidence integration), NRDC strongly supports EPA's reasoned approach regarding mechanistic information, stating that mechanistic events and associations are preferred, but that, "the lack of mechanistic data explaining an association did not discount results from human or animal health effect studies" (p. 38). To that end, NRDC disagrees with the comment from ATSDR, arguing that the lack of mechanistic information should be treated not as a data gap, but as a "reason to down-grade the evidence findings."

NRDC supports EPA's determination that, "Mechanistic understanding is not a prerequisite for judging the evidence, and thus absence of knowledge should not be used a basis for decreasing strength NTP (2015); NRC (2014a).The human relevance of animal findings is assumed unless there is sufficient evidence to the contrary [see IARC (2006); U.S. EPA (2005a)]." (p. 40) This is also consistent with the IARC Preamble, updated January 2019 following a global process of public comment and scientific peer review. EPA could update the IARC reference in the text.

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[2] Zhang L, Steinmaus C, Eastmond DA, Xin XK, Smith MT. Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. Mutat Res. 2009 Mar-Jun;681(2-3):150-168. doi: 10.1016/j.mrrev.2008.07.002. Epub 2008 Jul 15. Erratum in: Mutat Res. 2010 Jul-Sep;705(1):68. PMID: 18674636.

[3] Carlson LM, Angrish M, Shirke AV, Radke EG, Schulz B, Kraft A, Judson R, Patlewicz G, Blain R, Lin C, Vetter N, Lemeris C, Hartman P, Hubbard H, Arzuaga X, Davis A, Dishaw LV, Druwe IL, Hollinger H, Jones R, Kaiser JP, Lizarraga L, Noyes PD, Taylor M, Shapiro AJ, Williams AJ, Thayer KA. Systematic Evidence Map for Over One Hundred and Fifty Per- and Polyfluoroalkyl Substances (PFAS). Environ Health Perspect. 2022 May;130(5):56001. doi: 10.1289/EHP10343. Epub 2022 May 17. PMID: 35580034; PMCID: PMC9113544.

[4] Pelch KE, Kwiatkowski CF. Invited Perspective: The Promise of Fit-for-Purpose Systematic Evidence Maps for Supporting Regulatory Health Assessment. Environ Health Perspect. 2022 May;130(5):51303. doi: 10.1289/EHP10743. Epub 2022 May 17. PMID: 35580037; PMCID: PMC9113540.

CHARGE 2. Toxicokinetics. *Several assumptions and interpretations were applied in the Toxicological Review that were based on current research (although the draft acknowledges that some uncertainties remain). Please answer parts (a), (b), and (c) considering the extent to which the available science on the toxicokinetics of inhaled formaldehyde is clearly presented and appropriately applied in the assessment of potential respiratory and systemic (i.e., nonrespiratory) health hazards.*

a. Please comment on the Toxicological Review conclusion that inhaled formaldehyde is not likely to be distributed in appreciable amounts beyond the respiratory tract to distal tissues. This conclusion underpins the organization of the assessment and several key assumptions.

b. Please comment on the Toxicological Review assumptions (based on [a]) that:

- *o Inhaled formaldehyde is not directly interacting with tissues distal to the portal-of-entry (POE) to elicit systemic effects.*
- *o Formaldehyde levels in the blood or at systemic sites are not appreciably changed as a result of formaldehyde from exogenous sources (inhalation).*
- *o Inhaled formaldehyde does not cause appreciable changes in normal metabolic processes associated with formaldehyde in distal tissues. Therefore, studies examining potential associations between levels of formaldehyde or formaldehyde byproducts in tissues distal to the POE (e.g., formate in blood or urine; brain formaldehyde levels) and health outcomes are not considered relevant to interpreting the human health hazards of inhaled formaldehyde.*

c. Please comment on the Toxicological Review evaluation of considerations regarding endogenous formaldehyde in assessing the health risk due to inhaled formaldehyde.

NRDC RESPONSE TO CHARGE 2

EPA's presentation of the toxicokinetics – including the considerations of endogenous formaldehyde – is generally well-reasoned and well-presented. EPA acknowledges some uncertainty in the low dose-response due to the potential for endogenous formaldehyde levels to reduce the uptake of inhaled formaldehyde. Importantly, as EPA concludes, this limitation is negligent given robust scientific evidence demonstrating that formaldehyde has genotoxic, mutagenic and cytogenic mode of toxicity, thus supporting a linear low-dose extrapolation (p. 158, 171).

CHARGE 3. Respiratory System Health Effects (Noncancer). *For each noncancer POE health effect considered in the assessment and outlined in (a) to (e), below, please comment on whether the evidence integration decisions for hazard identification are clearly described and scientifically justified (considering the extent to which the available data have been appropriately synthesized to describe the strengths and limitations). In addition, please separately comment on whether the dose-response decisions are transparent and scientifically justified, including study selection for dose-response analyses; point of departure (POD) estimates, including modeling choices and assumptions, and dosimetric adjustments; selection of uncertainty factors and derivation of candidate values; selection of organ- or system-specific RfCs (osRfCs); and confidence in the calculated values. For these well-studied health effects, confidence was consistently judged as either medium or high.*

NRDC RESPONSE TO CHARGE 3

(no comment at this point)

CHARGE 4. Systemic (i.e., non-respiratory) Health Effects (Noncancer).

NRDC RESPONSE TO CHARGE 4

NRDC supports EPA's determination that inhalation of formaldehyde "likely causes" female reproductive or developmental toxicity in women – EPA's conclusion is supported by evidence in humans, including time-to-pregnancy (TTP) and spontaneous abortion risk. As NIEHS noted in its comments, "it is reasonable to conclude that female reproductive toxicity based on TTP (Taskinen et al. 1999) and spontaneous abortion (John et al. 1994, Taskinen 1994, 1999) is supported by epidemiological evidence" (NIEHS p. 6) EPA notes that "mechanistic evidence explaining such effects without systemic distribution of formaldehyde is lacking" (p. 54). However, NIEHS comments noted that, "it has been clearly demonstrated that formaldehyde is metabolized to formic acid" which is demonstrated to impair embryo viability and is linked to adverse developmental outcomes (NIEHS p. 6). NRDC agrees with NIEHS that the addition of this scientific evidence and proposed mechanism would strengthen EPA's evaluation. NIEHS identified this as a "Tier 1" necessary revision. Nonetheless, NRDC concurs with EPA that mechanistic information is not necessary, and a data gap or the absence of knowledge should <u>not</u> be used as a basis for downgrading the strength of evidence. (p. 40)

CHARGE 5. Noncancer RfC. *An RfC was selected based on the grouping of osRfCs for sensory irritation, decreased pulmonary function, allergy-related conditions, and increased prevalence of current asthma or decreased degree of asthma control. Please comment on whether the approach and selection of the proposed RfC was clear and scientifically justified, including consideration of other potentially sensitive health effects.*

RESPONSE
(no comment at this point)

CHARGE 6. Cancer. *The assessment concludes that formaldehyde is* ***Carcinogenic to Humans by the Inhalation Route of Exposure****. Please comment on whether the judgments in (a) to (f), below, are clearly described and scientifically justified. Note that the three judgments in (a), (b), and (c) outline the primary evidentiary support, and that each of these judgments would independently substantiate the carcinogenicity conclusion.*

NRDC RESPONSE TO CHARGE 6

NRDC supports the EPA conclusion that – with its highest rating of confidence - "evidence demonstrates" a causal link between formaldehyde exposure and three cancer endpoints, nasopharyngeal cancer (NPC), myeloid leukemia and sinonasal cancer (SNC). NRDC agrees that this is consistent with the scientific evidence.

<u>Myeloid Leukemia:</u>
NRDC supports EPA's evaluation that the scientific evidence demonstrates that exposure to formaldehyde causes myeloid leukemia. Although EPA has "low" confidence in its risk estimate for myeloid leukemia (compared to "medium" confidence in its NPC-based risk figure) EPA could increase scientific confidence in the data by leveraging the meta-analysis of Zhang et al 2009 (discussed above) to support the risk estimate. Use of the meta-analysis can increase the precision of an effect estimate, by

basing the estimate on a larger number of studies, and can also be used to quantify effects across sufficiently homogeneous studies. Meta-analyses frequently underpin Health Impact Assessments (HIA) and cost-benefit analyses (CBA) of interventions, such as policies to reduce air pollution. Meta-analyses can provide important opportunities when synthesizing study results to strengthen hazard evaluations, and should be used by EPA with appropriate considerations of study quality etc.

The 2010 IRIS report that "the associations between myeloid leukemia and formaldehyde exposure are positive and consistent" and that "human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure and nasopharyngeal cancer, nasal and paranasal cancer … [and] myeloid leukemia." There are no post-2010 data that casts doubt upon that connection. The risk of this endpoint should be included in EPA's overall cancer risk.

Sinonasal Cancer (SNC):
NRDC is concerned that the risk of SNC is not given appropriate weight; it should be included, quantitatively, in the overall cancer risk calculation. As NIEHS notes, "EPA has concluded that (1) formaldehyde is genotoxic in humans (based on studies using buccal, blood, and nasal tissues from exposed humans) and in experimental systems, (2) a genotoxic mode of action plays a role in the development of nasal tumors (SNC) and NPC, and (3) there is moderate confidence for a causal association between formaldehyde exposure and SNC risk from human studies," (NIEHS p. 12). The hazard for SNC from formaldehyde is established by the existing science; failure to include it in an overall risk estimate may result in an underestimate of risk.

CHARGE 7. Inhalation unit risk for cancer. *An IUR for cancer is derived on the basis of nasal cancers using data on nasopharyngeal cancers (NPCs) in a human study from the National Cancer Institute (NCI), specifically the results reported in (Beane Freeman et al., 2013). In addition, comparative estimates are provided on the basis of modeling of nasal tumors in exposed rodents. Finally, although not included in the draft IUR, an estimate for myeloid leukemia is presented. Please comment on the clarity and scientific justification for each specific decision in the draft cancer dose-response analyses outlined in (a) to (d), below, including study selection; POD estimates, including modeling choices and assumptions, dosimetric adjustments, and extrapolations; any other adjustments; and confidence in the calculated values. Part (e) includes a specific, additional question on myeloid leukemia.*

NRDC RESPONSE TO CHARGE 7

NRDC is concerned that the proposed IUR will strip away much-needed health protections, as it is roughly 10-fold less protective than EPA's 2010 draft risk estimate of 1.1 ×10-4 per ug/m3 (0.13 per ppm) based on myeloid leukemia. In fact, it sets IRIS back about a quarter-century, to the 1991 cancer risk estimate of 1.3 x 10-5 per ug/m3 that remains in the IRIS database.[5]

a. *The NCI study results on NPCs were ultimately selected and used to develop the draft IUR estimate. A lifetable analysis was used to develop a POD and given the mutagenic MOA for this cancer type, a linear extrapolation was applied. Age-dependent adjustment factors (ADAFs) were applied to this estimate, in accordance with EPA guidelines when a mutagenic MOA is supported. Confidence in the IUR is medium.*

[5] In the 1991 assessment, an inhalation unit risk of 1.3 × 10−5 per µg/m3 was developed based on nasal SCCs in F344 rats from Kerns et al. (1983). The data were modeled from the estimates of the probability of death with tumor and its variance using a linearized multistage procedure.

NRDC agrees with EPA's use of an ADAF-adjusted Inhalation Unit Risk (IUR) for NPC of 1.1×10-5 per ug/m3 (0.013 per ppm) (Table 2-40, p. 721). This value represents the upper-bound estimate of the increased lifetime risk of cancer from inhaling 1 ug/m3 of formaldehyde over a lifetime. The ADAF adjustments are to address exposure over a 70-year lifetime, which includes vulnerable periods of childhood, and are required by EPA's Cancer Guidelines because the NPC cancer is due, at least in part, to a mutagenic mode of action. (p. 58).

c. *For sinonasal cancer, the draft draws an evidence integration judgment of evidence demonstrates. Given the lack of quantifiable data to allow the use of dose-response information to identify a POD, the IUR does not incorporate potential contributions to risk for sinonasal cancer. Please comment on this decision and, if this is not supported, include a recommended method to account for this cancer risk.*

NRDC is concerned that the failure to include SNC in its overall risk finding (the inhalation unit risk, IUR), which is instead based only on the risk of NPC, will result in an underestimate of risk. Excluding both SNC and myeloid leukemia risk from the calculated IUR is pretending the risks don't exist when in fact they are scientifically established hazards.

NRDC suggests that EPA could instead present a range of overall cancer risk, from NPC-only to NPC and myeloid leukemia, and including SNC risks. This is more consistent with EPA policy to add cancer risks, and would provide both a scientific and policy honesty to EPA's evaluation. Providing this range of overall risk values will inform decisions by regulatory agencies at local and state levels, other countries, industry, unions, communities, consumers, and others.

d. *For myeloid leukemia, a unit risk estimate is presented using the NCI study results (Beane-Freeman et al., 2009). In line with recommendations from the NAS (NRC, 2011), this reassessment draws hazard conclusions and derives a unit risk estimate at the most specific cancer type supported by the available data. The selected data set used to derive the myeloid leukemia estimate combined the results from myeloid leukemia with results for other/unspecified leukemias. ADAFs were not applied to this estimate, as the assessment concludes that the MOA is unknown.*

NRDC urges EPA to consider applying ADAFs to the myeloid leukemia risk estimate. EPA did not apply ADAFs to this endpoint. NRDC supports the use of ADAF lifetime adjustments. NRDC joins the broad scientific community in advocating that this adjustment should be applied to all carcinogens, not just those that are mutagenic. This is done by Cal-EPA OEHHA, for example.

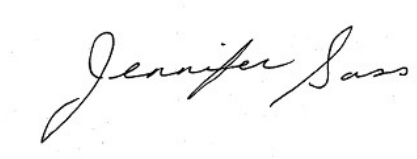
e. *Although the draft concludes that the evidence demonstrates that formaldehyde inhalation causes myeloid leukemia, the only data available to develop a unit risk estimate for myeloid leukemia are uncertain. The draft Toxicological Review discusses the strengths and limitations of the myeloid leukemia estimate in detail. Please comment specifically on how the unit risk estimate for myeloid leukemia should inform the IUR for cancer, if at all.*

NRDC disagrees with excluding the risk estimates for myeloid leukemia in EPA's overall risk estimate (the inhalation unit risk, IUR), which is instead based only on the risk of NPC. This is an especially significant oversight given that myeloid leukemia is a much more common disease than NPC, which is a very rare cancer. EPA explains its omission of the myeloid leukemia risk as due to some uncertainty and therefore a lower confidence in the exposure-response modelling results (Tox Draft p. 57). Nonetheless, the IRIS

draft calculates a risk estimate for myeloid leukemia risk, of 3.4×10-5 per ug/m3 (0.042 per ppm) (Table 2-35, p. 710).

Excluding both SNC and myeloid leukemia risk from the calculated IUR is pretending they aren't significant cancer risks, when in fact they are scientifically established hazards. NRDC suggests that EPA could instead present a range of overall cancer risk, from NPC-only to NPC and myeloid leukemia, and including SNC risks. This is more consistent with EPA policy to add cancer risks, and would provide both a scientific and policy honesty to EPA's evaluation, as well as informing decisions by regulatory agencies at local and state levels, other countries, industry, unions, communities, consumers, and others.

Thank you for your consideration of these comments.



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