Texas Commission on Environmental Quality
Comments Regarding the U.S. Environmental Protection Agency
Draft Toxicological Review of Formaldehyde in Support of
Summary Information on the Integrated Risk Information System (IRIS)
Notice of Public Comment Period and Listening Session
75 FR 30825, June 2, 2010
Docket ID No. EPA-HQ-ORD-2010-0396

On June 2, 2010, the U.S. Environmental Protection Agency (EPA) published a Federal Register notice (Federal Register/Vol. 75, No. 105/Wednesday, June 2, 2010/Notices) of a 90-day public comment period (ending August 31, 2010) for the, "Draft Toxicological Review of Formaldehyde in Support of Summary Information on the Integrated Risk Information System (IRIS)," hereafter referred to as the draft IRIS review (EPA/635/R-10/002A). The draft IRIS review provides draft inhalation unit risk factors (URFs) for nasopharyngeal cancer, leukemia, Hodgkin lymphoma, and a combined URF for formaldehyde. It also provides a draft inhalation reference concentration (RfC), although EPA has not historically calculated an RfC for formaldehyde. The Texas Commission on Environmental Quality (TCEQ) has developed comments on the draft IRIS review to the extent practicable in the time allotted by EPA, focusing on the draft URFs, and provides the following limited comments for EPA consideration.

General Comment:

The assessment of the carcinogenic (and non-carcinogenic) potential of formaldehyde has great implications both in a regulatory context and in the public's perception of risk. Given their important role in the protection of public health, EPA regulatory risk assessors have a duty to perform the most scientifically-defensible assessments possible while giving careful and due consideration to comments and recommendations from other regulatory agencies, the public, external experts, stakeholders, etc. Although regulatory risk assessors have a penchant for erring on the side of health-protectiveness and conservative defaults, if erring on the side of conservatism significantly overestimates risk or hazard and is not fully justified, then harm to public health may result from diverting public, industry, and government attention and resources away from chemicals which may represent more of a public health risk at environmental levels. Therefore, TCEQ encourages EPA to give full, thoughtful, and careful consideration and evaluation to comments and recommendations from TCEQ, other regulatory agencies, the public, and external experts.

90-Day Comment Period:

The 90-day comment period is insufficient for regulatory agencies and others to provide thorough and meaningful comments based on an in-depth review and analysis of the draft IRIS review. There is great complexity associated with multiple issues relevant to the assessment of formaldehyde inhalation risk and hazard. The draft IRIS review alone is 1,043 pages, and there are hundreds of pages (at a bare minimum) of other documents and studies relevant to the assessment of formaldehyde risk and hazard due to inhalation

exposure. Given the complexity and volume of relevant materials, it is impracticable for EPA to expect detailed specific comments from external experts given the short period allowed for a critical review of the draft IRIS review and procedures employed by EPA. The 90-day comment period only allows a very cursory review of the draft IRIS review at best, leads to a less-than-desirable level of transparency and peer review, and undermines confidence in the process. Consequently, TCEQ is only able to provide preliminary comments based on a cursory review. If EPA seeks detailed and meaningful public input and technical comments, at a minimum EPA should extend the comment period at least 90 days past the August 31 deadline to allow stakeholders to perform a more detailed review of the volumes of relevant information and to comment on problematic issues associated with the draft IRIS review.

Toxicology-Based Comments:

Key Study for Hodgkin Lymphoma and Leukemia Unit Risk Factors

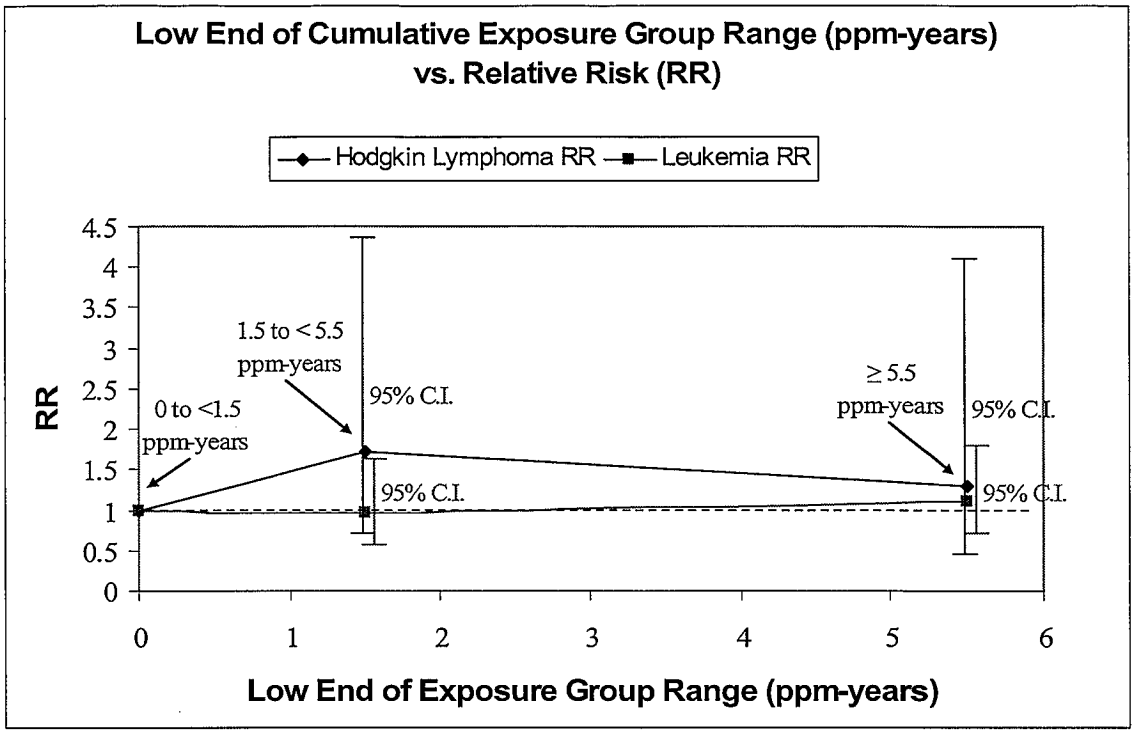
EPA utilizes the Beane Freeman et al. (2009) study to calculate draft URFs for Hodgkin lymphoma and leukemia. While there were statistically significant trends for Hodgkin lymphoma and leukemia with peak exposure, there were no statistically significant trends for any lymphohematopoietic malignancy with cumulative exposure. EPA indicates (p. 5-91) that it is not clear how to extrapolate risk estimates based on peak exposure estimates to meaningful estimates of lifetime extra risk of cancer from environmental exposures, and that the average exposure metric is also problematic because it suggests that duration of exposure is not important. Because EPA could not derive URFs for Hodgkin lymphoma and leukemia based on the dose metric for which there was a significant association (peak exposure), EPA used a dose metric for which there was no significant association (cumulative exposure) despite the fact that dose-response data for this dose metric are inadequate. EPA calculated draft URFs based on cumulative exposure despite that: (1) there were no statistically significant trends for Hodgkin lymphoma and leukemia with cumulative exposure; (2) regardless of statistical significance considerations, there is no apparent dose-response relationship between cumulative exposure and risk to provide adequate data for URF development; (3) if there is a causal relationship, study results indicate that peak exposure (as opposed to cumulative) is the most significant determinant of risk; and (4) if there is a causal relationship, study results suggest that duration of exposure, which is inherently part of the cumulative exposure dose metric, is not important (per EPA, p. 5-91).

Dose-Response Data

A primary reason that EPA used the cumulative exposure metric in order to be able to derive URFs is that, "the elevations in risk with that metric were consistent with significant elevations observed with the peak exposure (for Hodgkin lymphoma and leukemia)." However, this is not the case. While the relative risks (RR) for Hodgkin lymphoma and leukemia may show a monotonic dose-response relationship with peak exposure, the RRs do not appear to show a dose-response relationship for the cumulative exposure dose metric used by EPA. For example, for Hodgkin lymphoma the RR for the highest

cumulative dose group (RR of 1.30) is actually lower than that for the medium dose group (RR of 1.71). For leukemia, the RRs for the highest and medium cumulative dose groups are essentially equal to 1 (RRs of 1.11 and 0.96, respectively), consistent with no elevated risk. The RRs for Hodgkin lymphoma and leukemia based on cumulative exposure (RRs of 0.96-1.71) are not consistent with a strong relationship and all RR confidence intervals easily include 1 (i.e., the lower end of the RR confidence intervals range from 0.40 to 0.70), consistent with the possibility of no elevated risk. Additionally, the Beane Freeman et al. (2009) study is not informative regarding what the RR might be for environmental exposures, which would fall into the cumulative exposure category used as the referent group (0-1.5 ppm-years), and the intermittent peak exposures associated with elevated RRs for workers (> 2 ppm) are significantly higher than environmentally-relevant levels. EPA does not attempt to provide a robust justification for use of the cumulative exposure metric, and given the results of the Beane Freeman et al. (2009) study, TCEQ does not believe a robust justification is possible (i.e., use of the cumulative exposure metric is not scientifically defensible).

In addition, the cancer guidelines (EPA 2005a) recommend use of enough dose groups to provide an indication of the shape of the dose-response curve, as characterization of the shape of the dose-response curve is important in providing relevant dose-response data for assessing human risk. A relatively broad exposure range should make it relatively easy to discern the shape of any underlying dose-response curve in a well-conducted study. However, it is clear based on examination of the figure below that the data from Beane Freeman et al. (2009) provide too few dose groups and do not provide a monotonic dose-response curve, much less provide an indication of any reasonable shape of any underlying dose-response curve. As an example, for Hodgkin lymphoma the RR for the highest cumulative dose group (RR of 1.30) is actually lower than that for the medium dose group (RR of 1.71). These data are nonsensical from a dose-response perspective and clearly inadequate for derivation of a URF. For leukemia, again, the RRs for the highest and medium cumulative dose groups are essentially equal to 1 (RRs of 1.11 and 0.96, respectively) and do not provide an indication of a dose-response shape or increased risk relevant to environmental exposure for that matter. The ability to fit a line through data points does not necessarily mean that the underlying data adequately define the shape of the dose-response curve, including the critical low dose region. Based on the above considerations, the underlying data modeled by EPA clearly do not provide a basis for dose-response assessment. Dose-response is the cornerstone of toxicology, but the data modeled by EPA do not provide a solid foundation upon which to build these URFs.



In summary, EPA decided to use the cumulative exposure dose metric to calculate draft URFs despite the lack of statistically significant trends, despite not having the necessary dose-response data to do so in a scientifically-defensible manner, despite information suggesting that peak exposure (as opposed to cumulative) is the most significant determinant of any risk, and despite information suggesting that duration of exposure (inherently part of the cumulative exposure dose metric) is not important (per EPA). To restate EPA's sentence (p. 5-91) in a slightly different but equally valid manner, it is not clear how to extrapolate risk apparently associated with peak exposures to *meaningful* estimates of lifetime extra risk of cancer due to cumulative or average environmental exposure. As data indicate that risk (if any) is most closely related to peak exposure, not cumulative or average exposure, the scientific validity and predictive value of risk estimates (e.g., URFs) calculated based on a cumulative exposure dose metric for which there is no apparent dose-response relationship is highly questionable. These significant issues are in addition to arguments concerning the lack of biological plausibility.

Leukemia and Hodgkin Lymphoma Contribution to the Combined URF

Leukemia URF

The URF for leukemia is by far the highest of the three combined by EPA (nasopharyngeal, Hodgkin lymphoma, leukemia) for the draft URF, contributing 60% of the risk for the combined draft URF. However, the draft URF for leukemia is likely the least scientifically defensible. As indicated above, for leukemia the RRs for the highest and medium cumulative exposure dose groups are essentially equal to 1, with RRs of 1.11 and 0.96, respectively. Obviously, the RR confidence intervals for the highest (0.70-

1.74) and medium (0.60-1.56) cumulative exposure dose groups include 1. These RRs and confidence intervals for cumulative exposure are consistent with no elevated risk and there is no significant dose-response for leukemia with cumulative exposure, yet leukemia is the combined URF risk driver. Additionally, there is no dose-response based on average concentration; the RRs for the medium (RR of 1.13) and high (RR of 1.10) exposure groups show no dose-response and are essentially equal to 1 with confidence intervals containing 1 (i.e., the lower end of the RR confidence intervals range from 0.68 to 0.71). Even for peak exposure for which there was a trend, only the highest exposure group ($\geq$ 4 ppm) has a RR greater than 1 (RR of 1.42), and the confidence interval for that group includes 1 (0.92-2.18). The RR for the medium peak exposure group, comprised of workers exposed to much higher than environmentally-relevant concentrations (2 to < 4 ppm), was 0.98 and consistent with no elevated risk.

In summary, the draft combined URF is driven by the URF for leukemia, for which the only RR greater than 1 in the derivation is the RR of 1.11 for the highest cumulative exposure group ($\geq$ 4 ppm). This RR and the associated confidence interval containing 1 (0.70-1.74) are consistent with no excess risk yet will likely drive unachievable outdoor and indoor regulatory air levels (see relevant comment sections below). The URF for leukemia based on cumulative exposure is not scientifically defensible based on RRs essentially equal to 1 and the lack of a statistically significant or apparent dose-response (there are also biological plausibility issues). Based on Beane Freeman et al. (2009) study results, if any association exists between formaldehyde exposure and leukemia it may be with intermittent peak exposures levels greater than 4 ppm, an exposure scenario for which EPA acknowledges (p. 5-91) that no meaningful URF applicable to environmental concentrations can be calculated.

Hodgkin Lymphoma URF

The URF based on Hodgkin lymphoma contributes 23% of the risk for the combined draft URF. Several of the reasons why the URF for leukemia based on cumulative exposure is not scientifically defensible also apply to the URF for Hodgkin lymphoma. There is a lack of a statistically significant trend and lack of a monotonic dose-response relationship between Hodgkin lymphoma and cumulative exposure. The RR for the highest cumulative dose group (RR of 1.30) is actually lower than that for the medium dose group (RR of 1.71) and neither indicates a strong relationship. The RR confidence intervals include 1 (i.e., the lower end of the RR confidence intervals range from 0.40 to 0.66) consistent with the possibility of no excess risk, yet this URF will be a significant driver in likely unachievable outdoor and indoor regulatory air levels (see relevant comment sections below). In addition to no significant or apparent dose-response relationship with cumulative exposure, there is none between Hodgkin lymphoma and average exposure. If any association exists between formaldehyde exposure and Hodgkin lymphoma, it may be with intermittent peak exposures levels, an exposure scenario for which EPA acknowledges (p. 5-91) that no meaningful URF applicable to environmental concentrations can be calculated.

Conclusions Regarding the Leukemia and Hodgkin Lymphoma URFs

In summary, the draft URFs for leukemia and Hodgkin lymphoma based on cumulative exposure are not scientifically defensible (e.g., lack of dose-response). If a relationship does exist, it appears to be with peak exposure, and EPA indicates that it is not clear how to extrapolate risk estimates based on the peak exposure estimates to meaningful estimates of lifetime extra risk of cancer from environmental exposures. However, in effect this is exactly what EPA did, extrapolating apparently peak-associated risk to lifetime extra cancer risk by using a dose metric (cumulative exposure) for which there is no dose-response, resulting in URFs of highly questionable meaning. Clearly, EPA should redact these draft URFs. Alternatively, EPA should provide a robust justification for the need to derive URFs for leukemia and Hodgkin lymphoma in the absence of a dose-response for cumulative exposure and scientific defensibility.

Formaldehyde Exposure, Leukemia, and Lymphohematopoietic Cancers

Findings regarding associations between formaldehyde and leukemia are inconsistent across studies, and whether formaldehyde is capable of causing lymphohematopoietic malignancies is not scientifically established and is of great scientific debate and controversy. TCEQ disagrees with EPA (p. 4-535) that human epidemiological evidence is sufficient to conclude a causal association between formaldehyde exposure, leukemia, and lymphohematopoietic cancers as a group considering the inconsistency of the associations, the weakness of the associations as demonstrated by the RRs and confidence intervals discussed above for the principal study used by EPA, and biological implausibility considerations. As additional examples, for the cohorts summarized by EPA (pp. 4-493 to 4-495), no standardized mortality ratios (SMRs) for lymphohematopoietic cancers are greater than 3, with only 1 of 18 greater than 2, indicating a very weak association if any. In fact, 5 of 18 SMRs are less than 1 and 67% of the SMR confidence intervals include 1, consistent with a lack of association. For leukemia, only 3 of the 21 SMRs exceed 2, with 5 being less than 1, overall consistent with a lack of association. Additionally, in 100% of the cases where leukemia SMR confidence intervals are given they include 1. EPA should weigh the human epidemiological evidence more carefully before deciding to calculate URFs based on the Beane Freeman et al. (2009) study where the association was with peak exposure and not the cumulative exposure dose metric used by EPA (a separate issue).

Implications of Lu et al. (2010) for EPA URF Development

A well-conducted study by Lu et al. (2010) has very recently been able to clearly differentiate between endogenous and exogenous formaldehyde-induced DNA adducts and DNA-DNA cross-links, allowing the quantitative examination of formaldehyde-induced adducts and cross-links in a multitude of tissues following inhalation exposure. This study shows that even in rats exposed to much higher concentrations (10,000 ppb) than environmental exposures of humans, exogenous formaldehyde-induced adducts and cross-links only occur in the rat nasal mucosa (the clear target site of rat carcinogenesis) and not at sites remote to the portal of entry. In other words, this study clearly shows that

exogenous formaldehyde-induced genotoxic effects at sites remote to the portal of entry are implausible. Additionally and directly relevant to the hypothesis by EPA and others that hematopoietic stem cells/early progenitor cells in the circulation or residing in the nasal passages may be exposed in the nose and travel to the bone marrow to be transformed into leukemia cells (e.g., pp. 4-529 to 4-535), Lu et al. (2010) used a very sensitive method (the method could detect levels ≈ 30 times less than the number of adducts from endogenous formaldehyde) to show that neither white blood cells nor bone marrow contained exogenous formaldehyde-induced DNA adducts (or cross-links). The EPA draft IRIS review gives no serious evaluation of the significant implications of these study results for the scientific defensibility of deriving URFs for Hodgkin lymphoma and leukemia. The significant implications of this recent research are inconsistent with deriving URFs for Hodgkin lymphoma and leukemia and were simply ignored in the draft IRIS review document.

Regression Coefficient for Nasopharyngeal Cancer

EPA utilizes a regression coefficient (β) based on nasopharyngeal cancer *mortality* to calculate the URF for nasopharyngeal cancer *incidence* (pp. 5-83 to 5-84). However, the survival rate for nasopharyngeal cancer is significant (≈ 50%), and no robust justification is provided for the assumption or expectation that nasopharyngeal cancer mortality and incidence share the same dose-response relationship and therefore use of a β based on mortality is justified for incidence.

Application of Age-Dependent Adjustment Factors

EPA indicates that: (1) there is an adequate weight of evidence to consider formaldehyde-induced mutations relevant to human carcinogenic risk (p. 6-24); (2) that formaldehyde carcinogenicity can be attributed, at least in part, to a mutagenic mode of action (MOA) (p. 6-25); and (3) therefore, age-dependent adjustment factors (ADAFs) should be applied in accordance with EPA guidance (EPA 2005b) (p. 5-104). However, EPA provides no discussion concerning the scientific defensibility of applying ADAFs derived from data for mutagenic carcinogens to a chemical like formaldehyde with a mixed MOA for which EPA has only determined that mutagenicity plays a part.

Implementation-Based Comments:

Implications of the URF for Ambient and Indoor Air

TCEQ notes that the 1 in 100,000 excess risk air concentration of 0.08 ppb based on the draft URF is not met anywhere in the world, indoors or outdoors (or in our own breath). This includes remote locations such as Alert, Nunavut, Canada, located in the arctic only 500 miles from the north pole (average of 0.4 ppb), and the remote South Pacific island of Eniwetok Atoll (average of 0.4 ppb) (IARC 2006). The average reported for Alert, Nunavut is based on data collected during polar night, a time during which contributions from photochemical oxidation of hydrocarbons would be negligible.

TCEQ risk-based air monitoring comparison values are set at an excess risk level of 1 in 100,000. Using the draft URF and a 1 in 100,000 air concentration (0.08 ppb) would mean that formaldehyde levels at the arctic's Alert, Nunavut and the South Pacific's remote Eniwetok Atoll island would need to be reduced by a factor of at least 5 times. Even the 1 in 10,000 excess risk air concentration of 0.8 ppb based on the draft URF is almost not met anywhere in the world, with a few exceptions such as remote locations like Alert, Nunavut and Eniwetok Atoll (averages of 0.4 ppb) (IARC 2006). As levels of formaldehyde in indoor air are often significantly higher than levels outdoors, indoor air concentrations would be expected to significantly exceed (i.e., at least by an order of magnitude) even the 1 in 10,000 excess risk air concentration (IARC 2006). Use of the draft URF would imply that air neither indoors nor outdoors (or even your own breath, see below) is safe from a regulatory perspective.

Implications of the URF for Endogenously-Produced Formaldehyde

Formaldehyde is produced endogenously in the human body. TCEQ notes that the air concentration corresponding to the upper end of the EPA acceptable risk range (1 in 10,000 excess cancer risk) using the draft URF is 0.8 ppb (p. 5-143). However, even this highest regulatory-acceptable air concentration is over 5 times lower than the median normal human breath level (4.3 ppb) reported in 344 healthy men and women (positive alveolar gradient, negligible room air concentrations reported in Moser et al. 2005), and is 50 times lower than the reported 97.5th percentile normal formaldehyde breath level (40 ppb). At face value, use of this draft URF and data imply that formaldehyde breath levels resulting from normal endogenous production would clearly represent an unacceptable level of risk from a regulatory perspective (e.g., risk of 5.4E-04 to 5.0E-03 using EPA's draft URF and the median and 97.5th percentile normal breath levels). Using the lower end of the acceptable risk level (1 in 1,000,000), the corresponding air concentration is 0.008 ppb, which is 537 times lower than the median reported breath level and 5,000 times lower than the 97.5^{th} percentile normal formaldehyde breath level (positive alveolar gradient, negligible room air concentrations reported in Moser et al. 2005). Regulating formaldehyde at concentrations anywhere from 5-5,000 times lower than normal breath concentrations presumably resulting from normal endogenous production simply makes no sense as it offers insignificant risk reduction compared to the risk which would result from normal breath levels due to endogenous production (assuming there is in fact risk at these levels).

References

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