OFFICE OF INSPECTOR GENERAL
U.S. ENVIRONMENTAL PROTECTION AGENCY

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Hotline Report:
Ensuring the safety of chemicals

The EPA Needs to Improve the Transparency of Its Cancer-Assessment Process for Pesticides

Report No. 22-E-0053 **July 20, 2022**

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Abbreviations:

1,3-D	1,3-Dichloropropene
CARC	Cancer Assessment Review Committee
C.F.R.	Code of Federal Regulations
EPA	U.S. Environmental Protection Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
KMD	Kinetically Derived Maximum Dose
OCSPP	Office of Chemical Safety and Pollution Prevention
OIG	Office of Inspector General
OMB	Office of Management and Budget
OPP	Office of Pesticide Programs
PRIA	Pesticide Registration Improvement Act
U.S.C.	United States Code

Cover Image:

Left: Field being tarped in preparation for soil fumigant application. *Top right*: Tarped field and sign indicating that the field is being or has been fumigated and that no one should enter. *Bottom right*: The edge of a buffer zone, an area around a field that is off-limits during the fumigant application and for a specified period of time after the application is complete. (EPA photos)

Office of Inspector General
U.S. Environmental Protection Agency
At a Glance

22-E-0053
July 20, 2022

Why We Did This Evaluation

We performed this evaluation to examine the extent to which the U.S. Environmental Protection Agency followed policies and procedures in developing the cancer assessment for the 1,3-Dichloropropene pesticide-registration-review decision to prevent unreasonable adverse effects on human health. We initiated this evaluation based on multiple complaints submitted to the Office of Inspector General Hotline.

The Federal Insecticide, Fungicide, and Rodenticide Act requires the EPA to review every pesticide registration no later than 15 years after the active ingredient's initial registration to determine whether the pesticide continues to meet the statutory standard—that is, whether the pesticide performs its intended function without unreasonable adverse effects on human health and the environment. When registered pesticides are reviewed as part of the 15-year registration review process, the EPA does not typically initiate a new cancer assessment unless requested by the registrant through the Pesticide Registration Improvement Act.

This evaluation supports an EPA mission-related effort:

- *Ensuring the safety of chemicals.*

This evaluation addresses these top EPA management challenges:

- *Ensuring the safe use of chemicals.*
- *Safeguarding scientific integrity.*

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List of OIG reports.

The EPA Needs to Improve the Transparency of Its Cancer-Assessment Process for Pesticides

What We Found

Deficiencies and a lack of transparency in the 1,3-D pesticide cancer-assessment process has undermined scientific credibility and public confidence.

The EPA did not adhere to standard operating procedures and requirements for the 1,3-Dichloropropene, or 1,3-D, pesticide cancer-assessment process, which undermines public confidence in and the transparency of the Agency's scientific approaches to prevent unreasonable impacts on human health. Specifically, the EPA used two scientific approaches, kinetically derived maximum dose and weight-of-evidence, in its cancer-assessment process for 1,3-D, even though it did not have guidance outlining how to use those approaches. The EPA also did not adhere to docketing and transparency requirements to provide the public and stakeholders with information that may have influenced the EPA's cancer-assessment decision. Further, the EPA did not follow its literature-search procedures and neglected to document its review of all health effects data that may have impacted the results of the 1,3-D draft human health risk assessment, which is informed by the cancer assessment. The EPA's Cancer Risk Assessment Committee did not adhere to the EPA's *Peer Review Handbook* and the Office of Management and Budget's guidance on peer review in the areas of composition, independence, and expertise. These deficiencies undermined the scientific credibility of the 1,3-D cancer assessment, which led to questioning by multiple stakeholders. An external peer review would have improved the credibility of the 1,3-D cancer assessment.

Recommendations and Planned Agency Corrective Actions

We make nine recommendations to improve the transparency of the 1,3-D cancer-assessment process and restore the scientific credibility of the Agency's 1,3-D cancer classification. These recommendations address the lack of guidance for the EPA's use of the kinetically derived maximum dose and weight-of-evidence approaches, an incomplete public docket, an incomplete literature search, noncompliance with internal peer review standards, and the need for an external peer review. These recommendations will also improve the EPA's cancer-assessment process for pesticides more broadly.

The EPA was not in full agreement with Recommendations 1, 2, and 8, which remain unresolved. We are in discussions with the EPA on the unresolved recommendations. The EPA generally agreed with Recommendations 3–7 and 9, which are resolved with corrective actions pending.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

THE INSPECTOR GENERAL

July 20, 2022

MEMORANDUM

SUBJECT: The EPA Needs to Improve the Transparency of Its Cancer-Assessment Process for Pesticides
Report No. 22-E-0053

FROM: Sean W. O'Donnell

TO: Michal Ilana Freedhoff, Assistant Administrator
Office of Chemical Safety and Pollution Prevention

This is our report on the subject evaluation conducted by the U.S. Environmental Protection Agency's Office of Inspector General. The project number for this evaluation was OSRE-FY21-0214. This report contains findings that describe the problems the OIG has identified and corrective actions the OIG recommends. Final determinations on matters in this report will be made by EPA managers in accordance with established audit resolution procedures.

The Office of Chemical Safety and Pollution Prevention is primarily responsible for the issues discussed in this report, which contains nine recommendations. In accordance with EPA Manual 2750, your office provided acceptable planned corrective actions and estimated milestone dates for Recommendations 3–7 and 9. These recommendations are resolved.

Action Required

Recommendations 1, 2, and 8 are unresolved. EPA Manual 2750 requires that recommendations be resolved promptly. Therefore, we request that the EPA provide us within 60 days its responses concerning specific actions in process or alternative corrective actions proposed on the recommendations. Your response will be posted on the OIG's website, along with our memorandum commenting on your response. Your response should be provided as an Adobe PDF file that complies with the accessibility requirements of section 508 of the Rehabilitation Act of 1973, as amended. The final response should not contain data that you do not want to be released to the public; if your response contains such data, you should identify the data for redaction or removal along with corresponding justification. The Inspector General Act of 1978, as amended, requires that we report in our semiannual reports to Congress on each audit or evaluation report for which we receive no Agency response within 60 calendar days.

We will post this report to our website at www.epa.gov/oig.

Table of Contents

Chapters

Appendixes

Chapter 1
Introduction

Purpose

The U.S. Environmental Protection Agency's Office of Inspector General initiated this evaluation to examine the extent to which the EPA followed policies and procedures in developing the cancer assessment for the 1,3-Dichloropropene, or 1,3-D, pesticide-registration-review decision to prevent unreasonable adverse effects on human health. This evaluation was initiated based on multiple complaints submitted to the OIG Hotline.

Top Management Challenges Addressed

This evaluation addresses the following top management challenges for the Agency, as identified in OIG Report No. 22-N-0004, *EPA's Fiscal Year 2022 Top Management Challenges*, issued November 12, 2021:

- Ensuring the safe use of chemicals.
- Safeguarding scientific integrity.

Background

1,3-D is an agricultural pesticide used as a soil fumigant to primarily control nematodes, which are also known as roundworms, affecting the roots of plants. 1,3-D was first registered as a pesticide in 1954. In September 2013, the EPA initiated a registration review process for 1,3-D. As of March 2022, there were 49 active registered pesticide products on the market containing 1,3-D. It is registered for all types of food and feed crops, including vegetables; fruit and nut crops; tobacco; and forage crops, such as grass and legumes. It is not registered for household use.

1,3-D is one of the top three soil fumigants used in the United States. From 2014 through 2018, an average of approximately 37 million pounds of 1,3-D were applied to an average of 300,000 acres of agricultural crops annually. 1,3-D is mainly applied to the crops illustrated in Figure 1.

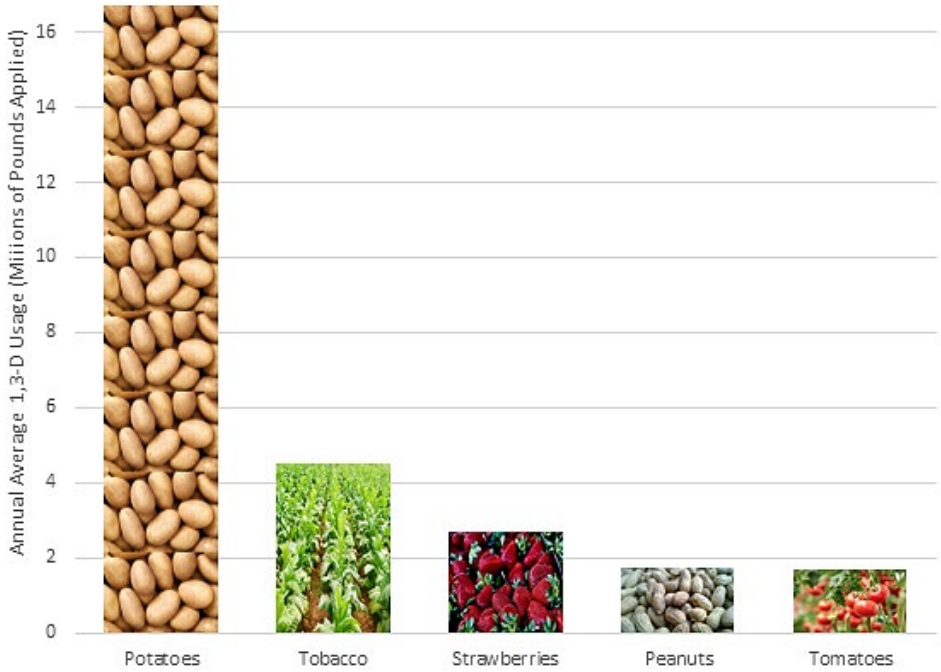
What Are Soil Fumigants?

Soil fumigants are a type of pesticide that, when applied to soil, form a gas to control pests that live in the soil. These pests can disrupt plant growth and crop production.

Soil fumigants are used to help control:

- Nematodes
- Insects
- Fungi
- Weeds
- Bacteria

Figure 1: Crops on which 1,3-D is mainly applied*

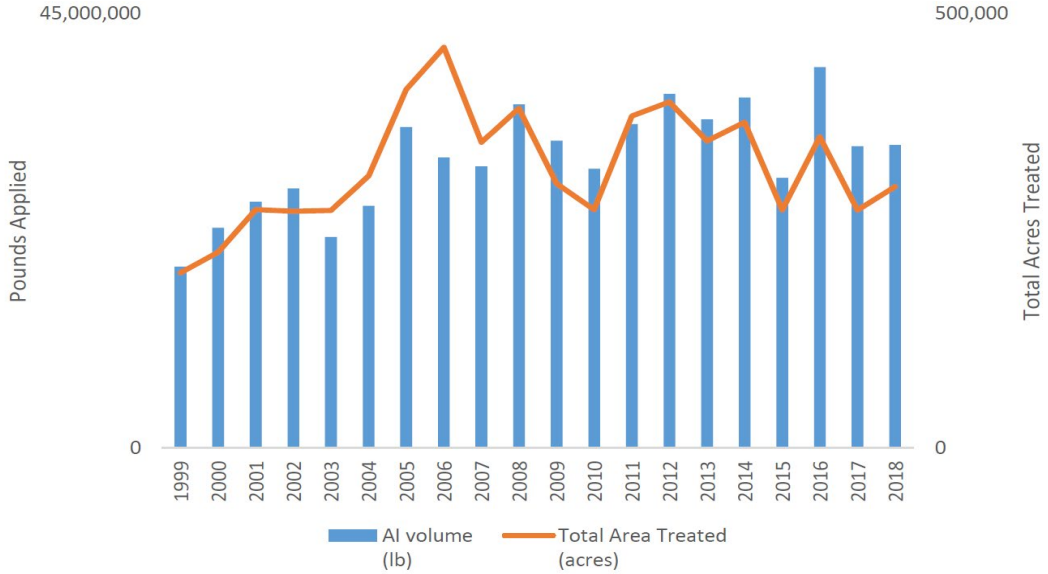


Source: OIG analysis based on EPA information. (EPA OIG image)

* National annual average from 2013 through 2017.

1,3-D is classified as a "Restricted Use Pesticide" by the EPA, which means that it may only be applied by certified applicators or under the supervision of a certified applicator. Nationally, 1,3-D agricultural use, measured by pounds of active ingredient applied, increased nearly 40 percent from 2001 through 2017. Figure 2 illustrates the total pounds of the 1,3-D active ingredient applied and the total acres treated from 1999 through 2018 in the United States.

Figure 2: Total pounds of 1,3-D's active ingredient applied; total acres treated



Source: EPA. (EPA image)

Note: Active ingredient (AI) is 1,3-D.

1,3-D Exposure and Human Health Risks

Workers may be exposed to 1,3-D during manufacturing, formulation, or application of the pesticide. The general public may be exposed to it by breathing near application areas or by consuming contaminated drinking water from wells. Acute inhalation exposure to high concentrations of 1,3-D is known to result in upper respiratory symptoms, including chest tightness and pain, difficulty breathing, irritated and watery eyes, and dizziness. Chronic dermal exposure may result in skin sensitization.

From 1985 through 2018, the EPA classified 1,3-D as "Likely to be Carcinogenic to Humans," which means that there is evidence of carcinogenic potential in two or more different species, sexes, or strains, or from two or more different sites or exposure routes.[1] With this classification, the EPA quantified 1,3-D's cancer risk, which was used to identify acceptable exposure levels, at the one-in-10,000 excess lifetime cancer risk level, meaning that if 10,000 people are exposed to the same concentration of this chemical over an estimated lifetime, one additional person would likely develop cancer from this exposure. In 2019, the EPA changed the classification for 1,3-D to "Suggestive Evidence of Carcinogenic Potential," which means that there is evidence of tumors in only a single animal cancer study or only at a single dose. With this classification change, the EPA does not quantify the chemical's cancer risk and establishes acceptable exposure levels based only on noncancerous effects. The cancer reclassification of 1,3-D allows the long-term exposure level considered an unreasonable risk to humans to increase 90-fold.

Changes to the cancer classification impact many aspects of a pesticide registration to address safety, including application rate; personal protective equipment—such as respirators, pants, and gloves—that applicators must wear; training requirements for applicators; and method of application, such as aerial spray. It may also impact the time farmers have to wait before they can safely reenter their fields after the pesticide is applied, such as 24 hours instead of one week.

Classification of Carcinogens

Under the 2005 *Guidelines for Carcinogen Risk Assessment*, the EPA classifies a chemical's carcinogenic potential as one of five categories:

- Carcinogenic to humans.
- Likely to be carcinogenic to humans.
- Suggestive evidence of carcinogenic potential.
- Inadequate information to assess carcinogenic potential.
- Not likely to be carcinogenic to humans.

A chemical's carcinogenic category determines how the EPA manages the public health risk posed by the chemical.

The Pesticide-Registration-Review Process

The Federal Insecticide, Fungicide, and Rodenticide Act, or FIFRA, section 3(g)(1)(A),[2] established the pesticide-registration-review program. FIFRA requires the EPA to review every pesticide registration no later than 15 years after the active ingredient's initial registration to determine whether the registered pesticide continues to meet the statutory standard—that is, whether the pesticide will perform its

[1] The EPA's cancer classification system has changed since 1,3-D was initially assessed, but 1,3-D's classification never effectively changed until the EPA reassessed and downgraded its cancer classification in 2019.
[2] 7 U.S.C. § 136a(g)(1)(A).

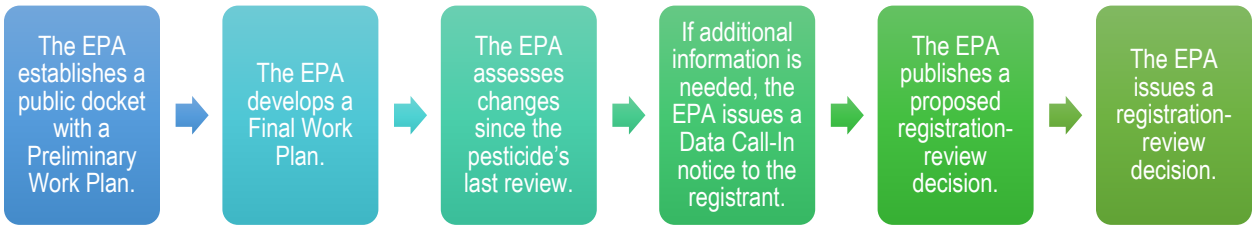
intended function without unreasonable adverse effects on human health and the environment. Per EPA regulations:

> Registration review is intended to ensure that each pesticide's registration is based on current scientific and other knowledge regarding the pesticide, including its effects on human health and the environment.[3]

For all pesticides registered as of October 1, 2007—like 1,3-D—the EPA must complete a pesticide-registration review by October 1, 2022. In December 2021, the EPA announced that, for some pesticides, it anticipated that its "review will extend beyond October 1, 2022 due to a number of challenges including delays in receiving data from registrants; the demands of responding to COVID-19; and a significant increase in recent years of resources devoted to litigation." The EPA's updated schedule of registration-review actions indicated that it will make an interim decision for 1,3-D in 2023.

As illustrated in Figure 3, the EPA initiates a registration review by establishing a public docket for a pesticide-review case and opening the docket for public comment. The docket contains a Preliminary Work Plan, which includes information the EPA has on the pesticide, anticipated risk assessment and data needs, and the projected timeline for the review. After a public comment period of at least 60 days, the EPA considers the information received and develops a Final Work Plan. The Agency then assesses changes since the pesticide's last review and conducts new assessments as needed. The EPA issues a "Data Call-In" notice to the registrant if additional data or information is needed to conduct the review. Next, the EPA publishes a *Federal Register* notice announcing the availability of a proposed registration-review decision and provides the public with another comment period of at least 60 days. After considering any comments concerning the proposed decision, the EPA issues a registration-review decision, including an explanation of any changes made since the proposed decision and a response to any significant comments received during the public comment period.

Figure 3: Pesticide-registration-review process



Source: OIG analysis of EPA information. (EPA OIG image)

The EPA's Cancer-Assessment Process for Pesticides

The Health Effects Division—which is under the Office of Pesticide Programs, or OPP, in the Office of Chemical Safety and Pollution Prevention, or OCSPP—is responsible for cancer assessments for pesticides. The results of these cancer assessments inform the EPA's overall human health risk assessment for pesticides. Cancer assessments are typically initiated by the EPA for new pesticides or when existing pesticides have a new active ingredient. When a registered pesticide is reviewed as part of the FIFRA-required 15-year pesticide-registration-review process, the EPA does not typically initiate a

[3] 40 C.F.R. § 155.40(a)(1).

new cancer assessment unless requested by a registrant through the Pesticide Registration Improvement Act, or PRIA.

Under PRIA, a registrant can request that the EPA perform a new cancer assessment on the registrant's pesticide. The registrant pays a fee, and the EPA has 18 months to complete the cancer assessment. Outside of the PRIA process, the EPA has the authority to initiate a new cancer assessment at any time should new information become available that would impact the EPA's original pesticide registration decision.

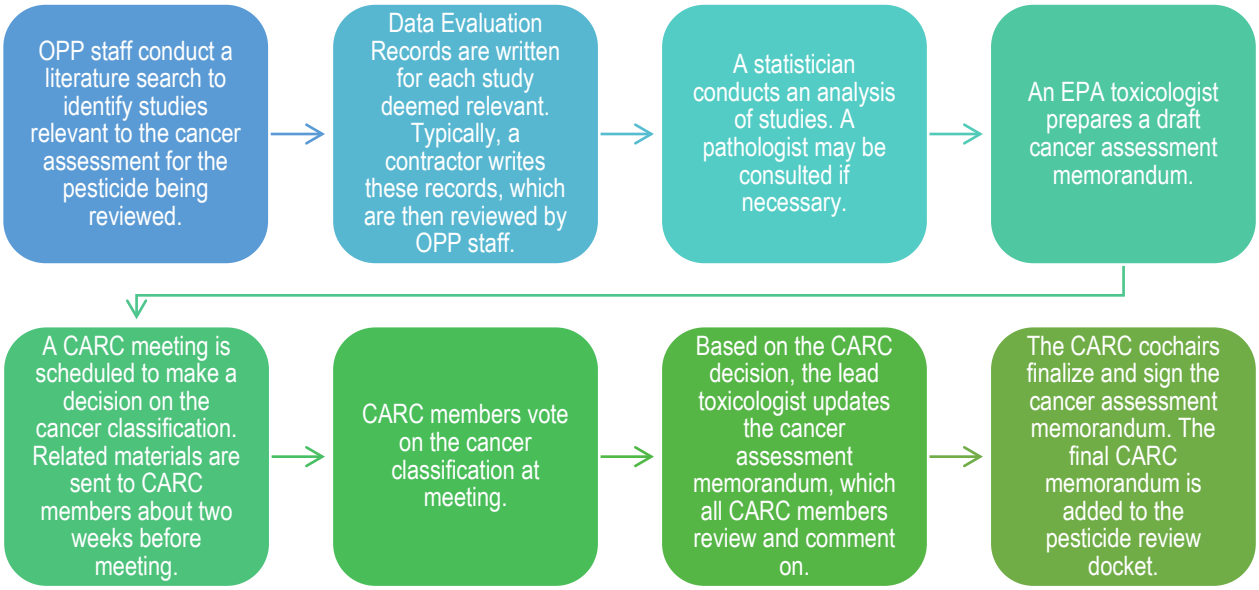
What Is PRIA?

The 2004 FIFRA amendments, also known as PRIA, "created a registration service fee system for applications for specific pesticide registration, amended registration, and associated tolerance actions. The goal of this fee system is to create a more predictable evaluation process for affected pesticide decisions and couple the collection of individual fees with specific decision review periods."

—EPA Pesticide Registration Fees and Fee Waivers webpage

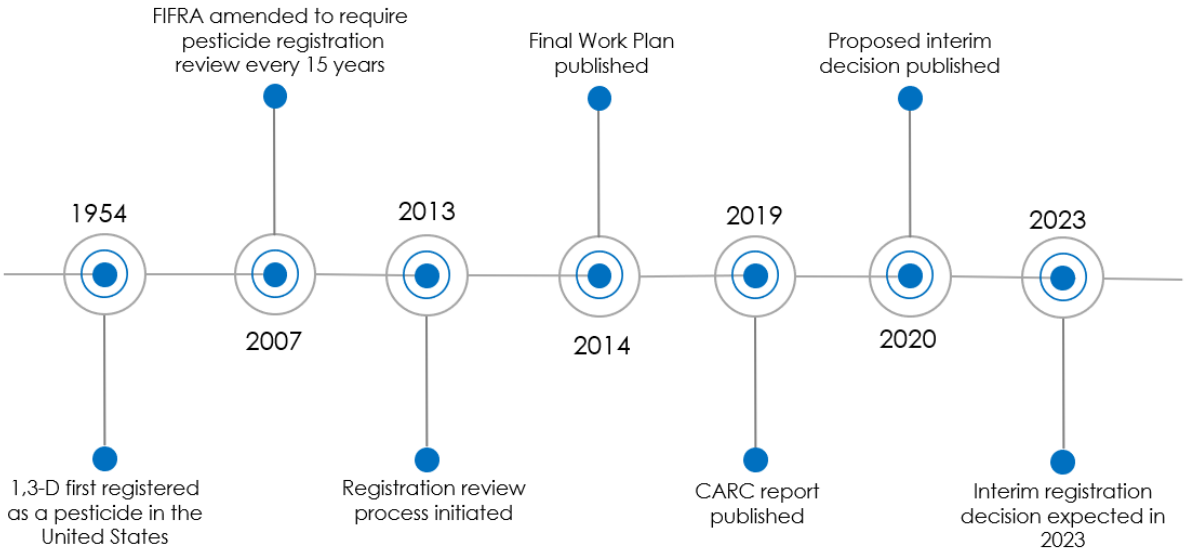
Per the EPA, the OPP's Cancer Assessment Review Committee, or CARC, is responsible for recommending cancer classifications for pesticides and ultimately issuing the final cancer assessment. According to the CARC standard operating procedures, CARC is an internal expert consultation panel that serves as a scientific peer review group. CARC members are selected by the Health Effects Division management team, and the CARC is primarily composed of Health Effects Division staff, but staff from other OPP divisions and EPA programs may be appointed to or consult with CARC. Figure 4 describes the cancer-assessment process. Figure 5 illustrates the history of 1,3-D's registration timeline.

Figure 4: The OPP's cancer-assessment process



Source: OIG analysis of EPA information. (EPA OIG image)

Figure 5: Timeline of the EPA's registration process for 1,3-D



Source: OIG analysis of EPA information. (EPA OIG image)

Carcinogen-Risk-Assessment Guidelines

CARC uses the EPA's 2005 *Guidelines for Carcinogen Risk Assessment* to assess the carcinogenic potential of a pesticide. According to the EPA, the guidelines promote consistency by providing EPA staff with sound and up-to-date scientific procedures for conducting cancer assessments. This guidance aims to enhance the application of the best-available science in the EPA's cancer assessments.

The guidelines recognize that the procedures for conducting cancer assessments will evolve over time and allow flexibility to incorporate new scientific information and approaches. The guidelines, however, caution that the EPA needs to clearly articulate its criteria when it departs from standard procedures so that its risk assessment are "scientifically credible and receive public acceptance." According to the guidelines, if different or novel approaches are used in cancer assessments, these new approaches will be validated through independent, expert peer-review panels to determine whether there is a consensus among scientific experts regarding whether these approaches should be used.

The guidelines state that "conclusions are drawn from weight-of-evidence evaluations" and "emphasize the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents." Weight-of-evidence refers to the method or approach used to integrate and assign weight to the various lines of evidence to form a single conclusion, such as a cancer classification. The goal of weight-of-evidence is to provide a transparent means for communicating decision-making so that decisions can be clearly understood by all stakeholders.

Since at least 1978, scientists have been using the maximum-tolerated-dose approach for selecting the highest dose in an animal carcinogenicity study. The selection of the "highest dose" is important because it determines the data set that the EPA will use to evaluate the pesticide's carcinogenicity. The maximum tolerated dose is the highest dose of the chemical being studied that does not alter the test animal's longevity or well-being because of noncancer effects.

For the 1,3-D cancer assessment, however, the EPA used a novel approach—known as kinetically derived maximum dose, or KMD—for selecting the highest dose in the animal carcinogenicity study.

Transparency and Peer Review Requirements to Enhance Scientific Credibility

The EPA has "a long tradition of fishbowl memos [that lay] out guidance for EPA employees on transparency."[4] The EPA began its commitment to transparency in 1983, when Administrator William Ruckelshaus issued the first such memorandum, which established a culture of integrity and openness for all employees by promising that the EPA would operate "in a fishbowl," meaning that it would attempt to communicate with everyone—from environmentalists to those it regulates—as openly as possible. In April 2021, Administrator Michael S. Regan reiterated that public trust requires transparency in his "Message to EPA Employees on Transparency and Earning Public Trust in EPA Operations." Further, the EPA's 2012 *Scientific Integrity Policy* recognizes links between being transparent and promoting a culture of scientific integrity.

The fishbowl memorandums emphasize the importance of transparency in Agency operations, stating that the EPA will provide for fullest possible public participation in decision-making and will not accept any recommendation without careful, critical, and independent examination. The fishbowl memorandums identify public dockets as a method for being transparent about EPA decision-making. Additionally, law and regulation—FIFRA section 3(g)(1)(B) and 40 C.F.R. § 155.52(a)—require the EPA to place information in the docket about meetings that the Agency has with individuals outside the government regarding pesticide-registration reviews.

What Is a Docket?

A docket is a collection of documents an agency makes available for public viewing. Often associated with an opportunity for public comment, EPA dockets consist of materials used in a rulemaking or other Agency action and may include information used by the Agency to explain or support its decisions.

Responsible Offices

The OCSPP is responsible for the issues in this report. Within the OCSPP, the OPP regulates the manufacture and use of all pesticides in the United States, as well as assesses pesticide risk. The Health Effects Division of OPP is responsible for reviewing data on the properties and effects of pesticides, as well as for characterizing and assessing exposure and risks to humans. The Health Effects Division oversees the CARC. The CARC conducts reviews to evaluate the carcinogenic potential of pesticides.

Scope and Methodology

We conducted this evaluation from June 2021 to March 2022 in accordance with the *Quality Standards for Inspection and Evaluation* published in January 2012 by the Council of the Inspectors General on Integrity and Efficiency. Those standards require that we perform the evaluation to obtain sufficient and appropriate evidence to support our findings.

To answer our objective, we reviewed relevant statutory and regulatory language. We also reviewed policies, procedures, reports, and supporting documents on the pesticide-registration-review process and the cancer-assessment process in general, as well as for 1,3-D in particular, including the:

- EPA's 2019 CARC standard operating procedures.
- OPP's 2019 *Quality Management Plan*.
- EPA's 2005 *Guidelines for Carcinogen Risk Assessment*.
- CARC's 2019 *Evaluation of the Carcinogenic Potential of 1,3-Dichloropropene* and supporting materials.

[4] EPA, "Message to EPA Employees on Transparency and Earning Public Trust in EPA Operations," April 12, 2021.

We also reviewed other applicable standards, including the:

- EPA's 2015 *Peer Review Handbook*.
- EPA's 2012 *Scientific Integrity Policy*.
- EPA's 2002 *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency*, known as the *EPA's Information Quality Guidelines.*
- Office of Management and Budget's 2004 *Final Information Quality Bulletin for Peer Review*.
- OMB's 2002 *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by Federal Agencies*, known as the *OMB's Information Quality Guidelines*.

Further, we interviewed managers, scientists, and staff from the OCSPP and the Office of Research and Development to assess their experience with—and their roles and responsibilities for—the 1,3-D cancer-assessment process and the pesticide-registration-review process more broadly. While evaluating the involvement of senior officials was not part of our objective, we did not see indicators of interference from senior officials during our fieldwork.

Prior Reports

The following prior OIG reports are relevant to our objective and relate to the EPA's adherence to regulations, policies, and procedures, as well as its use of peer review.

OIG Report No. 21-P-0070, *EPA Mostly Adheres to Regulations When Assessing Risks of New Pesticides but Should Improve Internal Controls,* issued February 8, 2021, looked at policies and procedures applicable to new pesticide registrations and recommended that the EPA develop additional internal controls over initial registrations. As reported in the Agency's audit tracking system, the EPA agreed with all OIG recommendations and completed all corrective actions to address these recommendations in January 2022.

OIG Report No. 21-E-0146, *EPA Deviated from Typical Procedures in Its 2018 Dicamba Pesticide Registration Decision*, issued May 24, 2021, looked at whether the EPA followed policies and procedures in its 2018 dicamba registration decision and made three recommendations to the EPA, including that a procedure should be implemented to document changes to scientific opinions and analysis, as well as the basis for such changes. All three recommendations are resolved, with corrective actions scheduled to be completed by September 30, 2022.

OIG Report No. 2003-P-00003, *Science to Support Rulemaking*, issued November 15, 2002, detailed how 61 percent of the scientific information used to support rulemaking was not peer reviewed. The report concluded, "The critical science supporting the rules often was not independently peer reviewed. Consequently, the quality of some science remains unknown." While the report did not contain any recommendations, it did offer several suggestions to the EPA, including that the "critical science behind EPA's rules should consistently be independently peer reviewed." The EPA stated in its response that it concurred with the suggestions "to improve the transparency and consistency with which science is applied to Agency rulemaking."

Chapter 2
The EPA's Cancer Assessment for 1,3-D Lacked Compliance with Established Standards, Undermining Its Credibility and Transparency

The EPA did not adhere to standard operating procedures and federal requirements for the 1,3-D cancer-assessment process. Specifically:

- The OPP used two scientific analysis techniques—KMD and weight-of-evidence—in its 1,3-D CARC report, but as of June 2022, the OPP had not published guidance on how to use these techniques for cancer assessments.
- The OPP did not comply with FIFRA requirements to place certain information in the public docket when the Agency meets with "individuals that are not government employees" regarding pesticide-registration reviews.
- The OPP did not comply with its own literature-search procedures for the 1,3-D cancer-assessment review by not using the proper search terms.
- CARC did not have adequate oversight to confirm adherence to the standards for internal peer review.
- CARC used KMD—a novel, precedent-setting, and controversial approach—without an external peer review.

These departures from established standards during the cancer assessment for 1,3-D undermine the EPA's credibility, as well as public confidence in and the transparency of the Agency's scientific approaches, in its efforts to prevent unreasonable impacts on human health.

The OPP Applied Scientific Approaches That Lacked Guidance

In 2019, the OPP applied the novel KMD scientific approach to its cancer assessment for 1,3-D. This was the first time the EPA applied the KMD approach to a cancer assessment, and the EPA did not have guidance for applying it to cancer assessments. Several CARC participants expressed concerns about the lack of guidance on how to implement the KMD approach.

In addition, even though the EPA's 2019 CARC report on 1,3-D used the term "weight-of-evidence" 15 times, the report does not describe how CARC applied the weight-of-evidence approach to its 1,3-D cancer classification. OPP staff stated that section 2.5 of the *Guidelines for Carcinogen Risk Assessment* provides guidance on applying the weight-of-evidence approach to cancer assessments. However, we found that the guidance does not provide procedures on how to integrate and assign weight to the various lines of evidence to form a single conclusion.

The EPA has not issued agencywide guidance on how to conduct a weight-of-evidence analysis in a human health risk assessment. In 2014, the National Academy of Sciences found that the term "weight-of-evidence" has no specific scientific meaning and "as used in practice has become too vague

and is of little scientific use." Guidance for how to apply a weight-of-evidence approach exists for other OPP assessments, such as those for endocrine disruptors and ecological risk assessments, but the OPP does not have any guidance on how to implement a weight-of-evidence analysis in cancer assessments for pesticides. In September 2020, the EPA cosponsored a KMD symposium at which several participants indicated that having KMD guidance on dose selection in carcinogenicity studies would be helpful.[5] In October 2021, a peer-reviewed article, which included multiple EPA contributors and was published in the journal *Regulatory Toxicology and Pharmacology,* concluded that "the lack of consensus on how a KMD should be estimated or when such an approach is appropriate may be due to different interpretations of the KMD definition and applications."[6]

The *OMB's Information Quality Guidelines* establish the standard for influential scientific information, which requires all federal agencies' data and analysis methods to be sufficiently transparent so that their influential scientific information can be independently reproduced by qualified third parties. The *Guidelines for Carcinogen Risk Assessment* identifies cancer assessments as "highly influential" scientific information. For both the KMD and weight-of-evidence approaches, the OPP did not meet the OMB's transparency standard for influential scientific information. Since the OPP lacks guidance for applying the KMD and weight-of-evidence approaches in its cancer assessments, qualified third parties are unable to independently reproduce the OPP's cancer assessment findings.

The EPA Did Not Docket Some Meetings Related to the 1,3-D Pesticide-Registration Review

According to FIFRA section 3(g)(1)(B), "after meeting with 1 or more individuals that are not government employees to discuss matters relating to a registration review, the Administrator shall place in the docket minutes of the meeting, a list of attendees, and any documents exchanged at the meeting." From 2016 through 2018, the EPA met with the 1,3-D registrant at least five times regarding the cancer reassessment for 1,3-D. No information from these meetings appeared in the pesticide-registration review docket, even though some of these meetings included discussions on the application of KMD for the 1,3-D cancer assessment. The docket included information from two meetings between the EPA and the registrant related to other aspects of the registration review, but it did not include required meeting minutes and lists of attendees.

The OPP said that the 1,3-D cancer reassessment was not directly part of the 1,3-D registration review; therefore, meetings related to the cancer reassessment were not required to be docketed. While they are generally separate processes, they were related in the case of 1,3-D, and we conclude that the meetings should have been docketed. The OPP conducted two separate but related regulatory processes for 1,3-D during the same time frame: a cancer reassessment at the request of the registrant under PRIA, and a registration review, as required under FIFRA. The 1,3-D cancer reassessment concluded in 2019, after the EPA established the docket for the 1,3-D pesticide-registration review in 2013 and before the EPA concluded the pesticide-registration review, which was ongoing as of June 2022. The EPA detailed its decision on the 1,3-D cancer reassessment in the final CARC report, which is included in the 1,3-D pesticide-registration-review docket. The EPA also incorporated the 1,3-D cancer reassessment into the human health risk assessment and into the pesticide-registration review itself. The EPA's actions

[5] U.S. Department of Health and Human Services, "Opportunities and Challenges in Using the Kinetically Derived Maximum Dose Concept to Refine Risk Assessment," symposium webinar, September 30, 2020.

[6] Tan, Yu-Mei et al., "Opportunities and Challenges Related to Saturation of Toxicokinetic Processes: Implications for Risk Assessment," *Regulatory Toxicology and Pharmacology*, volume 127, December 2021.

connecting the cancer reassessment and pesticide-registration review negate the position that the Agency viewed each as separate processes. As such, the EPA should have included all meetings with the registrant on the cancer reassessment in the public-registration-review docket.

In the 2021 fishbowl memorandum, Administrator Regan stated that the "EPA will provide for the fullest possible public participation in decision-making." Without access to the information from meetings between the EPA and the pesticide registrant, the public and stakeholders lacked the full picture of information or views that may have influenced the EPA's decision to change the 1,3-D cancer classification.

The OPP Did Not Comply with Its Own Literature-Search Procedures for the 1,3-D Cancer-Assessment Review

According to the EPA, one of the first steps in conducting a risk assessment is the literature search. The literature search is used to identify and evaluate publicly available data that may be relevant to the pesticide registration. The quality of the final risk assessment depends on a thorough, comprehensive, and unbiased literature search. When evaluating a pesticide's potential adverse effects on human health, the OPP's own standard operating procedures require the OPP to complete a literature search to consider health-effects data from published studies. These procedures call for using the full chemical name in conducting literature searches.

In its literature search, the OPP used the abbreviation "1,3-D," and the brand name of the pesticide, "Telone," but did not include the full chemical name. The OPP identified eight studies as a result of its search. In 2015, the California Environmental Protection Agency conducted a literature search for 1,3-D using both the trade name and the full chemical name and identified 91 potentially relevant studies. In 2021, we conducted a literature search with the full chemical name and identified over 100 studies.

The OPP excluded all eight studies that it identified as a result of its literature search from the draft human health risk assessment without providing a rationale. The OPP's draft human health risk assessment specifically stated that "no studies were identified as containing potentially relevant information (either quantitative or qualitative) for the 1,3-D human health registration review risk assessment." According to the *EPA's Information Quality Guidelines*, the Agency is to publicly identify all the peer-reviewed scientific studies that support and fail to support an Agency's risk-assessment decision and the methodology the Agency used to reconcile inconsistencies in the scientific data. Therefore, the OPP should have provided the rationale and methodology for excluding each study in 1,3-D's draft human health risk assessment, but it did not. According to the EPA, "Effective risk characterization is achieved through transparency in the risk assessment process and clarity, consistency, and reasonableness of the risk assessment product."

The OPP did not have an explanation for why it did not follow its written standard operating procedures when conducting 1,3-D's literature search. The literature search is typically conducted by a different branch within the OPP that is not part of the CARC process. According to one CARC cochairperson, it is the lead toxicologist's responsibility to review the literature search results and to consult the relevant OPP branch with any concerns. While the CARC standard operating procedures describe the responsibilities of the lead toxicologist and CARC chairperson related to the CARC process, the procedures do not specifically address conducting a literature search. The lead toxicologist for 1,3-D did not believe lead toxicologists were responsible for reviewing the literature search, and the CARC chairperson said that CARC normally conducts its own literature search, but there is no set process.

Without a thorough, comprehensive literature search, the EPA neglected to review all health-effects data and potential adverse effects on human health. An incomplete literature search could have impacted the results of the 1,3-D draft human health risk assessment, which is informed by the cancer assessment. It is important to screen and evaluate all potentially relevant studies to uphold the scientific credibility of the literature search and the risk-assessment conclusions. The findings and review of the literature search should be documented and transparent. CARC proceeded to use the incomplete literature search during its assessment and may have neglected to review all relevant studies. To uphold the EPA's mission to prevent adverse effects on human health, the EPA should have followed the written procedures for the literature search for 1,3-D and included the rationale and methodology for excluding the eight studies it identified in the draft risk assessment.

CARC Did Not Comply with Internal Peer Review Standards

The OPP considers CARC to be an internal scientific peer review group, but CARC did not follow applicable internal peer review standards. It also did not have controls in place to detect when standards were not followed or to correct the deficiencies. The OPP's 2019 Draft *Health Effects Division Quality Management Plan* describes how following standards,[7] such as the *Peer Review Handbook* and the OMB's guidance on peer review, will enhance the quality and credibility of the OPP's decisions. The *Peer Review Handbook* states that it "should be used as guidance by EPA staff and managers to ensure that the Agency's Peer Review Policy is implemented effectively and that the integrity of our peer review activities can be demonstrated transparently to the American public."

The OPP's *Health Effects Division Quality Management Plan* provides the authority and guidance for how the Health Effects Division's quality assurance activities are planned, documented, and assessed.

The *Peer Review Handbook* describes an internal peer review as a technical or scientific review by individuals from within the Agency who have the appropriate expertise and are independent from the development of the work product. In 2019, CARC did not adhere to the EPA's standards for internal peer review for the 1,3-D cancer assessment because it did not confirm that all CARC members:

- Were independent from the development of the work product.
- Were located in a different organizational unit than the one in which the work originates.
- Had the appropriate expertise.

The CARC standard operating procedures allow other ad hoc voting members, such as scientists from other EPA offices, to be added to the committee. All nine CARC members during the 1,3-D cancer assessment were from the Health Effects Division, where the work originated. Some CARC members were even from the originating branch of the Health Effects Division and thus did not have independence from the development of the work product or come from a different organizational unit than the one in which the work originated.

We interviewed all nine CARC members regarding the 1,3-D CARC proceedings. Some members expressed concerns about the lack of knowledge of—and the lack of guidance on how to implement—the KMD approach. Some believed that not all members possessed the appropriate scientific expertise for using and implementing the KMD approach for evaluating the evidence of the carcinogenic potential of 1,3-D. For example:

[7] While the plan is described as a "draft," it is the most recently signed version provided to us as of September 2021.

- One scientist opined that some CARC members were not qualified to be making decisions and voting on the KMD approach.
- There was some confusion on the use of KMD.
- CARC members do not have written guidance that walks them through the KMD process.

The OPP, and specifically CARC, did not conduct timely reviews of CARC processes to determine whether CARC followed applicable internal peer review standards or its standard operating procedures. The U.S. Government Accountability Office's *Standards for Internal Control in the Federal* states that controls should be implemented to monitor and correct deficiencies on a timely basis.[8] Without conducting timely reviews, CARC cannot ensure that the quality of published information in its report met "the standards of the scientific and technical community," per the *Peer Review Handbook*.

External Peer Review Would Improve the OPP's 1,3-D Cancer-Assessment Credibility

The deficiencies described in our report raise concerns about the credibility of the OPP's 1,3-D cancer-assessment process and the OPP's decision to not have the cancer assessment externally peer reviewed. The scientific credibility of the 1,3-D cancer assessment was also questioned by various stakeholders, such as, nongovernmental organizations and multiple attorneys general. Among them were the attorneys general of California and Oregon, two states with a high use of 1,3D. The green sidebar describes the letter the attorneys general sent to the EPA raising concerns about the revised cancer rating. Absent clear EPA procedures on how to implement the KMD and weight-of-evidence techniques, some outside parties independently analyzing the 1,3-D cancer data did not come to the same findings as the EPA on the 1,3-D cancer classification.

Concerns from External Stakeholders

In an April 6, 2020 letter to the EPA, the California attorney general, along with six other state attorneys general and the Washington, D.C. attorney general, commented on the EPA's revised cancer assessment of 1,3-D, which downgraded the cancer rating from "Likely to be Carcinogenic to Humans" to "Suggestive Evidence of Carcinogenic Potential." The letter describes how 1,3-D exposure tends to disproportionately impact disadvantaged agricultural communities that already suffer from significant environmental hardship. The California Department of Pesticide Regulation identified two communities with elevated levels of 1,3-D in the air, noting that these two communities are also exposed to more pollution overall than 80–95 percent of the rest of California.

The OPP's lack of transparency about its scientific-analysis methods undermines the Agency's ability to build consensus among stakeholders on the 1,3-D cancer classification. When the EPA completes its pesticide-review decision for 1,3-D, these stakeholders may decide to take legal action or petition Congress to overturn the Agency's decision on 1,3-D.

The cancer risk posed by 1,3-D needs to be accurately assessed to protect people from potentially harmful exposure. As described earlier, the 1,3-D cancer classification downgrade allows for an increase in the pesticide's permissible chronic exposure level to humans 90 times over current levels.

[8] The Government Accountability Office's *Standards for Internal Control in the Federal Government*, GAO-14-704G, published in September 2014, sets internal control standards for federal entities. Internal control is a process used by management to help an entity achieve its objectives and run its operations efficiently and effectively, report reliable information about its operations, and comply with applicable laws and regulations. Management evaluates and documents internal control issues and determines appropriate corrective actions for internal control deficiencies on a timely basis.

Importance of Accurate Cancer Assessment

If the OPP's 1,3-D cancer reclassification is faulty, the revised uses of 1,3-D after the OPP's issuance of the pesticide review decision may expose humans to higher levels of the potential carcinogen. For example, the OPP's cancer reclassification of 1,3-D allows the long-term exposure level considered unreasonable risk to humans to increase from 7.7 $\mu g/m^3$ to 690 $\mu g/m^3$, which is a 90-fold increase.

The established mechanism to enhance the quality and credibility of any influential scientific information is to have it externally peer reviewed by a panel of scientists. Using the established peer-review process on the OPP's 1,3-D cancer assessment would increase the transparency and confirm the accuracy of the 1,3-D cancer classification downgrade before the EPA alters the 1,3-D pesticide registration.

EPA Guidance Recommends that Novel, Precedent-Setting, or Controversial Influential Scientific Information Be Externally Peer Reviewed

Multiple guidance documents recommend external peer review for novel, precedent-setting, or controversial influential scientific information. The KMD is a novel risk-assessment approach that is not present in the *Guidelines for Carcinogenic Risk Assessment*, nor has it been externally peer reviewed. Further, CARC's application of the novel KMD approach is pivotal to cancer assessment findings resulting in the downgrade of the 1,3-D cancer classification and not quantifying cancer risk from 1,3-D. The 1,3-D cancer assessment is the first time the OPP has applied the novel KMD approach, setting a precedent for applying the KMD approach to future cancer assessments.

The *Guidelines for Carcinogenic Risk Assessment* state that the use of a novel scientific procedure can "undercut the scientific credibility of a risk assessment," that cancer-assessment decisions should strive to be "scientifically defensible," and that "scientific defensibility" is "evaluated through use of EPA's Science Advisory Board, EPA's [FIFRA] Scientific Advisory Panel, or other independent expert peer review panels to determine whether a consensus among scientific experts exists." While the guidelines state that cancer-risk assessment procedures will continue to evolve and encourage risk assessors to be receptive to new scientific information, the guidance also stipulates that the EPA needs sufficient criteria to depart from the typical risk assessment procedures articulated in the guidelines. Further, the guidelines state that cancer assessments conducted differently than originally prescribed, such as the use of new scientific approaches, will be tested through peer review. The *EPA's Information Quality Guidelines* also state that influential scientific information that is related to Agency decisions and that is precedent setting, novel, or controversial should be externally peer reviewed.

The 2019 CARC standard operating procedures allow the conclusions of the CARC meeting to be referred to the FIFRA Scientific Advisory Panel if there are new or scientifically complex issues concerning the pesticide. The *Peer Review Handbook* states that influential scientific assessments or products that include novel scientific methods or approaches are most suited for external peer review by the Agency's Science Advisory Board.

Further, the OMB's *Final Information Quality Bulletin for Peer Review* requires all highly influential scientific information to be externally peer reviewed and states that highly influential scientific information that is based on novel methods or precedent-setting practices, or that has significant interagency interest, requires more rigorous peer review. The OMB grants agencies discretion on whether to conduct an external peer review for permit proceedings, including registration processes, for specific product development activities. The OPP is generally not required to conduct external peer reviews of influential scientific information supporting a pesticide registration "unless the Agency determines that peer review is practical and appropriate, and the influential information is scientifically

or technically novel or likely to have precedent-setting influence on future adjudications and/or permit proceedings."

The OPP's *Quality Management Plan* acknowledges that work products can be externally peer reviewed by the FIFRA Scientific Advisory Panel or the EPA's Science Advisory Board, but the trigger for referring an assessment to external peer review is not clear. Although the OPP has discretion whether to conduct external peer review of influential scientific information supporting a pesticide registration decision, the OPP has not established specific criteria for when scientific information is sufficiently novel or precedent setting to warrant external peer review.

Benefits of Peer Review

The OMB's peer review bulletin highlights that peer reviews can:

- Lead to policy outcomes with more benefits and fewer costs.
- Strengthen the science behind agency decisions.
- Build consensus among stakeholders.
- Reduce the temptation for courts and legislators to second guess or overturn agency actions.

Conclusions

The lack of guidance for KMD and weight-of-evidence, the incomplete public docket, the incomplete literature search, the failure to adhere to internal peer review standards, and the lack of external peer review undermine transparency and the scientific credibility of the 1,3-D cancer-assessment process. The EPA's resulting cancer classification downgrade could lead to significant increases in exposure levels to humans and affect the pesticide's application rate and level of personal protective equipment required by applicators. The EPA needs to take action to improve the scientific credibility of and bolster public trust in the Agency's 1,3-D decision. Our recommendations will also enhance the EPA's cancer-assessment process for pesticides more broadly.

Recommendations

We recommend that the assistant administrator for Chemical Safety and Pollution Prevention:

1. Issue guidance on when and how to conduct the kinetically derived maximum dose approach in cancer-risk assessments for pesticides.

2. Issue guidance on using and applying a weight-of-evidence approach in cancer-risk assessments for pesticides.

3. Update the docket for 1,3-Dichloropropene to include all required materials, including minutes and a list of participants, for meetings between the EPA and the registrant related to the 1,3-Dichloropropene pesticide-registration review and cancer assessment.

4. Issue guidance to clarify when to docket meetings related to a registration for other related activities that occur concurrent to the pesticide-registration-review process, such as the cancer-reassessment process.

5. Conduct a comprehensive literature search that identifies all published scientific studies concerning the potential carcinogenicity of 1,3-Dichloropropene, including a methodology to reconcile inconsistencies in the scientific data, and publish the results of the literature search and reconciliations.

6. Update the Cancer Assessment Review Committee standard operating procedures to comply with the Office of Pesticide Programs' literature search standard operating procedures and the broader quality principles in the Office of Management and Budget's 2002 *Information Quality Guidelines*, which includes a methodology to reconcile inconsistencies in the scientific data.

7. Issue procedures to document:

    a. The independence of Cancer Assessment Review Committee members from the work products they review.

    b. That appropriate expertise is represented on the Cancer Assessment Review Committee for each meeting.

    c. When other ad hoc voting members, such as scientists from other EPA offices, should be added to the Cancer Assessment Review Committee.

    d. Regular assessments of the Cancer Assessment Review Committee to monitor and correct deficiencies and to determine whether applicable internal peer review standards are being met.

8. Conduct an external peer review on the 1,3-Dichloropropene cancer-risk assessment.

9. Issue specific criteria requiring external peer review of Office of Pesticide Programs' risk assessments that use scientifically or technically novel approaches or that are likely to have precedent-setting influence on future risk assessments, in accordance with the Office of Management and Budget's *Final Information Quality Bulletin for Peer Review*.

Agency Response and OIG Assessment

The OCSPP was not in full agreement with Recommendations 1, 2, and 8 but generally agreed with Recommendations 3–7 and 9. Appendix A includes the Agency's response to our draft report. Subsequently, the Agency clarified that the intent of its corrective action to Recommendation 3 was to search both paper *and* electronic files and update the public docket accordingly. Given this amendment to the Agency's original response, Recommendation 3 is resolved with corrective actions pending. Recommendations 4–7 and 9 are also resolved with corrective actions pending. For the reasons described below, Recommendations 1, 2, and 8 are unresolved.

For Recommendation 1, the Agency did not agree with our characterization of how the KMD approach was used to inform the OPP's cancer assessment of 1,3-D and of the KMD being a "novel" approach. In its response, the Agency stated that KMD was used in combination with other information to "interpret" the tumor findings in the mouse carcinogenicity study and that although "specific guidance on the KMD does not exist, incorporating toxicokinetic information to provide context for interpreting animal dose-response data is not a novel concept." We note that using KMD to inform the selection of the highest dose, rather than applying the maximum tolerated dose, is still a departure from the EPA's *Guidelines for Carcinogen Risk Assessment*. Further, our report cites, and the EPA's response highlights, that the EPA cohosted an international symposium in September 2020 on "Opportunities and Challenges in Using the Kinetically Derived Maximum Dose Concept to Refine Risk Assessment." This symposium occurred *after* the EPA's use of the KMD in its 1,3-D cancer assessment in 2019. In support of our view

that the EPA's application of KMD is novel, the symposium webpage states, "In contrast to its routine use in pharmaceutical development, consideration of the KMD in the design or interpretation of animal toxicity studies for environmental chemicals is *rare*" (italics added). The webpage further states, "Interest is growing in use of the KMD to interpret animal dose-response data or set top dose in chronic toxicity studies of these chemicals, but many technical and scientific issues hinder its proper use." We continue to believe that without specific, detailed KMD guidance, the OCSPP does not comply with the transparency standard as described in the *OMB's Information Quality Guidelines* because qualified third parties are unable to independently interpret the original 1,3-D data using the OPP's methods and reproduce the same conclusion that the cancer classification for 1,3-D should be downgraded. We consider the OCSPP's proposed corrective action to update its public website to point to a third party's guidance on integrating kinetic information into risk assessments inadequate. Consistent with the OMB's *Information Quality Guidelines* and the EPA administrator's commitment to transparency as described in Chapter 2, the OCSPP should issue and publicly release its own KMD guidance to allow qualified third parties to independently reproduce the OCSPP's results. Therefore, Recommendation 1 is unresolved.

For Recommendation 2, the OCSPP's response states that it followed the EPA's *Guidelines for Carcinogen Risk Assessment* to weigh the evidence to determine the appropriate cancer classification for 1,3-D. However, as we explained in Chapter 2, this EPA guidance lacks procedures on how to integrate and assign weight to the various lines of evidence to form a single conclusion. Without specific, detailed weight-of-evidence guidance for pesticide cancer assessments, the OCSPP does not comply with the OMB's transparency standard because qualified third parties are unable to independently interpret the original 1,3-D data using the OPP's methods and reach the same conclusion. The OCSPP's proposed corrective action to update the CARC standard operating procedures to include guidance to state the weight-of-evidence process more clearly is a first step but, consistent with *OMB's Information Quality Guidelines* and the EPA administrator's commitment to transparency as described in Chapter 2, the OCSPP should commit to publicly release its weight-of-evidence process to allow qualified third parties to independently reproduce the OCSPP's results from the original data. Recommendation 2 is unresolved.

For Recommendation 8, the Agency believes the external peer review sponsored by the registrant meets the intent of the recommendation to conduct an external peer review on the 1,3-D cancer assessment. We do not accept the registrant-sponsored peer review as comparable to one performed by the FIFRA Scientific Advisory Panel. While the registrant-sponsored peer review appears to have many similarities to a peer review that would be conducted by the FIFRA Scientific Advisory Panel, it lacks specific elements—such as independence from the regulated business, a preparatory public meeting to consider the scope and clarity of the draft charge questions for the peer review, an opportunity for written public comments to be considered by the peer review, and public participation for oral comments during the peer review meeting. These elements are needed to improve the transparency and scientific credibility of the 1,3-D cancer-assessment process. Thus, Recommendation 8 is unresolved.

We are in discussions with the EPA on the unresolved recommendations.

Status of Recommendations

RECOMMENDATIONS

Rec. No.	Page No.	Subject	Status[1]	Action Official	Planned Completion Date
1	15	Issue guidance on when and how to conduct the kinetically derived maximum dose approach in cancer-risk assessments for pesticides.	U	Assistant Administrator for Chemical Safety and Pollution Prevention	
2	15	Issue guidance on using and applying a weight-of-evidence approach in cancer-risk assessments for pesticides.	U	Assistant Administrator for Chemical Safety and Pollution Prevention	
3	15	Update the docket for 1,3-Dichloropropene to include all required materials, including minutes and a list of participants, for meetings between the EPA and the registrant related to the 1,3-Dichloropropene pesticide-registration review and cancer assessment.	R	Assistant Administrator for Chemical Safety and Pollution Prevention	12/15/23
4	15	Issue guidance to clarify when to docket meetings related to a registration for other related activities that occur concurrent to the pesticide-registration-review process, such as the cancer-reassessment process.	R	Assistant Administrator for Chemical Safety and Pollution Prevention	12/15/23
5	15	Conduct a comprehensive literature search that identifies all published scientific studies concerning the potential carcinogenicity of 1,3-Dichloropropene, including a methodology to reconcile inconsistencies in the scientific data, and publish the results of the literature search and reconciliations.	R	Assistant Administrator for Chemical Safety and Pollution Prevention	3/31/23
6	16	Update the Cancer Assessment Review Committee standard operating procedures to comply with the Office of Pesticide Programs' literature search standard operating procedures and the broader quality principles in the Office of Management and Budget's 2002 *Information Quality Guidelines*, which includes a methodology to reconcile inconsistencies in the scientific data.	R	Assistant Administrator for Chemical Safety and Pollution Prevention	6/30/23
7	16	Issue procedures to document: a. The independence of Cancer Assessment Review Committee members from the work products they review. b. That appropriate expertise is represented on the Cancer Assessment Review Committee for each meeting. c. When other ad hoc voting members, such as scientists from other EPA offices, should be added to the Cancer Assessment Review Committee. d. Regular assessments of the Cancer Assessment Review Committee to monitor and correct deficiencies and to determine whether applicable internal peer review standards are being met.	R	Assistant Administrator for Chemical Safety and Pollution Prevention	6/30/23
8	16	Conduct an external peer review on the 1,3-Dichloropropene cancer-risk assessment.	U	Assistant Administrator for Chemical Safety and Pollution Prevention	
9	16	Issue specific criteria requiring external peer review of Office of Pesticide Programs' risk assessments that use scientifically or technically novel approaches or that are likely to have precedent-setting influence on future risk assessments, in accordance with the Office of Management and Budget's *Final Information Quality Bulletin for Peer Review*.	R	Assistant Administrator for Chemical Safety and Pollution Prevention	6/30/24

[1] C = Corrective action completed.
R = Recommendation resolved with corrective action pending.
U = Recommendation unresolved with resolution efforts in progress.

Agency Response to Draft Report

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY
AND POLLUTION PREVENTION

MEMORANDUM

SUBJECT: Response to Draft Report entitled "The EPA Needs to Improve Transparency of Its Cancer-Assessment Process for Pesticides"

FROM: Michal Ilana Freedhoff, Ph.D.
Assistant Administrator

MICHAL FREEDHOFF Digitally signed by MICHAL FREEDHOFF
Date: 2022.05.16 17:33:15 -04'00'

TO: Sean W. O'Donnell
Inspector General

This memorandum responds to the Office of Inspector General's (OIG's) Draft Report entitled "The EPA Needs to Improve Transparency of Its Cancer-Assessment Process for Pesticides" Report No. OSRE-FY21-0214, April 20, 2022.

I. General Comments:

The Office of Chemical Safety and Pollution Prevention (OCSPP) appreciates OIG's effort in evaluating the extent to which EPA followed policies and procedures in developing the cancer assessment for the 1,3-dichloropropene pesticide registration review decision to prevent unreasonable adverse effects on human health.

EPA remains committed and continues its mission to protect human health and the environment, while maintaining scientific integrity, transparency to all stakeholders, and decisions grounded in sound, high-quality science. The Draft Report appropriately observes that the OCSPP's Office of Pesticide Programs (OPP) must follow appropriate policies and procedures when conducting pesticide evaluations, such as the cancer risk assessment process. OCSPP places high importance on consistency and transparency, and will be taking action to further strengthen our continued efforts in these areas.

While OCSPP agrees on the importance of continued efforts to increase the transparency of its cancer assessment process for pesticides, we disagree with the Draft Report's conclusion that "EPA did not adhere to standard operating procedures and requirements for the 1,3-dichloropropene, or 1,3-D, pesticide cancer-assessment process." The Draft Report identified two specific scientific analysis techniques that OPP used in its assessment of the carcinogenic potential of 1,3-dichloropropene (1,3-D): kinetically-derived maximum dose (KMD) and weight of evidence (WoE). OCSPP is not in agreement with the Draft Report's description of how OPP used these approaches in the 1,3-D cancer assessment.

The Draft Report does not accurately describe how KMD was used to inform the cancer assessment for 1,3-D. Specifically, the Draft Report mistakenly states:

> "For the 1,3-D cancer assessment, the EPA used a novel alternative approach for selecting the highest dose in an animal carcinogenicity study known as kinetically-derived maximum dose, or KMD."

To clarify, OPP did not use information on the KMD to select the highest dose in an animal carcinogenicity study; instead KMD was used in combination with other mechanistic and toxicokinetic information to interpret the tumor findings in the mouse carcinogenicity study. The mouse inhalation carcinogenicity study was conducted in accordance with OCSPP test guidelines and the doses were considered adequate to assess carcinogenicity. Animal studies conducted to support pesticide registration are conducted at much higher doses than anticipated human exposures to pesticides. When interpreting the findings of animal studies for use in human health risk assessments, the relevance of those findings must be considered. In the case of 1,3-D, chemical-specific toxicokinetic studies and other mechanistic information were evaluated to understand how/if the toxicokinetics of the chemical changes with increasing dose.

As stated in the Agency's 2005 Guidelines for Carcinogen Risk Assessment (EPA/630/P-03/001B), changes in toxicokinetics and metabolic pathways may result in significant differences between high and low dose levels in disposition of the agent at the target organs/tissues or generation of its active forms. The toxic effects of high dose exposures on target organs/tissues may be caused by alteration of the physiology of the test species, rather than directly attributable to the agent. In the case of 1,3-D, chemical-specific studies were available to evaluate dose-dependent changes in toxicokinetic behavior and glutathione depletion, and these data were used with other data to interpret the relevance of the high dose lung tumors observed in the mouse carcinogenicity study. In other words, the KMD was one line of evidence in the totality of information that OPP's Cancer Assessment Review Committee (CARC) used to inform the cancer classification decision for 1,3-D.

Although a specific guidance on the KMD does not exist, incorporating toxicokinetic information to provide context for interpreting animal dose-response data is not a novel concept. Considering the impact of toxicokinetics when interpreting animal toxicity data has been recommended by EPA (USEPA 2003; 2005) and multiple international organizations, such as the Organisation for Economic Co-operation and Development (OECD), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), and the European Chemicals Agency (OECD, 1998; 2007; 2010; 2012; 2013; 2014; 2018;

ICH 1995a, 1995b, 1997, 2008a; 2008b; 2020; ECHA 2017). In addition, EPA is working with the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) to develop a guidance document to provide a framework for evaluating KMD submissions.

OCSPP also disagrees with the OIG's finding related to the use of "weight of evidence" (WoE) for cancer risk assessments. While it is true that OPP has not published guidance on the use of WoE for cancer risk assessments, OPP follows the Agency's 2005 Guidelines for Carcinogen Risk Assessment, which provide guidance for all EPA programs on establishing lines of evidence and data gaps, determining data reliability, uncertainty and relevance and using scientific judgement to weigh and integrated those data for carcinogen risk assessments. The term "weight of evidence" is not a unique or novel approach to evaluate and assess toxicological findings for regulatory decision making. OCSPP is concerned that developing a separate cancer WoE guidance outside of the CARC Standard Operating Procedure (SOP) may undermine the 2005 Guidelines for Carcinogen Risk Assessment or negatively impact other program offices. Furthermore, guidance on the use of WoE for chemical assessments already exists for OECD (OECD, 2019) member countries, including the United States. OPP recommends that additional guidance be incorporated into the CARC SOP on evaluating and integrating lines of evidence consistent with the WoE approach described in the 2005 Guidelines for Carcinogen Risk Assessment.

While OCSPP is not in full agreement with OIG Recommendations 1, 2, and 8, we generally agree with recommendations 3-7, and 9, to help improve transparency in decision making. OCSPP therefore proposes the corrective actions and target completion dates described below.

II. OCSPP's Response to the Recommendations:

Recommendation 1: Issue guidance on when and how to conduct the kinetically-derived maximum dose approach in cancer risk assessments for pesticides.

- **OCSPP Response:** The vague definition of the term "kinetically-derived dose (KMD)" has contributed to confusion and debate surrounding the KMD approach. Rather than developing a guidance on the KMD approach, OPP scientists in conjunction with representatives from numerous countries, including Australia, Japan and UK, are currently in the process of drafting a guidance on integrating kinetic information into the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) evaluations of pesticide risk assessment, which can be linked to an OPP public website and utilized by OPP staff once available. After JMPR panel review and revision, this guidance will be considered for adoption in the Fall of 2023. In addition to the JMPR guidance, OPP is leading multiple efforts to further facilitate the use of kinetic information in a weight-of-evidence (WoE) approach to inform dose selection in toxicity testing studies, and to aid better interpretation of dose-response data for pesticide risk assessment. For example, OPP co-hosted an international symposium in September 2020; conducted several case studies which resulted in three publications in peer-reviewed journals to date; and presented at several international conferences, including the Society of Toxicology annual meeting, the British Toxicology Society Annual Congress, and the International Congress of Toxicology.

- **Proposed Corrective Action 1**: By June 30, 2024, OCSPP will update an OPP public website that points to the kinetic guidance currently being developed by JMPR, which is anticipated to be available in final in the Fall of 2023.

- **Target Completion Date**: June 30, 2024

Recommendation 2: Issue guidance on using and applying a weight-of-evidence approach in cancer-risk assessments for pesticides.

- **OCSPP Response:** EPA was one of the first regulatory bodies to provide guidance on the application of a WoE approach for human risk assessment when it published the "Guidelines for Carcinogenic Risk Assessment" in the 1980s. These guidelines were updated in 2005 to reflect advances in the scientific understanding of carcinogenesis and currently serve as the guidance for the entire Agency for weighing and integrating evidence when evaluating the carcinogenic potential of a chemical. As Agency guidance, the Cancer Assessment Review Committee (CARC) follows the 2005 "Guidelines for Carcinogenic Risk Assessment," when assessing the carcinogenic potential of a pesticide and when determining the appropriate cancer classification.

  The 2005 Guidelines for Carcinogenic Risk Assessment "emphasizes the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents" and includes additional discussion of WoE considerations when evaluating multiple lines of evidence throughout the document. The WoE approaches described in the Guidelines are consistent with EPA WoE guidance documents for some non-cancer effects, such as endocrine disruption (2011) and ecological risk assessment (2016).

  Although the 2014 National Academies (NAS) Report cited in the Draft Report expressed concerns with using the phrase WoE, the NAS' concerns were not related to the process. The NAS preferred the term "evidence integration" over WoE because they considered it more useful and descriptive of the process. Regardless of the term used, the NAS still supported a qualitative process for integrating multiple lines of evidence to reach a scientific judgement using a WoE narrative that describes "the strength of the case for or against a specific hazard when all the available evidence is taken into account," which is consistent with the 2005 Guidelines for Carcinogenic Risk Assessment.

  To avoid developing a separate WoE guidance for pesticides that could impact other program offices, OPP will develop guidance within the CARC Standard Operating Procedure (SOP) to more clearly state how the Committee establishes relevant lines of evidence, determines the reliability of the data, identifies uncertainties, and qualitatively weighs and integrates the data in its cancer-risk assessments for pesticides. This process is consistent with guidance presented in the 2005 Guidelines for Carcinogenic Risk Assessment, but will be more explicitly stated in the updated CARC SOP.

- **Proposed Corrective Action 2**: OPP will update the CARC SOP to include guidance to more clearly state the WoE process.

- **Target Completion Date**: June 30, 2023

Recommendation 3: Update the docket for 1,3-dichloropropene to include all required materials, including meeting minutes and a list of participants, for meetings between EPA and the registrant related to the 1,3-dichloropropene pesticide-registration review and cancer assessment.

- **OCSPP Response:** 40 CFR 155.152 requires that minutes of meetings with outside parties to discuss matters relating to a Registration Review be placed in the registration review docket. Meetings on other regulatory actions are not for public participation and there is not a docketing requirement for these meetings in the regulations. OPP staff have just completed the physical transition from offices in Arlington Virginia to the Federal Triangle Complex. For this corrective action, OPP will search for any available additional meeting materials and/or notes in the existing paper files on the cancer assessment and, if additional relevant materials are identified, will add to the 1,3-dichloropropene registration review docket.

- **Proposed Corrective Action 3**: OPP will complete its search of any available existing meeting materials and/or meeting notes on the 1,3-dichloropropene cancer assessment and add any additional materials found to the 1,3-dichloropropene registration review docket.

- **Target Completion Date**: December 15, 2023

Recommendation 4: Issue guidance to clarify when to docket meetings related to a registration for other related activities that occur concurrent to the pesticide-registration-review process, such as the cancer-reassessment process.

- **Proposed Corrective Action 4**: OPP will develop and implement internal guidance to clarify when to docket meetings related to pesticide registration review for the specific related activity of a cancer assessment that occurs concurrent to the registration review process.

- **Target Completion Date**: December 15, 2023

Recommendation 5: Conduct a comprehensive literature search that identifies all published scientific studies concerning the potential carcinogenicity of 1,3-dichloropropene, including a methodology to reconcile inconsistencies in the scientific data and publish the results of the literature search and reconciliations.

- **OCSPP Response**: OCSPP recognizes that there was an oversight in the literature search conducted to support registration review for 1,3-dichloropropene, such that all synonyms for the chemical name were not included. As a result, some open literature studies were

missed that could inform the potential carcinogenicity of 1,3-dichloropropene and subsequently not evaluated for relevance and/or acceptability. To supplement the original literature search, in 2021 OPP conducted a comprehensive literature search with updated search terms that identifies all published scientific studies for 1,3-dichloropropene, which includes any studies that may inform the carcinogenic potential of 1,3-dichloropropene. A preliminary screen of the results did not identify any studies that would change the conclusion of the CARC. The results of the search and rationale for excluding any studies will be published in the 1,3-dichloropropene registration review docket.
OPP's *Guidance for Considering and Using Open Literature Toxicity Studies to Support Human Health Risk Assessment* outlines procedures to conduct comprehensive searches, but OPP will augment the SOP used by staff to conduct literature searches to ensure these procedures are effectively followed and to avoid a similar oversight in the future. Any inconsistencies in the scientific data should be addressed when studies are evaluated and as part of the WoE process.

- **Proposed Corrective Action 5**: OPP will upload into the 1,3-dichloropropene registration review docket the results of its 2021 comprehensive literature search (with updated search terms that identify all published scientific studies for 1,3-dichloropropene, including studies that may inform the carcinogenic potential of 1,3-dichloropropene) as well as its rationale for excluding any studies.

- **Target Completion Date**: March 31, 2023

Recommendation 6: Update the Cancer Assessment Review Committee (CARC) standard operating procedures (SOPs) to comply with the Office of Pesticide Programs' literature search standard operating procedures and the broader quality principles in the Office of Management and Budget's 2002 Information Quality Guidelines, which includes a methodology to reconcile inconsistencies in the scientific data.

- **OCSPP Response**: OPP conducts chemical-specific literature searches as part of registration review to identify toxicological studies in the published literature that may impact the human health risk assessment. Although studies identified as part of this literature search may be used to assess the carcinogenic potential of a chemical, the CARC SOP does not currently include a procedure to conduct a literature search for chemicals that are undergoing a reassessment of the cancer classification. The CARC SOP will be updated to include a literature search procedure.

- **Proposed Corrective Action 6**: OPP will revise the Cancer Assessment Review Committee (CARC) SOP to include a literature search process for all pesticides that are brought to the CARC for cancer reclassification

- **Target Completion Date**: June 30, 2023

Recommendation 7: Issue procedures to document:

a. Independence of Cancer Assessment Review Committee members from the work products they review.

b. That appropriate expertise is represented on the Cancer Assessment Review Committee for each meeting.
c. When other ad-hoc voting members, such as scientists from other EPA offices, should be added to the Cancer Assessment Review Committee.
d. Regular assessments of the Cancer Assessment Review Committee to monitor and correct deficiencies and to determine whether applicable internal peer review standards are being met.

- **OCSPP Response:** The Health Effects Division (HED) Cancer Assessment Review Committee (CARC) is an internal expert consultation panel that provides the internal forum for scientists to present and defend their conclusions concerning the carcinogenic potential of a pesticide chemical and for interpretation of the required Part 158 cancer studies. CARC members are selected by the HED Management Team from candidates who apply to the HED Special Project Announcement for CARC membership. Membership on this committee is based on the individual's scientific expertise and experience in the relevant subject matter. Committee members are primarily chosen from HED staff; however, representative members from other OPP science divisions (e.g., Antimicrobials Division, Biopesticides and Pollution Prevention Division) may be appointed by their respective Division Directors. Ad hoc members of the committee include the scientist presenting the data to the committee and scientists from other offices (Office of Research and Development (ORD), Office of Pollution Prevention and Toxics (OPPT), etc.), as assigned.

  The CARC SOP will be updated to address the independence of CARC members from the work products they review, to ensure there is the appropriate expertise on the CARC for each meeting, and to better describe the voting process for ad hoc scientists when needed. As part of OPP's Quality Assurance Plan, all policies and procedures including the CARC SOP are currently re-evaluated on a regular basis.

- **Proposed Corrective Action 7**: OPP will revise the CARC SOP to include the above OIG recommendations specifically addressing the independence of CARC members from the work products they review, ensuring there is the appropriate expertise on the CARC for each meeting, including ad hoc voting scientists when needed. OPP will continue to regularly assess CARC processes and procedures and update the SOP as needed.

- **Target Completion Date**: June 30, 2023

Recommendation 8: Conduct an external peer review on the 1,3-dichloropropene cancer-risk assessment.

- **OCSPP Response:** The KMD and toxicokinetic information aided in the interpretation of the tumor findings in the mouse carcinogenicity study as this piece of information helped to elucidate the shape of the dose-response curve observed in the OCSPP test guideline studies. This, along with newer data that addressed previous uncertainties provided a more robust understanding of the toxicologic pathways and carcinogenic potential of 1,3-dichloropropene, which impacted the cancer classification and subsequent risk assessment. This cancer WOE assessment that considered toxicokinetics,

genotoxicity, and carcinogenicity data for 1,3-dichloropropene has been peer reviewed by a third-party (SciPinion) organized panel, sponsored by the registrant (Hays *et al.*, 2020). SciPinion's peer review process is similar to a FIFRA SAP review (see comparison in Table 1). The scope and purpose of this specific review are the same as the one proposed by the OIG (Table 2).

Given the highly-specialized disciplines required for such a review, finding additional qualified, objective reviewers who are willing to participate will be extremely challenging. Several of the reviewers on the SciPinion panel are likely to be nominated as potential candidates. As such, conducting an additional external peer review specific to the 1,3-dichloropropene cancer risk assessment is unlikely to result in a different conclusion reached by the SciPinion panel or the OPP CARC. Specifically, the SciPinion panel concluded that a cancer WOE classification of "not likely to be carcinogenic to humans" is best supported for 1,3-dichloropropene; and the OPP CARC classified 1,3-dichloropropene to "suggestive evidence of carcinogenic potential." Both the CARC review and the SciPinion expert panel concluded that a downgrade in the previous cancer classification of "likely to be carcinogenic to humans" is appropriate and supported by the available data.

Table 1. Comparison of the review processes between the SciPinion panel and a FIFRA SAP

	SciPinion	**FIFRA SAP**
Time frame	~4 to 5 months	~ 9 months
Standard operating procedures	Methods for recruiting, verifying, assembling, and managing expert panels follow internal SOP (published in Kirman 2019)	Methods for recruiting, verifying, assembling, and managing expert panels follow agency SOP
Number of panel members	14 for the 1,3-D WoE review (four former EPA)	7 tier-1 committee members + 10-12 ad hoc reviewers
Potential panel members considered	1,491 for the 1,3-D WoE review	Public call for nominations, Usually resulting in 20-30, sometimes 70-100
Candidate selection criteria	Have expertise, objective, available and willing to participate	Have expertise, objective, available and willing to participate
Panel selection criteria	Conflict of interest, expertise verification, engagement analysis	Conflict of interest, expertise, verification, balance of the committee

Panel selection analysis	Quantitative	Qualitative; semi quantitative to meet FACA balance requirements
Restrictions	US and international experts	US citizens, occasionally non-US citizens who waive salary or satisfy certain requirements toward seeking citizenship
Sources for identifying panel members	Internal database, authors of recent publications on the topic, profiles on social media, general internet searches, referrals	Nominations, internal database, referrals
Meeting format	Virtual and private	Hybrid and public
Review process	Individuals review materials and answer charge questions The panel participate in online comment and debate Finalize responses to charge questions	Individuals review materials and answer charge questions The panel participate in comment and debate Finalize responses to charge questions
Quantitative consensus analysis	Yes	No, but seek and encourage consensus
Public comments	No	Yes

Table 2. Comparison between the SciPinion panel review and the OIG-recommended review

	SciPinion	**OIG-recommended review**
Topic	Cancer weight of evidence assessment considering kinetic, genotoxicity, and cancer data	Cancer weight of evidence assessment considering kinetic, genotoxicity, and cancer data
Areas of expertise needed to answer charge questions	Genotoxicity, kinetics, cancer bioassay, weight of evidence	Genotoxicity, kinetics, cancer bioassay, weight of evidence
Number of questions	53	Likely to be less
Review findings	Publicly available as a publication in a peer-reviewed journal and in an online report	Publicly available on the docket

	(https://app.scipinion.com/surveys/145/results	

While an additional peer review specific to the 1,3-dichloropropene is unlikely to provide new insights into this chemical's cancer risk assessment, OCSPP acknowledges that technical comments and scientific recommendations provided by an external peer review entity (e.g., the FIFRA SAP) on the broader topic of data interpretation using modernized approaches would be of great value. For example, a peer review package that includes discussions on (1) incorporating mechanistic data from *in vivo* and *in vitro* studies, as well as computational modeling (such as pharmacokinetic and pharmacodynamic modeling, computational chemistry, and statistical methods), to interpret dose response data obtained from animal toxicity studies; (2) using *in vivo*, *in vitro* and *in silico* methods to optimize animal toxicity studies for generating human relevant dose-response data; and (3) multiple case studies, including 1,3-dichloropropene. When additional case studies are developed to establish scientific confidence in these modernized approaches, OPP plans to take this more comprehensive package to the SAP for peer review.

- **Proposed Corrective Action 8**: In lieu of conducting an external peer review on the 1,3-dichloropropene cancer-risk assessment, OPP will rely upon the comprehensive 1,3-dichloropropene peer review conducted by SciPinion in 2020.

- **Target Completion Date:** Completed

Recommendation 9: Issue specific criteria requiring external peer review of Office of Pesticide Programs' risk assessments that use scientifically or technically novel approaches, or are likely to have precedent-setting influence, on future risk assessments, in accordance with the Office of Management and Budget's Final Information Quality Bulletin for Peer Review.

- **Response:** OCSPP agrees with Proposed Recommendation 9 and proposes the following Corrective Action to implement it.

- **Proposed Corrective Action 9**: OCSPP will develop a Standard Operating Procedure to determine when an external peer review is required for assessments using scientifically or technically novel approaches or likely to have precedent-setting influence. This guidance will be used to ensure consistency in the external peer review process across OSCPP.

- **Target Completion Date**: June 30, 2024

References:

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Appendix B

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