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Michelle Nolan
Pesticide Reevaluation Division (7508P)
Office of Pesticide Programs
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001

OPP Docket
Environmental Protection Agency
Docket Center (EPA/DC), (28221T)
1200 Pennsylvania Ave. NW
Washington, DC 20460-0001

Attention: EPA-HQ-OPP-2013-0154

RE: Pesticide Registration Review: Draft Human Health and/or Ecological Risk Assessments for Several Pesticides (1,3-Dichloropropene)

Dear Ms. Nolan:

On February 4, 2020, EPA published a notice of availability of draft risk assessments for 1,3-Dichloropropene (1,3-D).[1] The Attorneys General of California, the District of Columbia, Illinois, Minnesota, New Mexico, New York, Oregon, and Vermont have reviewed the draft risk assessments and submit these comments to the regulatory docket.

In the draft human health risk assessment, EPA downgrades 1,3-D's cancer rating from "likely to be carcinogenic to humans" to "suggestive evidence of carcinogenic potential." This change contravenes decades of consistent findings by EPA, the California Department of Pesticide Regulation (DPR), and the California Office of Environmental Health Hazard Assessment (OEHHA) that 1,3-D is a likely human carcinogen. EPA's new cancer risk classification dangerously ignores science and downplays the risks individuals face when they are exposed to 1,3-D. Before proposing to re-register 1,3-D, EPA should prepare and circulate for public comment a revised human health risk assessment that restores its prior cancer risk classification for 1,3-D and quantifies the cancer risk from all routes of 1,3-D exposure.

I. 1,3-D

1,3-D, also often known by the brand name Telone, is a fumigant commonly used as an insecticide in soil prior to planting. According to EPA data, an average of 33,755,000 pounds of 1,3-D active ingredient were applied on an average of 320,000 acres from 2013 to 2017.[2] Data from DPR further indicate that 1,3-D is one of the most-used non-organic pesticides in California in terms of total pounds applied for agricultural uses.[3]

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[1] EPA-HQ-OPP-2013-0154-0100.
[2] 1,3-Dichloropropene (Telone): Draft Human Health Risk Assessment for Registration Review, EPA-HQ-OPP-2013-0154-0102 ("EPA Draft Risk Assessment"), at 13.
[3] DPR Pesticide Use Report, Top 100 Pesticides by Pounds in Total Statewide Pesticide Use in 2017, *available at* https://www.cdpr.ca.gov/docs/pur/pur17rep/top_100_ais_lbs_2017.htm.

When 1,3-D is applied, it rapidly volatizes into the air.[4] Once in the air, 1,3-D can travel and persist as an air contaminant. The main route of human exposure to 1,3-D is bystander inhalation. When inhaled, 1,3-D can cause coughing, throat and lung irritation, and difficulty breathing.[5] Long-term exposure to 1,3-D is associated with elevated cancer risk. 1,3-D is also commonly combined with chloropicrin, another likely human carcinogen that shares the same route of exposure.[6]

Based on concerns that agricultural communities may inhale harmful amounts of 1,3-D, DPR monitors ambient air concentrations of 1,3-D in several locations across California. Although results vary seasonally and by location, they have shown elevated 1,3-D levels at certain times in agricultural communities.[7] Agricultural communities and farmworkers exposed to 1,3-D also tend to suffer from other pollution exposures and social disadvantages that make them especially susceptible to the health effects resulting from 1,3-D. For example, two communities where DPR has detected elevated levels of 1,3-D in the air, Parlier and Shafter, are also exposed to more pollution overall than 80-95% of the rest of California.[8] Furthermore, these communities have high rates of adverse health conditions, including asthma and cardiovascular disease, and they face significant socioeconomic challenges, like high poverty and unemployment rates, all of which make them more vulnerable to this disproportionate pollution exposure.[9] Because the communities most exposed to 1,3-D already face these significant disadvantages, it is especially critical that EPA accurately analyze 1,3-D's health risks.

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[4] DPR, 1,3-Dichloropropene Risk Characterization Document: Inhalation Exposure to Workers, Occupational and Residential Bystanders and the General Public, *available at* https://www.cdpr.ca.gov/docs/risk/rcd/dichloro_123115.pdf ("DPR 2015 Risk Assessment"), at 32.

[5] *Id*. at 42-43.

[6] *Id*. at 181.

[7] DPR Monitoring of 1,3-Dichloropropene in Merced and Fresno Counties Results for 2018 (2019), https://www.cdpr.ca.gov/docs/emon/airinit/monitoring_1,3-d_merced_fresno.pdf; DPR Air Monitoring Network Results for 2018 (2019), https://www.cdpr.ca.gov/docs/emon/airinit/air_monitoring_results/2018/main_report.pdf.

[8] According to CalEnviroScreen 3.0, an OEHHA screening tool that uses environmental, health, and socioeconomic information to rank every census tract in the state for pollution and vulnerability, Parlier ranks among the 5% most polluted and socially vulnerable census tracts in California and Shafter ranks among the 15% most polluted and socially vulnerable. CalEnviroScreen 3.0, *available at* https://oehha.ca.gov/calenviroscreen. *See also* Office of Environmental Health Hazard Assessment, CalEnviroScreen 3.0 Report (January 2017), *available at* https://oehha.ca.gov/media/downloads/calenviroscreen/report/ces3report.pdf

[9] CalEnviroScreen 3.0.

II. Pesticide Registration under FIFRA

All pesticides must receive regulatory approval before their use.[10] EPA registers pesticides pursuant to FIFRA, which includes several registration requirements. Most relevant here, EPA cannot register a pesticide unless it determines that the pesticide "will perform its intended function without unreasonable adverse effects on the environment," and that "when used in accordance with widespread and commonly recognized practice it will not generally cause unreasonable adverse effects on the environment."[11] These requirements are crucial to ensure that pesticides do not unreasonably harm public health or the environment.

EPA must reevaluate pesticide registrations every 15 years.[12] As part of registration review, EPA releases updated risk assessments evaluating the pesticide's impacts on public health and the environment.[13] These documents form the basis for EPA's analysis of whether the pesticide will cause unreasonable adverse effects on the environment.

III. EPA Assessments of Pesticide Carcinogenicity

EPA evaluates pesticides for carcinogenicity pursuant to guidelines most recently updated in 2005.[14] Under those guidelines, EPA classifies pesticides into five categories of cancer risk: carcinogenic to humans, likely to be carcinogenic to humans, suggestive evidence of carcinogenic potential, inadequate information to assess carcinogenic potential, and not likely to be carcinogenic to humans.[15] The highest risk category—carcinogenic to humans—requires either convincing epidemiological evidence of a causal association between human exposure and cancer or some epidemiological evidence strengthened by significant other evidence.[16] The next category—likely to be carcinogenic to humans—is used when adequate evidence demonstrates carcinogenic potential in humans, but the evidence is not sufficiently overwhelming to satisfy the highest risk category.[17] The third category—suggestive evidence of carcinogenic potential—is appropriate where there is limited evidence suggesting that a pesticide could be carcinogenic, such as where a small, but not statistically significant, increase in tumors is noted in a single animal study.[18] If a pesticide's cancer risk is classified as carcinogenic or likely to be carcinogenic to humans, EPA must quantify the cancer risk associated with exposure to the

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[10] 7 U.S.C. § 136a(a).
[11] 7 U.S.C. § 136a(c)(5)(C)-(D).
[12] 40 C.F.R. § 155.40(a).
[13] 40 C.F.R. § 155.53.
[14] EPA Guidelines for Carcinogen Risk Assessment, March 2005, *available at* https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf.
[15] *Id*. at 2-54 to -58.
[16] *Id*. at 2-54.
[17] *Id*. at 2-54 to 55.
[18] *Id*. at 2-56 to -57.

pesticide.[19] This requirement does not apply to pesticides classified as having suggestive evidence of carcinogenic potential.

To assess a pesticide's cancer risk, EPA considers several lines of evidence, depending on data availability. Different types of data EPA may evaluate include short- and long-term animal studies, studies of a pesticide's mutagenicity (its ability to induce genetic mutations) and genotoxicity (its ability to damage or mutate DNA and related systems), case reports of exposure in humans, and human epidemiological data.[20] Other relevant data may be a pesticide's physical, chemical, and structural properties, such as its pharmacokinetics or its structural similarity to other known carcinogens; and information on how a pesticide may cause carcinogenicity or genotoxicity, referred to as its mode of action.[21]

IV. For Decades, Scientific Consensus Has Considered 1,3-D A Likely Human Carcinogen.

Since at least the mid-1980s, reviews have consistently found that 1,3-D is a likely human carcinogen. EPA first described 1,3-D as a probable human carcinogen at least as early as 1985.[22] That early classification was based on two 1985 studies by the National Toxicology Program finding "clear evidence of carcinogenicity" in rats and mice, as well as two other studies finding mutagenicity and genotoxicity.[23] The next year, in 1986, EPA began a Special Review of 1,3-D based on cancer concerns for workers.[24] As a result of that Special Review, EPA placed new label restrictions on 1,3-D to reduce worker and nearby resident exposure.[25]

Building on EPA's review of 1,3-D's carcinogenicity, OEHHA listed 1,3-D as a chemical known by the State of California to cause cancer in 1989.[26] DPR then performed its own risk assessment of 1,3-D, independently concluding in 1997 that 1,3-D was a probable human

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[19] *Id*. at 3-1 to -2.
[20] *See generally id.* at 2-2 to -49.
[21] *Id*. at 2-25 to -49.
[22] *See* 1,3-Dichloropropene: Report of the Cancer Assessment Review Committee, EPA-HQ-OPP-2013-0154-0104 ("CARC Report"), at 4; 1,3-D Fact Sheet, September 1986, *available at* https://nepis.epa.gov/Exe/ZyPDF.cgi/91024KU5.PDF?Dockey=91024KU5.PDF, at 3.
[23] EPA Draft Risk Assessment, at 55. As discussed further below, the National Toxicology Program studies used a formulation of 1,3-D that included 1% epichlorohydrin, a known mutagen, as a stabilizer.
[24] 1,3-D Registration Eligibility Decision Fact Sheet, December 1998, *available at* https://archive.epa.gov/pesticides/reregistration/web/pdf/0328fact.pdf, at 2.
[25] *Id*.
[26] OEHHA, 1,3-Dichloropropene, *available at* https://oehha.ca.gov/chemicals/13-dichloropropene.

carcinogen.[27] In its review, DPR relied on the earlier studies considered by EPA, but it also incorporated additional animal studies submitted by Dow (1,3-D's manufacturer), new studies of 1,3-D's genotoxicity, and a study of first responders to a 1,3-D tank spill who later developed cancer.[28] DPR additionally noted 1,3-D's structural similarity to other known carcinogens.[29]

Both EPA and DPR have since reaffirmed their original evaluations. EPA reconvened its Peer Review Committee in 1989 and found that new inhalation studies in rats and mice confirmed 1,3-D's classification as a probable human carcinogen.[30] EPA also updated its risk assessment in 2005, again classifying 1,3-D as "likely to be carcinogenic to humans."[31] EPA determined that its prior findings were bolstered by several studies showing that 1,3-D is a mutagen or genotoxic. Notably, EPA rejected Dow's theory that the tumors seen in the animal studies were caused by something other than 1,3-D's carcinogenicity, because EPA found that the data showed that 1,3-D acts as a mutagen, raising the inference that 1,3-D's mutagenicity causes cancer.[32] As EPA stated, 1,3-D "acts as a genotoxic agent consistent with the carcinogenicity pattern seen throughout the database."[33]

DPR bolstered these—and all prior—conclusions that 1,3-D likely causes cancer in its latest risk assessment in 2015.[34] In over 15 pages of primary analysis, DPR considered new animal and genotoxicity studies, as well as a 2003 epidemiological study that found a strong correlation between exposure to 1,3-D and pancreatic cancer deaths in several California agricultural counties. Although several of the new studies were submitted by Dow to refute 1,3-D's carcinogenicity, DPR found that the weight of the evidence clearly supported the finding that 1,3-D was a likely human carcinogen. As DPR summarized, "there is little uncertainty regarding 1,3-D's ability to induce tumors in a variety of tissues, species and exposure routes."[35]

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[27] DPR, Risk Assessment of 1,3-Dichloropropene (1997), *available at* https://www.cdpr.ca.gov/docs/risk/rcd/dichloro.pdf ("DPR 1997 Risk Assessment"), at 6-7.
[28] *Id*.
[29] *Id*. at 6.
[30] EPA Health Effects Division Peer Review Committee, Second Peer Review of Telone II, Dec. 8, 1989, *available at* https://www3.epa.gov/pesticides/chem_search/cleared_reviews/csr_PC-029001_8-Dec-89_073.pdf ("1989 HED Report"), at 1. Notably, these new inhalation studies administered a formulation of 1,3-D that did not contain epichlorohydrin.
[31] 1,3-Dichloropropene: HED Human Health Risk Assessment for Phase 2, EPA-HQ-OPP-2005-0124-0004, at 17. EPA revised its classification system between 1986 and 2005, resulting in the slightly different wording, but this classification was essentially equivalent to the prior one.
[32] *Id*.
[33] *Id*. at 18.
[34] DPR 2015 Risk Assessment.
[35] *Id*. at 178.

V. EPA's Draft Human Health Risk Assessment Improperly Downgrades 1,3-D's Cancer Risk Classification.

EPA's new draft risk assessment turns all of this previous science on its head. Contrary to decades of prior risk assessments by multiple different agencies, EPA now suggests for the first time that there is only "suggestive evidence of [1,3-D's] carcinogenic potential." EPA reaches this conclusion by improperly excluding entire categories of evidence that it and DPR had previously found relevant, changing its position on 1,3-D's mutagenicity without sufficient new evidence, and crediting an unsupported Dow theory that 1,3-D induces tumors only above a high exposure threshold.

A. EPA Improperly Refuses to Consider Entire Categories of Evidence It Had Previously Found Relevant.

In past risk assessments, EPA and DPR have considered extensive databases of studies, including independent and peer reviewed studies, and found that the evidence demonstrates 1,3-D's likely carcinogenicity. Here, however, EPA restricts the evidence it considers to roll back 1,3-D's health-protective cancer classification. Specifically, EPA proposes to exclude the foundational studies of 1,3-D's carcinogenicity and never mentions studies of 1,3-D's links to cancer in humans. Having omitted all other studies from consideration, EPA's carcinogenicity determination is now based entirely on industry-sponsored studies.

The first animal studies of 1,3-D's carcinogenicity were conducted by the National Toxicology Program (NTP) in 1985.[36] The NTP, run by the U.S. Department of Health and Human Services, aims to identify toxic substances and further public knowledge of their hazards. To further public knowledge of 1,3-D, it ran two-year studies in which it found "clear evidence of carcinogenicity" in male rats and female mice following oral administration.[37] The NTP also found "some evidence of carcinogenicity" in female rats.[38] These studies informed EPA's earliest determination that 1,3-D is a likely human carcinogen, and they have been central to all cancer risk classifications by EPA and DPR since.[39]

Faced with this evidence, Dow conducted its own two-year studies of oral 1,3-D administration in mice and rats in 1995. Even though Dow conspicuously omitted the highest dose in the NTP studies—the dose that found the highest cancer rates—from its rat study, the study still found statistically significant increases in cancer rates in both male and female rats.[40]

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[36] *Id*. at 177-78.
[37] EPA Draft Risk Assessment at 55.
[38] *Id.*
[39] *See, e.g.*, 1989 HED Report, at 3-4, 13, 15; DPR 1997 Risk Assessment, at 7.
[40] Although others have determined that Dow's 1995 rat study found "a notable increase in benign adenomas" in females, DPR 2015 Risk Assessment at 72, EPA here argues that the statistically significant increase in cancer in females was not treatment-related because it "was at the high end of the historical control range." CARC Report at 12.

Dow's 1995 mouse study found no evidence of carcinogenicity, but even in the draft risk assessment EPA acknowledges that it is "not adequate for assessment" because it was poorly designed and conducted.[41]

EPA now omits the foundational NTP studies from its review. EPA argues that those studies must be excluded because the 1,3-D formulation at the time contained 1% epichlorohydrin, a known carcinogen, as a stabilizer. But this issue was known even in 1985 when EPA first classified 1,3-D as a probable human carcinogen—Dow removed the 1% epichlorohydrin from its 1,3-D formulation in 1983.[42] All prior cancer reviews by EPA and DPR have addressed this objection and, despite Dow's insistence, have determined that it did not nullify the NTP study results. For example, in its 2015 risk assessment, DPR acknowledged that epichlorohydrin "has oncogenic properties of its own," but found that "it is unlikely that it was present in sufficient quantities to be responsible for the [cancer findings in the NTP studies]."[43] Similarly, prior EPA reviews noted that NTP recognized in 1985 that epichlorohydrin "may be partially responsible" for the carcinomas seen in the rat forestomach because a study has linked epichlorohydrin with that effect, but that it does not explain the other observed tumors.[44] EPA dealt with this issue by not using the forestomach carcinoma data to quantify cancer risk, instead basing that assessment on data from the tumors not linked to epichlorohydrin.[45]

EPA's explanation for excluding the NTP studies now is significantly less robust than these prior discussions of the same issue. EPA now simply asserts without further analysis that the NTP studies cannot be used because they administered an old 1,3-D formulation that included a known carcinogen. But the NTP studies provide useful data that should inform the cancer risk classification. Indeed, all past cancer risk assessments considered the NTP studies despite their use of a formulation containing epichlorohydrin and discussed how that fact influenced their interpretation of the results. EPA does not mention, much less refute, any of these prior discussions. EPA's decision to wholesale exclude the foundational studies of 1,3-D's carcinogenicity—particularly when the remaining studies EPA does consider are funded by Dow and have shortcomings themselves—is unjustified.

EPA also inappropriately omits all studies linking 1,3-D to cancer in humans. Most significantly, a study by Clary and Ritz in 2003 used DPR's Pesticide Use Report to examine

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[41] EPA Draft Risk Assessment at 55. Despite this finding, the Cancer Assessment Review Committee relies in part on the 1995 mouse study's negative result to conclude that there is no suggestive evidence of 1,3-D's carcinogenicity.
[42] CARC Report at 4.
[43] DPR 2015 Risk Assessment, at 178 (citing Konishi, Y., Kawabata, A., Denda, A., Ikeda, T., Katada, H., and Maruyama, H., *Forestomach tumors induced by orally administered epichlorohydrin in male Wistar rats*, GANN Journal of Japanese Cancer Research, 71:922-923 (1980)).
[44] EPA Toxicological Review of 1,3-Dichloropropene (2000), *available at* https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0224tr.pdf, at 28, 38, 50.
[45] *Id*. at 50.

correlations between pesticide exposure and pancreatic cancer in three agricultural counties in California.[46] In that study, 1,3-D exposure had the highest odds ratio for pancreatic cancer mortality of all of the pesticides studied.[47] Another paper, by Markovitz and Crosby in 1984, reported two fatal cases of lymphoma that developed in first responders six years after they responded to a 1,3-D tank truck spill.[48] While the Markovitz 1984 evidence is anecdotal, the authors also noted structural similarities between 1,3-D and two known human carcinogens.[49] DPR in its 2015 risk assessment found that both of these studies implicated 1,3-D in human oncogenesis, but EPA inexplicably makes no mention of either of these studies. EPA must include these and all studies it excluded for using a 1,3-D formulation with epichlorohydrin in its revised risk assessment.

B. EPA's Changed Position on 1,3-D's Genotoxicity Lacks Justification.

EPA also proposes to reverse its prior position that 1,3-D is genotoxic and mutagenic without sufficient justification. Here too EPA's assessment improperly eliminates all of the studies demonstrating 1,3-D's genotoxicity with little explanation. As in its analysis of the animal studies, EPA excludes relevant studies that used 1,3-D with epichlorohydrin as a stabilizer. That issue is addressed generally above—EPA should not exclude studies that provide relevant information, even if the studies used epichlorohydrin as a stabilizer or have other imperfections. Excluded studies include an *in vivo* mutagenicity study conducted by NTP finding that 1,3-D induced chromosomal mutations in mice—a study DPR considered.[50] As EPA's conclusion that 1,3-D is not genotoxic rests on "clear negative findings for mutagenicity *in vivo*," omission of these NTP data is particularly notable.[51]

EPA also excludes studies that used dimethyl sulfoxide (DMSO) as a solvent. However, DMSO is a widely-accepted and used solvent in the Ames Test despite its moderate cytotoxicity. EPA has not raised this concern in prior assessments when it evaluated the exact same studies, even though DMSO's cytotoxicity has been known for decades. Yet, here EPA uses its DMSO argument to exclude a swathe of relevant studies demonstrating that 1,3-D is a mutagen. EPA provides the absurd excuse that the results must all be false positives, which is not likely to coincidentally occur across all of the studies EPA excludes even if DMSO had a confounding effect. Notably, EPA does not exclude the results of one assay that used DMSO as a solvent

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[46] DPR 2015 Risk Assessment, at 178 (citing Clary, T., and Ritz, B., *Pancreatic cancer mortality and organochlorine pesticide exposure in California, 1989-1996*, American Journal of Industrial Medicine, 43:306-313 (2003)).
[47] *Id*.
[48] DPR 2015 Risk Assessment, at 178 (citing Markovitz, A., and Crosby, W. H., *Chemical carcinogenesis: a soil fumigant, 1,3-dichloropropene, as possible cause of hematologic malignancies*, Archives of Internal Medicine, 144:1409-1411 (1984)).
[49] *Id*.
[50] DPR 2015 Risk Assessment, at 84.
[51] CARC Report, at 38.

because its finding was negative, without reciprocally considering the possibility of a false negative.[52]

In addition, EPA's overall analysis of the genotoxicity studies is shallow. For example, EPA notes that "[m]any investigators have reported on the mutagenicity of 1,3-D in the Ames assay," but it dismisses these reports on the uncited and unexplained basis that "[s]ome authors have proposed that polar impurities were responsible for the mutagenicity."[53] If anything, EPA's extraordinary decision to exclude from consideration every single test result demonstrating that 1,3-D acts as a mutagen demands more discussion, not less. EPA's two brief paragraphs in which it asserts, but does not explain, that all of the studies showing positive results suffer from technical flaws, are plainly inadequate.

Similarly, for its affirmative conclusion that 1,3-D is not a mutagen, EPA relies almost entirely on a new study it barely describes. EPA's description of the study procedure is so minimal that its adequacy cannot be verified. Moreover, the only results EPA reveals are that five rats in each of the four groups were analyzed for mutations, and that "[t]here was no *statistically significant* increase in mutations in the target tissues."[54] Statistical significance is a demanding standard to reach with a sample size of five. For example, the data could have showed a trend that, because mutations were or were not observed in a single rat, failed to reach statistical significance. EPA's limited description does not supply the needed clarity, and, regardless, the database with this single study added still does not warrant the conclusion that 1,3-D is not a mutagen.

By contrast, DPR in its 2015 risk assessment devotes a 24-page appendix to the technical details of the numerous genotoxicity and mutagenicity tests, including procedural objections like those EPA raises. Moreover, DPR's primary evaluation of 1,3-D's genotoxicity spans nine pages and reviews the strengths and weaknesses of all studies, including those that run counter to its ultimate finding. This thorough analysis led DPR to the conclusion—consistent with its and EPA's previous assessments—that "[c]ollectively, these studies provide convincing evidence that 1,3-D, its oxidative metabolites and autoxidation products have genotoxic potential."[55] As DPR summarized, "there is ample evidence both from *in vitro* and *in vivo* testing to suggest that 1,3-D is in fact genotoxic."[56]

C. EPA Erroneously Dismisses Evidence of 1,3-D's Carcinogenicity Based on a Flawed Dow Theory.

EPA also erroneously disregards further evidence of 1,3-D's carcinogenicity when it adopts for the first time Dow's theory of a kinetically-derived maximum tolerated dose (KMD).

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[52] *Id*.
[53] *Id*. at 37-38.
[54] *Id*. at 38 (emphasis added).
[55] DPR 2015 Risk Assessment, at 77.
[56] *Id*. at 179.

In 1987, Dow conducted inhalation studies of mice and rats in which it administered 0, 5, 20, and 60 parts per million (ppm) of 1,3-D.[57] In the mouse study, results showed a statistically significant increased incidence of bronchioloalveolar adenomas in male mice administered 60 ppm 1,3-D.[58] Male mice in the 20 ppm group also exhibited high rates of bronchioloalveolar tumors (27%) outside the historical control range, though this observation fell short of statistical significance due to high incidence in the control group (16%).[59] Past risk assessments by EPA and DPR have considered this study sufficient and supportive of 1,3-D's classification as a likely human carcinogen.[60]

In this registration review, Dow argued to EPA that the agency should not consider results from the 60 ppm group because that dose exceeded the KMD. Specifically, Dow asserted that the 60 ppm dose was so high that the mice's systemic clearance mechanisms were saturated—i.e., their biological mechanisms for processing the chemical were overwhelmed. According to Dow, when the mice's systems were saturated, other biological havoc occurred that caused the observed cancers. Therefore, Dow's argument goes, the tumors found in mice given 1,3-D were caused by something other than 1,3-D's carcinogenicity.

To attempt to substantiate this theory, Dow submitted two studies that measured 1,3-D blood levels in mice that inhaled 1,3-D at various doses. Dow contended, without evidence, that saturation of clearance mechanisms occurred where mice's dose-blood level relationship shifted from linear to nonlinear. The point at which the dose-blood level curves became nonlinear, Dow asserted, was the kinetically-derived maximum tolerated dose, or KMD. In the draft risk assessment, EPA accepts Dow's contention and omits the inhalation study's carcinogenicity finding from its analysis.[61]

Dow's argument—and thus EPA's conclusion—is deeply flawed for six reasons. First, use of the KMD theory is controversial and not currently accepted as reliable by the broader scientific community. As DPR noted in its 2015 risk assessment, "[s]everal recent reviews on the general issue of the absence or presence of thresholds in chemical carcinogenesis emphasized the difficulty of convincingly establishing thresholds in oncogenesis, especially considering the complications of hormetic effects, metabolism and the statistical power inherent in standard study designs."[62] Unless and until the KMD theory is more established, EPA should primarily

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[57] EPA Draft Risk Assessment, at 25.
[58] *Id*. at 26.
[59] *Id*.
[60] *See, e.g.*, DPR 2015 Risk Assessment, at 65-66.
[61] EPA Draft Risk Assessment, at 34.
[62] DPR 2015 Risk Assessment, at 179 (citing Purchase, I. F. H., and Auton, T. R., *Thresholds in chemical carcinogenesis*, Regulatory Toxicology and Pharmacology, 22:199-205 (1995); Fukushima, S., Kinoshita, A., Puatanachokchai, R., Kushida, M., Wanibuchi, H., and Morimura, K., *Hormesis and dose-response-mediated mechanism in carcinogenesis: evidence for a threshold in carcinogenicity of non-genotoxic carcinogens*, Carcinogenesis, 26:1835-1845 (2005); Neuman, H.-G., *Risk assessment of chemical carcinogens and thresholds*, Critical Reviews in Toxicology 39:449-461 (2009)).

derive maximum tolerated doses based on standard criteria, such as observation of an overly toxic response to a dose. If EPA elects to consider a KMD theory, it should demand heightened proof to ensure its conclusions are scientifically defensible.

Second, EPA need not resort to a KMD theory to account for any alleged nonlinear dose-response. Nonlinear relationships are fairly common and can be handled by existing methods. Using the existing database, EPA can model nonlinear dose-response, which would inform knowledge of 1,3-D's carcinogenicity at doses below 60 ppm or any other possible maximum tolerated dose. Such an approach also has the advantage of not predetermining the absence of cancer risk at lower doses. EPA's decision to entirely discount data because it demonstrates a nonlinear relationship is atypical and demands commensurate justification.

Third, EPA's adoption of Dow's KMD theory contradicts EPA's own Guidelines for Carcinogen Risk Assessment. Under those guidelines, "[a] nonlinear approach should be selected when there are sufficient data to ascertain the mode of action and conclude that it is not linear at low doses and the agent does not demonstrate mutagenic or other activity consistent with linearity at low doses."[63] 1,3-D's mode of carcinogenesis is unproven and 1,3-D is a mutagen. EPA plainly states in its review that "[n]o tumor mode of action data were submitted for 1,3-D."[64] And, as discussed above, strong evidence supports the conclusion that 1,3-D is a mutagen. EPA's use of a nonlinear dose-response curve is therefore inappropriate according to EPA's own Guidelines.

Fourth, even if it is acceptable to use a KMD theory in certain circumstances, it is not warranted here. Dow submitted two studies to support its assertion that systemic clearance mechanisms are saturated at inhalation doses of 60 ppm in mice: a systemic absorption/bioavailability study of inhaled 1,3-D and a steady state pharmacokinetics study. As EPA noted, the two studies' results conflicted. The steady state pharmacokinetics study indicated that blood concentrations transition from linearity to nonlinearity at an upper confidence interval bound of 39.1 ppm.[65] However, the systemic absorption/bioavailability study "indicated that the only dose level that caused nonlinearity in the dose response curve was 150.0 ppm."[66] Accordingly, "an analysis including the highest dose level as 59.8 ppm would not result in a nonlinear dose response curve," and "the results … do not adequately support Dow's proposal that the dose level of 59.8 ppm should be excluded."[67] Moreover, the "data also do not support a role of either decreased respiratory delivery or saturated systemic clearance until exposures greater than 59.8 ppm."[68] In fact, "it was not possible to discern between the 19.8 and

[63] EPA Guidelines for Carcinogen Risk Assessment, at 3-22.
[64] CARC Report at 42.
[65] *Id*. at 34.
[66] *Id*. at 32.
[67] *Id*.
[68] *Id*.

59.8 ppm treatment groups."[69] EPA therefore cannot conclude—much less affirm with "high confidence"—that the dose-response curve is nonlinear at exposure levels of 40 ppm and above.

Fifth, even if it were not contradicted by the systemic absorption/bioavailability study, the steady state pharmacokinetics study alone does not prove Dow's KMD theory. The steady state pharmacokinetics study estimates the exposure concentrations at which blood concentrations of 1,3-D and its isomers transition from linear to non-proportionality. At most, that study design can suggest nonlinear dose response above a certain dose. It cannot, however, prove Dow's theory that clearance mechanisms are saturated above that dose—saturation of clearance mechanisms is one of many possible explanations for nonlinearity, but Dow simply assumes it to be true. Accordingly, EPA errs in finding that the steady state pharmacokinetic study alone is sufficient to adopt Dow's KMD theory.

Finally, even if Dow is correct that the 60 ppm dose exceeded the maximum tolerated dose such that the resulting data should be excluded, the inhalation study showed concerning results at lower doses. Male mice experienced elevated levels of bronchioloalveolar tumors at the 20 ppm dose. While tumor incidence at the upper end of the historical control range in the control group precluded a finding of statistical significance, the percentage of animals with tumors at the 20 ppm dose lay firmly outside the historical control range. At minimum, these results alone constitute the type of "small, and possibly not statistically significant, increase in tumor incidence observed in a single animal [study]" that EPA considers sufficient to establish a "suggestive evidence of carcinogenic potential" classification. When combined with the wealth of other evidence elaborating 1,3-D's carcinogenic effects—the NTP studies, the 1995 Dow study in rats, and the evidence of genotoxicity are just a few examples—the mouse inhalation study bolsters the conclusion that 1,3-D is a likely human carcinogen.

VI. EPA Must Restore 1,3-D's Prior Cancer Risk Classification and Quantify the Cancer Risk of Exposure to 1,3-D.

As demonstrated above, EPA's proposal to downgrade 1,3-D's cancer classification is unsupported by the evidence. An administrative agency must give adequate reasons for its decisions, and "must examine the relevant data and articulate a satisfactory explanation for its action including a rational connection between the facts found and the choice made."[70] As here, where an agency reverses course, it is "obligated to supply a reasoned analysis for the change"[71] and show that "there are good reasons" for the reversal.[72] Moreover, EPA must "provide a more detailed justification than what would suffice for a new policy created on a blank slate" because "its new policy rests upon factual findings that contradict those which underlay its prior

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[69] *Id*.
[70] *Motor Vehicle Mfrs. Ass'n of U.S.,Inc. v. State Farm Mutual Automobile Ins. Co.*, 463 U.S. 29, 43 (1983).
[71] *Id*. at 42.
[72] *F.C.C. v. Fox Television Stations, Inc.*, 556 U.S. 502, 515 (2009)

policy."[73] If EPA proposes re-registration of 1,3-D based on the erroneous cancer risk classification, it may also violate FIFRA, which bars registrations that would "cause unreasonable adverse effects on the environment."[74] EPA must therefore restore 1,3-D's cancer risk classification as likely to be carcinogenic to humans and quantify the cancer risk of exposure to 1,3-D. Before proposing to re-register 1,3-D, EPA should recirculate its revised 1,3-D human health risk assessment for public review and comment.

VII. Conclusion

The undersigned Attorneys General are committed to protecting the health of all individuals in their states. Because 1,3-D is heavily used in many agricultural operations, 1,3-D exposure tends to be disproportionately concentrated among farmworkers and residents of disadvantaged agricultural communities that are especially susceptible to the resulting health effects. EPA has a particular responsibility to those communities to faithfully follow the science and accurately describe the cancer risks of 1,3-D exposure. In accordance with the evidence, EPA must classify 1,3-D as likely to be carcinogenic to humans and quantify the cancer risks of 1,3-D exposure before proposing to re-register 1,3-D.

Sincerely,

ROBERT D. SWANSON
Deputy Attorney General

For XAVIER BECERRA
California Attorney General

STEVE NOVICK
Special Assistant Attorney General

For ELLEN ROSENBLUM
Oregon Attorney General

[73] *Id*.
[74] 7 U.S.C. § 136a(c)(5)(D).

PETER N. SURDO
Special Assistant Attorney General

For KEITH ELLISON
Minnesota Attorney General

NICHOLAS F. PERSAMPIERI
Assistant Attorney General

For THOMAS J. DONOVAN
Vermont Attorney General

ROBERT F. LUNDIN
Special Assistant Attorney General

For HECTOR H. BALDERAS
New Mexico Attorney General

MATTHEW J. DUNN
Chief, Environmental Enforcement/Asbestos
Litigation Division

JASON E. JAMES
Assistant Attorney General

For KWAME RAOUL
Illinois Attorney General

KATHLEEN KONOPKA
Deputy Attorney General

For KARL RACINE
District of Columbia Attorney General

LAURA MIRMAN-HESLIN
Assistant Attorney General

For LETICIA JAMES
New York Attorney General