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SUBJECT: DPR-HHAB RESPONSES TO THE EUROPEAN FOOD SAFETY AUTHORITY-MEMBER STATE DRAFT RISK ASSESSMENT ON 1,3-DICHLOROPROPENE

On May 10, 2017, the European Food Safety Authority (EFSA) posted a Consultation Notice indicating that it was seeking comments on a draft risk assessment report for 1,3-dichloropropene (1,3-D). Following that notice, DPR management requested that the Human Health Assessment (HHA) Branch review and respond to the draft risk assessment composed by two EFSA member states, Spain (primary) and France (secondary).

The EFSA-Member State draft, hereafter referred to as the Draft Assessment Report (DAR), can be found at http://www.efsa.europa.eu/en/consultations/call/170510. It covers a range of issues surrounding the use of 1,3-D and two of its formulations, GF-3035 and GR-3036. These include chemical and product identity, relevant chemical structures, physico-chemical properties, storage, emergency procedures, analytical methods, pharmacokinetic and toxicology study summaries, human health risk assessment, epidemiological observations, residue data, environmental fate, and ecotoxicology. Most importantly from HHA's standpoint, the DAR contains approaches to the risk assessment of inhaled 1,3-D vapors that relate directly to HHA's own assessment of this compound (DPR, 2015) (http://www.cdpr.ca.gov/docs/risk/rcd/dichloro_123115.pdf). For this reason, HHA restricted its comments on the DAR to those particular sections.

The following paragraphs replicate HHA's *verbatim* comments that were submitted by email to EFSA on Friday July 7, 2017 to be considered for the completeness and clarity of the DAR, as per EFSA guidelines on Public Consultations (www.efsa.europa.eu/sites/default/files/corporate_publications/files/consultationpolicy.pdf).

1. Summary of long-term carcinogenicity (DAR level 2.6.5) – DAR 01, p. 33

HHA comment: EFSA-MS cited the 2-yr. mouse oncogenicity study of Stott *et al.* (1987) as evidence for the ability of 1,3-D vapors to induce benign pulmonary adenomas. Based on this study, along with studies indicating oncogenic effects by other exposure routes, EFSA-MS recommended listing 1,3-D as a "possible human carcinogen". We agree with this action. However, EFSA-MS set an oncogenic NOAEL at 20 ppm (*note*: at 0, 5, 20 and 60 ppm, the mouse adenoma incidence rate was 9/49, 6/50, 13/49, 22/50* ($p<0.05$). DPR would set a NOEL for oncogenicity only when there is an accepted threshold for oncogenesis, which EFSA-MS did not demonstrate for 1,3-D. Even if a threshold mechanism had been established, DPR would likely consider 20 ppm as a LOEL since tumor incidence increased compared to controls at that air concentration.

HHA further explanation: Based on (a) appropriate model fit, (b) genotoxic potential, and (c) lack of evidence for a "biologically based" model, DPR characterized the concentration dependent rise in pulmonary adenoma incidence in mice by calculating oncogenic Air Unit Risk (AUR) values in ppm^{-1} using the Multistage Cancer algorithm (BMDL Multistage Cancer, v. 3.4) (DPR, 2015).This approach necessitated scaling the mouse air concentrations to Human Equivalent Concentrations (HECs), for which we used the Regional Gas Dose Ratio (RGDR) approach (http://www2.epa.gov/osa/methods-derivation-inhalation-reference-concentrations-and-application-inhalation-dosimetry). This allowed us to differentiate between portal-of-entry (POE) and systemic (SS) modes of action. AURs (both POE & SS) were then calculated for ambient and occupational exposure scenarios and multiplied by the relevant estimated lifetime exposures to generate oncogenic risk values. This approach was different than that used by EFSA-MS, which appeared instead to calculate pulmonary oncogenic risk by estimating an oncogenic NOAEL (20 ppm). Incidentally, the EFSA-MS oncogenic NOAEL was higher than the NOAEL of 10 ppm and accompanying AOEC of 0.1 ppm used to calculate non-oncogenic risk. Since DPR ultimately calculated oncogenic risk values that were greater for some exposure scenarios than the standard cutoffs for negligible oncogenic risk, we recommend that EFSA-MS reconsider its approach to this subject.

2. Toxicological endpoint for assessment of occupational, bystander and resident risks-AOEL (DAR level 2.6.13) – DAR 01, pp. 37-38

HHA comment: EFSA-MS established one non-oncogenic regulatory value, 0.1 ppm, which they referred to as the "AOEL" or "AOEC" (Acceptable Operator Exposure Concentration). EFSA-MS's AOEC of 0.1 ppm was calculated by dividing the critical NOAEL of 10 ppm, established in the subchronic (13-week) rat inhalation study of Stott *et al*. (1984), by a safety factor of 100. This approach did not take into account the possibility that different exposure durations or exposures to children *vs*. adults may require different critical endpoints or endpoint values, thus limiting the sensitivity of their risk analysis.

HHA further explanation: DPR used a different approach to the non-oncogenic risk assessment of 1,3-D (DPR, 2015).

a. DPR calculated separate reference concentrations (RfCs) for short term, intermediate term and annual exposure scenarios.
b. DPR differentiated between occupational (8-hr) and bystander (24-hr) exposure scenarios for each exposure length (*i.e.*, short term, intermediate term and annual exposures).
c. For bystander exposures, DPR produced separate RfCs for children and adults.
d. Before calculating RfCs, DPR determined Human Equivalent Concentrations by scaling the rat or mouse critical NOELs to humans using the RGDR approach. EFSA-MS did not scale their critical inhalation NOAEL value before calculating the AOEC.

For a summary of DPR's non-oncogenic reference concentrations, see DPR (2015), p. 199. Detailed descriptions of the RfC calculations are also found there.

3. Summary of product exposure and risk assessment (DAR level 2.6.14) – DAR 01, pp. 38-40

HHA comment: In the "operator" and "worker" exposure scenarios, EFSA-MS used directly measured air concentrations or the 75th percentile of the measured air concentration data to estimate exposure.

HHA further comment: EFSA-MS's "operator" scenario is equivalent to the loader and applicator exposure scenarios in DPR's risk characterization document (RCD) (DPR, 2015). EFSA-MS's "worker" scenario is equivalent to the re-entry worker scenario in the RCD.

In the DPR RCD, the 95th percentiles of the natural logarithms of the measured air concentrations – adjusted for recovery, product label maximum application rate and use of personal protective equipment (PPE) when appropriate – were used to estimate short-term exposure (*i.e.*, exposures lasting from 8-hr/day for up to 1 week) (DPR, 2009): http://www.cdpr.ca.gov/docs/whs/memo/hsm09004.pdf).
Each of these air concentrations was referred to as the short-term air concentration (STAC).

Long-term exposures for each scenario were also assessed. The long-term air concentration estimates consist of the seasonal, annual, and lifetime air concentrations or SAC, AAC, and LAC, respectively. The SAC is the daily (8-hr TWA) 1,3-D breathing-zone air concentration anticipated for the use season (months where use is ≥ 5% of the annual total) in the highest use county in California. To estimate the SAC, the arithmetic means of the measured air concentrations---adjusted for recovery, estimated seasonal application rate and use of PPE when

appropriate---were utilized. The AAC is the estimated 1,3-D air concentration that a loader, applicator or re-entry worker is exposed to throughout the year. The LAC is the AAC multiplied by the assumed total number of years worked (40 years) divided by the assumed worker's lifetime of 75 years.

4. Genotoxicity (DAR level B.6.4) – DAR 08, pp. 96-136

DPR-HHAB comment: EFSA-MS reviewed multiple positive and negative genotoxicity tests, both *in vitro* and *in vivo*, concluding that there is sufficient evidence to consider 1,3-D to be potentially genotoxic. EFSA-MS summarized their position in DAR 1, p. 31:

"Although, in November 2005, the Technical Committee for Classification and Labelling agreed not to classify 1,3-D as mutagenic, unless epichlorhydrin (a known carcinogen) had been used as a stabiliser, RMS considers that taking into account the uncertainties described, the weight of evidence indicates that 1,3-D is an *in vivo* genotoxic agent (even without using epichlorhydrin as a stabilizer) for somatic cells, acting directly or after activation by cytochrome P450, and glutathione protects against the genotoxicity."

DPR-HHAB further comment: DPR agrees with EFSA-MS's statement.

5. Long-term toxicity and carcinogenicity (DAR level B.6.5) – DAR 08, pp. 153-159

DPR-HHAB comment: In its review of the Lomax *et al.* (1987) 2-yr rat inhalation toxicity study, EFSA-MS set the NOAEL at 20 ppm based on body weight decrements, olfactory epithelial pathology, and decreased total protein and albumin at 60 ppm.

DPR-HHAB further comment: DPR set the NOEL for this study at 5 ppm based on a single 20-ppm male with nasal epithelial histopathology.

6. Long-term toxicity and carcinogenicity (DAR level B.6.5) – DAR 08, pp. 172-179

DPR-HHAB comment: In its review of the Stott *et al.* (1987) 2-yr mouse inhalation toxicity study, EFSA-MS set an oncogenic NOAEL at 20 ppm based on a statistically increased incidence of pulmonary adenomas at 60 ppm.

DPR-HHAB further comment: DPR considered the nonstatistically significant rise in pulmonary adenomas at 20 ppm to be due to 1,3-D exposure. DPR would not set an oncogenic NOEL in a case like this (*i.e.*, where there is evidence of genotoxicity, irritation of the nasal

mucosa, no convincing evidence for a "biological mode of action," and statistical fit of the incidence data with the Multistage Cancer algorithm).

7. Reproductive toxicity (DAR level B.6.6) – DAR 08, pp. 193-196

DPR-HHAB comment: In its review of the John (1983) rat / rabbit developmental toxicity study, EFSA-MS set its developmental NOAEL at >120 ppm (*i.e.*, to fetotoxic effects).

DPR-HHAB further comment: DPR set a developmental NOEL at 60 ppm based on delayed ossification of the pup vertebral centrum at 120 ppm. DPR considers this type of delayed ossification to be indicative of a decrease in maternal body weight gain (r maternal weight loss at the LOEL of 120 ppm.

References

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