MEMORANDUM

DATE: April 14, 2021

SUBJECT: 1,3-Dichloropropene (1,3-D): Revised Tier II Incident and Epidemiology Report

PC Code: 029001
Decision No.: 573108
Petition No.: NA
Risk Assessment Type: NA
TXR No.: NA
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This memorandum supersedes the previous version [D455269, S. Recore, 12/02/2019] and has been amended to reflect the correct search code that was used in 2019 to conduct the epidemiology literature search of the open literature for 1,3-D. The prior version of this memo included a transcription error and did not contain the actual search code that was used in the literature search for 1,3-D. The correct search string is included here in this revised memorandum to replace the incorrect version and is listed in Table 3. No changes were necessary or made to our analysis or conclusion. HED is reissuing this memorandum to address this technical correction only.

Summary and Conclusions

This memo is the 1,3-Dichloropropene (1,3-D) Tier II Incident and Epidemiology Report. Prior to this memorandum, 1,3-D incidents were last reviewed in May 2013 (E. Evans and S. Recore, D411762, 5/15/2013). In 2013, the Health Effects Division (HED) prepared a preliminary Tier I human incident review of 1,3-D human incident reports by consulting the Office of Pesticide Programs (OPP) Incident Data System (IDS) for reports of poisoning incidents. In 2013, based on the low frequency and severity of incident cases reported for 1,3-D in both IDS and NIOSH SENSOR-Pesticides, further investigation was not warranted.1

For this 1,3-Dichloropropene (1,3-D) Tier II Incident and Epidemiology Report, HED found the majority of incidents involving 1,3-D were low in severity (82% in IDS and 89% in SENSOR-Pesticides). Most of the incidents reviewed for this memorandum reported that individuals experienced minor symptoms such as burning eyes and coughing. These are symptoms which were minimally traumatic and resolved rapidly, and are likely the result of chloropicrin exposure. Chloropicrin is used as a warning agent with other more toxic active ingredients, such as 1,3-D because it has a strong odor and causes respiratory and eye irritation.

In IDS (71%), SENSOR-Pesticides (83%), and CA PISP (96%), exposure from drift/volatilization was responsible for the most reported 1,3-D incidents. These incident events, often involving multiple cases, resulted from off-target drift or volatilization of the a 1,3-D product onto nearby farms, fields and residential areas. These events exposed workers and residents of neighboring communities.

Epidemiological studies investigating the association between 1,3-D and health outcomes available in the open literature were reviewed. Overall, there was insufficient evidence to suggest a clear associative or causal relationship exists between 1,3-D exposure and the health outcomes investigated in the studies reported here. The Agency will continue to monitor the epidemiology data and -- if a concern is triggered -- additional analysis will be conducted.

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1 For this review, no medical case reports were investigated.
1. BACKGROUND

1,3-Dichloropropene (1,3-D) is a nematicide/fungicide/insecticide/herbicide registered for preplant application to terrestrial food crop (field and vegetable crop and orchard crop) and terrestrial nonfood (nursery stock and tobacco) use sites. 1,3-D is a Restricted Use Pesticide (RUP) and is often combined with chloropicrin which is used as a warning, or sentinel agent because it has a strong odor and causes minor respiratory and eye irritation.

HED is currently re-evaluating the toxicity, exposure, and risk profile of 1,3-D under the Food Quality Protection Act (FQPA)-mandated Registration Review program. The registration review program is designed to ensure EPA evaluates new information regarding pesticides on a 15-year cycle, and to update the risk assessment and initiate new regulatory requirements, when appropriate, to ensure the protection of human health and the environment. Pesticides included in the registration review program are pesticides for which EPA completed a Re-registration Eligibility Decision under the FQPA.

A Tier II incident and epidemiology report, as compared to a Tier I incident and epidemiology report, provides additional details and greater depth in scope of review of information relating to human exposure. Utilization of these data will aid HED in better defining and characterizing the potential risk of 1,3-D pesticide products to the U.S. population, and particular sub-groups such as workers and children.

This 1,3-D Tier II Incident and Epidemiology Report reviews human observation data from a variety of sources including:

- Human incident (poisoning) data from the following sources:
  - OPP’s Incident Data System (IDS) database;
  - National Institute of Occupational Safety and Health (NIOSH) SENSOR-Pesticides;
  - National Pesticide Information Center (NPIC) (Agency Sponsored); and,
  - California’s Pesticide Incident Surveillance Program (PISP).
- Epidemiological studies from the open literature.

Incident data are collected systematically, but differently, across the different databases used by the Agency with respect to such issues as coverage, certainty/confidence, fields/parameters reported, and usability. The aforementioned four pesticide incident data sources (IDS, NIOSH SENSOR-Pesticides, NPIC, and California PISP) were used in this 1,3-D report since they provide useful content and historical perspective. Various other comparable sources of data are available (e.g. the Bureau of Labor Statistics, emergency room outpatient surveillance, National Poison Data System (NPDS), etc.) but are not included in this review. By looking across the five data sources which were used, the Agency is confident that we are considering adequate and appropriate information to discern trends and patterns in permethrin-associated acute pesticide poisonings, or “incidents.”

It is important to recognize, however, that reports of adverse health effects allegedly due to a specific pesticide exposure (i.e., an “incident”) are largely self-reported and therefore, generally speaking, neither exposure to a pesticide nor reported symptoms (or the connection between the two) are validated. Therefore, only rarely can causation be determined or definitively identified based on incident data. However, incident information can provide important feedback to the Agency. Human incident data, in concert with other human observational studies (biomonitoring and epidemiological studies) and the human health risk assessment, can assist the Agency in determining potential risks of pesticides/pesticide product exposure, and can help characterize that risk. This review assesses acute pesticide poisoning incidents and published epidemiology studies to inform the preliminary risk assessment for 1,3-D.
2. REVIEW OF HUMAN INCIDENT DATA


The OPP IDS includes reports of alleged human health incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6 (a) (2) reports from registrants and reports from other federal and state health and environmental agencies and individual consumers. Since 1992, OPP has compiled these reports in IDS. IDS contain reports from across the U.S. and most incidents contained in the system have all relevant product information recorded. Case reports or “narratives” are provided for each incident, with varying levels of detail; however, there is no effort at validating or assessing how likely it is that the reported exposure is causally related to the reported outcome. Because IDS has such extensive coverage, it is useful for providing temporal trend and geographic pattern information. The system is also useful for determining whether risk mitigation has helped reduce potential pesticide exposure through a decreased number of reported incidents.

For this evaluation, the OPP IDS was utilized for pesticide incident data on the active ingredients 1,3-D (PC Code: 029001). IDS records incidents in one of two modules: Main IDS and Aggregate IDS. Main IDS contains incidents resulting in higher severity outcomes and provides more detail with regard to case specifics. This system stores incident data for death, major and moderate incidents, and it includes information about the location, date and nature of the incident. Main IDS incidents involving only one active ingredient (as opposed to pesticide products with multiple active ingredients) are considered to provide more certain information about the potential effects of exposure from the pesticide. The higher severity outcomes include:

- H-A (death): If the person died;
- H-B (major): If the person alleged or exhibited symptoms which may have been life-threatening, or resulted in adverse reproductive effects or in residual disability; and
- H-C (moderate): If the person alleged or exhibited symptoms more pronounced, more prolonged or of a more systemic nature than minor symptoms, usually some form of treatment of the person would have been indicated, symptoms were not life threatening and the person has returned to his/her pre-exposure state of health with no additional residual disability.

Aggregate IDS contains incidents resulting in less severe human incidents (minor, unknown, or no effects outcomes). These are reported by registrants only as counts in what are aggregate summaries. The less severe human incidents include:

- H-D (minor): If the person alleged or exhibited some symptoms, but they were minimally traumatic, the symptoms resolved rapidly and usually involve skin, eye or respiratory irritation; and
- H-E (unknown or no effects): If symptoms are unknown, unspecified or are alleged to be of a delayed or chronic nature that may appear in the future.

For the Main IDS, from January 1, 2014 to September 17, 2019, there are seven cases reported that involve the active ingredient 1,3-D. Two of these incidents involved the single active ingredient 1,3-D only and the other five incidents involved multiple active ingredients. Three incidents were classified as minor severity and four incidents were classified as moderate severity. The incidents are described in Appendix A. Two incidents were the result of a product spill, two incidents were attributed to drift exposure following aerial application of the product and three were attributed to volatilization exposure following shank injection of the product.
The symptoms most often reported were neurological and included headache, sensory irritation and dizziness. Other symptoms included coughing, sore throat, eye irritation, dermal swelling and redness and nausea.

In Aggregate IDS, queried from January 1, 2014 to September 17, 2019, there are 15 incidents involving 1,3-D. These incidents were classified as minor severity.

2.2. SENSOR-Pesticides (2010-2015)

The Center for Disease Control’s National Institute for Occupational Safety and Health (CDC/NIOSH) manages a pesticide surveillance program and database entitled the Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides. All cases must report at least two adverse health effects. Evidence for each case is evaluated for its causal relationship between exposure and illness based on the NIOSH case classification index. Using standardized protocol and case definitions, SENSOR-Pesticides state coordinators, operating out of the state’s department of health, receive state pesticide incident reports from local sources, then follow up with case sources to get incident scenario to obtain medical records and verify exposure scenario information. This database includes pesticide illness case reports from multiple states from 1998-2015.

A query of SENSOR-Pesticides from 2010-2015 identified a total of 36 cases involving 1,3-D. Two cases involved a single active ingredient and 34 cases involved multiple active ingredients. Thirty-two cases were low in severity and four cases were moderate in severity. Twenty-three cases were classified as non-occupational and 13 cases were classified as occupational. All four of the moderate severity cases were work related. All but three of the 36 cases involved 1,3-D and chloropicrin, with latter added as a warning agent.

The symptoms reported most often were ocular, respiratory, and neurological (Table 1). The most frequently reported health effects among cases were: eye pain/irritation/inflammation (n=26) and lacrimation (tearing of the eyes) (n=16), followed by upper respiratory pain/irritation (n=13), nausea (n=11) and headache (n=9).

<table>
<thead>
<tr>
<th>Health Effect</th>
<th># of Occurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular</td>
<td>28</td>
</tr>
<tr>
<td>Respiratory</td>
<td>19</td>
</tr>
<tr>
<td>Nervous System</td>
<td>15</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>12</td>
</tr>
<tr>
<td>Misc.</td>
<td>9</td>
</tr>
<tr>
<td>Dermal</td>
<td>4</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1</td>
</tr>
</tbody>
</table>

* Cases may report multiple health effects

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2 SENSOR-Pesticides webpage: http://www.cdc.gov/niosh/topics/pesticides/overview.html
3 https://www.cdc.gov/niosh/topics/pesticides/pdfs/casedef.pdf
5 Currently participating states are: California, Florida, Illinois, Louisiana, Michigan, Nebraska, New Mexico, North Carolina, Oregon, Texas and Washington. The participating states for a given year vary depending on state and federal funding for pesticide surveillance.
The majority of cases were conducting either routine fieldwork (n=9) or routine indoor living activities (n=21) at the time of their exposure. Most (83%) of the cases (n=30) were classified as drift. It is important to note that the SENSOR definition of “drift” includes volatilization. Twenty-eight cases were classified as low severity and two cases were classified as moderate severity. Notably all 23 of these non-occupational cases were coded for drift exposure. The drift/volatilization events are described below:

- In North Carolina in 2011, case was exposed to 1,3-D C-17 (Reg No. 62719-12) that was sprayed in a field about 50 yards from his house.
- In North Carolina in 2012, two cases experienced burning eyes and bad taste in their mouths due to drift from an application of 1,3-D C-17 (Reg No. 62719-12) to a farm across the road from their home.
- In Washington in 2012, a multiple exposure drift event led to 19 cases made ill from a pre-plant soil application of 1,3-D C-35 (Reg. No. 67219-302) that drifted/volatilized into a nearby residential community. WSDA cited the applicator for not following the product label requirements on soil preparation and this applicator’s license was suspended.
- In California in 2013, five cases performing miscellaneous agricultural work were exposed the product (Reg No. 8536-43) when wind blew the plastic cover off an adjacent field that had been fumigated. The field was about 420 feet away from their work site.
- In North Carolina in 2014, three cases were exposed when a neighboring farmer was fumigation tobacco with 1,3-D C-17 (Reg No. 62719-12).


The National Pesticide Information Center or NPIC is a cooperative effort between Oregon State University and EPA which is funded by EPA to serve as a source of objective, science-based pesticide information and respond to inquiries from the public and to incidents. NPIC functions nationally during weekday business hours through a toll-free telephone number in addition to the internet (www.npic.orst.edu) and email. Similar to Poison Control Centers, NPIC’s primary purpose is not to collect incident data, but rather to provide information to inquirers on a wide range of pesticide topics, and direct callers for pesticide incident investigation and emergency treatment. Nevertheless, NPIC does collect information about incidents (approximately 4000 incidents per year) from inquirers and records that information in a database. NPIC is a source of national incident information but generally receives fewer reports than IDS. Regardless, if a high frequency is observed in IDS, NPIC provides an additional source of information to see whether there is evidence of consistency across national data sets or possibly duplication and additional information about the same incident(s).

From January 1, 2008 to August 31, 2019, one human incident involving 1,3-D was reported to NPIC. This incident was classified by NPIC as unlikely related to 1,3-D and was not further reviewed.

2.4. California Pesticide Illness Surveillance Program (PISP) (2012-2016)

The Pesticide Illness Surveillance Program (PISP) maintains a database of pesticide-related illnesses and injuries. Case reports are received from physicians and via workers’ compensation records. The local County Agricultural Commissioner investigates circumstances of exposure. Medical records and investigative findings are then evaluated by DPR technical experts and entered into an illness registry.

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6 The SENSOR-Pesticides definition of drift: “Indicates whether the individual was exposed via the movement of pesticides away from the treatment site. The pesticide spray, mist, fumes or odor are carried from the target site by air”
PISP contains both residential and occupational pesticide incidents. PISP has limited coverage (only California) and is therefore not particularly useful for identifying trends over time. However, the incident information is entered by professionals with expertise in pesticides who extensively follow-up on each reported case, establishing a high degree of confidence in the information provided for each reported incident.

In PISP from 2012 to 2016 there were 129 case reports involving 1,3-D. All of cases were classified as agricultural cases which indicates that the pesticide use intended to contribute to production of an agricultural commodity. One of these cases was classified as having a possible relationship to 1,3-D and 122 cases were classified as having probable relationship with 1,3-D and six cases were classified as having a definite relationship with 1,3-D. Most (71%) individuals reported being exposed as a field worker. Ninety six percent (n=124) of the incidents were reported as exposure from drift. The complete list of exposure scenarios is in Table 2.

Table 2. Exposure Scenario Frequency of 1,3-D Incidents Reported to CA PISP (2012-2016)

<table>
<thead>
<tr>
<th>Exposure Scenario</th>
<th>Number of Reported Incidents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field Worker</td>
<td>91</td>
</tr>
<tr>
<td>Packaging/Processing</td>
<td>12</td>
</tr>
<tr>
<td>Routine Indoor</td>
<td>7</td>
</tr>
<tr>
<td>Routine Outdoor</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
</tr>
<tr>
<td>Applicator</td>
<td>3</td>
</tr>
<tr>
<td>Mixer/Loader</td>
<td>2</td>
</tr>
<tr>
<td>Routine (Other or Unspecified)</td>
<td>1</td>
</tr>
</tbody>
</table>

The symptoms most often reported were ocular (n=110), respiratory (n=49), neurological (n=46), gastrointestinal (n=36), and dermal (n=4). Note that a patient could exhibit multiple symptoms. Ocular symptoms reported were burning, tearing, irritation, and itchiness. Respiratory symptoms reported included shortness of breath, throat irritation, nose irritation, wheezing, coughing, and difficulty breathing. Neurological symptoms reported include dizziness, headache, weakness, numbness, and tingling. Gastrointestinal symptoms reported were nausea, diarrhea, abdominal pain, and vomiting. Dermal symptoms reported include itchiness, rash, redness, and burning sensation.

2.5. Acute Incident Summary

The majority of incidents reported involving 1,3-D were low in severity (82% in IDS and 89% in SENSOR-Pesticides). Most of the incidents reviewed for this memorandum reported that individuals experienced minor symptoms such as burning eyes and coughing. These are symptoms, which were minimally traumatic and resolved rapidly and are likely the result of chloropicrin exposure. Chloropicrin is used as a warning agent with other more toxic active ingredients, such as 1,3-D, because it has a strong odor and causes respiratory and eye irritation. These minor symptoms from chloropicrin exposure are

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7 **Definite relationship** indicates that both physical and medical evidence document exposure and consequent health effects. **Probable relationship** indicates that limited or circumstantial evidence supports a relationship to pesticide exposure. **Possible relationship** indicates that health effects correspond generally to the reported exposure, but evidence is not available to support a relationship.
likely leading to evacuations of individuals from residences before developing more severe symptoms from 1,3-D exposure.

In IDS (71%), SENSOR-Pesticides (83%), and CA PISP (96%) exposure from drift/volatilization was responsible for the most reported 1,3-D incidents. Incident events, often involving multiple cases, resulted from off-target drift or volatilization of the a 1,3-D product onto nearby farms, fields and residential areas. These events exposed workers and residents of neighboring communities. The cases reported experiences symptoms such as burning and tearing eyes, coughing, headaches and dizziness.

3. REVIEW OF PUBLISHED EPIDEMIOLOGY

3.1. Introduction

As part of registration review, EPA’s OPP is responsible for assessing if there is new data or information that warrants a new human health risk assessment. To support this effort, OPP conducted a systematic literature review of peer reviewed epidemiology studies that examined the association between 1,3-D and adverse health effects. The specific aims of the epidemiology literature review were to:

1. Conduct a literature search and assemble a database of epidemiological studies examining the human health effects associated with 1,3-D exposure; and,
2. Review, summarize, and assess the quality of the assembled literature.

This report describes the systematic literature review approach and results of OPP’s evaluation of epidemiology study findings. This evaluation focused on characterizing results and identifying strengths and limitations with respect to health outcomes evaluated in the literature. Specific sections of this report will include a description of the literature search and methodology and evaluation approach, a synthesis of findings by health outcomes evaluated in the literature, and finally a summary of conclusions.

3.2. Review Framework

The National Academy of Sciences National Research Council (NRC) and the National Academy of Medicine (formerly the Institute of Medicine) define systematic review as “a scientific investigation that focuses on a specific question and uses explicit, pre-specified scientific methods to identify, select, assess, and summarize the findings of similar but separate studies. In a 2014 report, NRC identified systematic literature review strategies as “appropriate for EPA” and “specifically applicable to epidemiology and toxicity evaluations.”

EPA OPP published a framework for incorporating epidemiological data into risk assessments for pesticides which described a systematic review process relying on standard methods for collecting, evaluating, and integrating the scientific data supporting Agency decisions. The epidemiology framework characterized “fit for purpose” systematic reviews for incorporating human epidemiology data into OPP risk assessments for pesticides, meaning that the complexity and scope of each systematic

review is tailored to a specific analysis and follows the key characteristics outlined in the Cochrane Handbook:\footnote{Higgins, J. P., & Green, S. (Eds.). (2011). Cochrane handbook for systematic reviews of interventions (Vol. 4). John Wiley & Sons.}

- Clearly stated set of objectives with pre-defined eligibility criteria for studies;
- Explicit, reproducible methodology;
- Systematic search to identify all relevant studies;
- Assessment of the validity of the findings from the identified studies; and,
- Systematic presentation and synthesis of the characteristics and findings of the included studies.

Following the procedures described in the OPP epidemiology framework, OPP conducted a formalized literature review to collect, evaluate, and integrate evidence from relevant epidemiological literature on the association between 1,3-D exposure and human health outcomes to evaluate whether exposure to this chemical is associated with an increased (or decreased) risk of adverse health outcomes.

3.3. Methods

3.3.1. Systematic Literature Search

The literature search methodology followed the guidance provided in the National Toxicology Program/Office of Health Assessment and Translation (NTP/OHAT) Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration, January 9, 2015. For the search, the following population, exposure, comparator, and outcome of interest (PECO) criteria below guided the inclusion/exclusion criteria and selection of term:

- Population of interest: Population studied must be humans with no restrictions, including no restrictions on age, life stage, sex, country of residence/origin, race/ethnicity, lifestyle, or occupation
- Exposure: Exposure studied must be to 1,3-D in any application via any route of exposure.
- Comparator: Exposed or case populations must be compared to a population with low/no exposure or to non-cases to arrive at a risk/effect size estimate of a health outcome associated with 1,3-D exposure.
- Outcome: All reported human health effects, with no restrictions on human system affected (effects could be based on survey or other self-report, medical records, biomarkers, publicly available health data, or measurements from human sample populations).

Based on these PECO criteria, inclusion/exclusion terms were identified, and a literature search was conducted in PubMed, PubMed Central, Science Direct, and Web of Science. The literature search included all peer-reviewed publications through September-2019. Results were limited to those with human subjects and an English language abstract. The search code used to identify publications is listed in Table 3.
Table 3. 1,3-D Literature databases, search strategies, search dates, and publications returned\(^{11}\)

<table>
<thead>
<tr>
<th>Database</th>
<th>Search Strategy</th>
<th>Search Date</th>
<th>Publications Returned</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed</td>
<td>(((&quot;telone&quot; OR &quot;1,3-dichloropropene&quot; OR &quot;1,3-DCP&quot; OR &quot;1,3-D&quot;) AND (human AND (&quot;adverse health effect&quot; OR epidemiologic study OR cohort OR case control OR case-control OR cross section OR cross-section OR cluster OR environmental exposure OR occupational exposure OR ecologic study OR aggregate study OR &quot;pancreatic&quot; OR &quot;pancreas&quot; OR &quot;hematologic malignancy&quot;))))</td>
<td>9/26/2019</td>
<td>38</td>
</tr>
<tr>
<td>PubMed Central</td>
<td>(((&quot;telone&quot; OR &quot;1,3-dichloropropene&quot; OR &quot;1,3-DCP&quot; OR &quot;1,3-D&quot;) AND (human AND (&quot;adverse health effect&quot; OR epidemiologic study OR cohort OR case control OR case-control OR cross section OR cross-section OR cluster OR environmental exposure OR occupational exposure OR ecologic study OR aggregate study OR &quot;pancreatic&quot; OR &quot;pancreas&quot; OR &quot;hematologic malignancy&quot;))))</td>
<td>10/3/2019</td>
<td>183</td>
</tr>
<tr>
<td>Web of Science</td>
<td>(((&quot;telone&quot; OR &quot;1,3-dichloropropene&quot; OR &quot;1,3-DCP&quot; OR &quot;1,3-D&quot;) AND (human AND (&quot;adverse health effect&quot; OR epidemiologic study OR cohort OR case control OR case-control OR cross section OR cross-section OR cluster OR environmental exposure OR occupational exposure OR ecologic study OR aggregate study OR &quot;pancreatic&quot; OR &quot;pancreas&quot; OR &quot;hematologic malignancy&quot;))))</td>
<td>9/26/2019</td>
<td>25</td>
</tr>
</tbody>
</table>
| Science Direct    | ((("telone" OR "1,3-dichloropropene" OR "1,3-DCP" OR "1,3-D"
OR") AND human AND ("adverse health effect" OR epidemiologic study OR cohort OR case-control OR cross-sectional OR cluster OR "environmental exposure" OR "occupational exposure")) | 9/27/2019   | 107                   |

* indicates truncation (i.e., that alternate endings were searched)

Based on the PECO criteria and search terms described above, the literature search aimed to identify original, peer-reviewed publications on epidemiologic studies. Exclusion criteria were also identified prior to collecting potentially relevant publications. Publications were excluded for the following reasons: not full text (e.g., abstracts); not peer-reviewed; not in English; non-human study subjects; in-vitro studies; fate and transport studies; outcome other than human health effects (e.g., environmental measures); experimental model system studies; no 1,3-D-specific investigation (e.g., general herbicide); no risk/effect estimate reported (e.g., case studies/series); no original data (e.g., review publications). In addition, the review focused on epidemiology studies and excluded publications on acute poisonings and overexposure.

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\(^{11}\) The number of publications reported reflects a net return and does not consider duplicates (the same publication returned in multiple databases and/or multiple times in one database).

\(^{12}\) While the search focused on original peer-reviewed publications, the OPP does seek out and consider other sources of information that are not peer-reviewed (e.g., letters to the editor, corrections, commentary) on a case-by-case basis when this information provides clarification or other material findings or information of relevance to our evaluation of the literature.
A key element of the inclusion/exclusion criteria hinged on the definition of “human health effect” outcomes. For the purposes of the epidemiology literature review, OPP considered human health effects via the toxicological paradigm presented by the NRC as pathologies or health impairments subsequent to altered structure/function. Thus, studies with outcomes of altered structure (e.g., DNA alteration, sister chromatid exchange, cell proliferation) or biomarker or other exposure outcomes (e.g., in breast milk, urine, cord blood, or plasma) that did not also include an associated health pathology (e.g., cancer, asthma, birthweight) failed to meet the inclusion criteria for “human health effects” for the purposes of this epidemiology literature review.

3.3.2. Supplemental Literature Search

To supplement the open literature search described above, OPP reviewed publications resulting from the Agricultural Health Study (AHS) for publications that satisfied the inclusion/exclusion criteria. The AHS is a federally funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC’s National Institute of Occupational Safety and Health (NIOSH), and the US EPA.

The AHS maintains on its website an electronic list of publications resulting from AHS studies using the AHS cohort. These publications were imported into Endnote, and Endnote was used to run a full text search (“Any Field + PDF with Notes”) for “1,3-D”, “1,3-D”, “1,3-d”, “telone”, and “DCP”, to ensure all AHS publications relevant to the epidemiology literature review were identified. AHS publications that satisfied the inclusion/exclusion criteria as described above were selected for inclusion in the epidemiology literature review.

The final phase of data collection was a reference review of publications captured in the open literature search, the AHS publication search, and previously published OPP documents. References were examined to identify relevant publications that were not captured in either the open literature search or the AHS publication search. Resulting publications from this reference review that satisfied inclusion/exclusion criteria were selected for inclusion in the epidemiology literature review.

3.4. Literature Search Results

The search of the open literature returned 342 unique publications across PubMed, PubMed Central, Science Direct, and Web of Science and these publications were assembled into an EndNote Library (version x9) (7 duplicates were removed). The title and abstract of each publication were screened for potential relevance using the PECO criteria and exclusion criteria described in the Systematic Literature Search section. EPA identified 59 publications based on this approach and eight additional publications were identified that were cited by the publications screened during reference review. Of these 67 publications reviewed, 55 did not include 1,3-D-specific analysis. This yielded a total of 12 publications that reported effect estimates for 1,3-D exposure.

The supplemental search of the AHS EndNote Database identified one additional publication that included the term “1,3-D” in the text. The publication (Alavanja et al, 2007) was reviewed, but did not

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include 1,3-D-specific analysis. Review of the AHS publications did not yield any additional publications that reported effect estimates for 1,3-D exposure.

A summary of the literature search and supplemental AHS search is provided in Figure 1 below.

**Figure 1. Summary of Literature Search Results**

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342 Publications Retrieved from Literature Search

1 AHS Publications Identified in Supplemental Search that were not retrieved in Systematic Literature Search

276 Publications Excluded based on PECO criteria

67 Publications Selected for Systematic Literature Search

12* Publications Selected for Systematic Literature Search

1 Pancreatic Cancer
1 Prostate Cancer
4 Kidney function
2 Liver function
3 Neurodevelopment/ Autism
1 Parkinson’s disease
2 Respiratory Effects
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* Number of publications on health outcomes do not sum because some publications reported on multiple outcomes in a single publication.

### 3.5. Literature Review and Evaluation Approach

#### 3.5.1. Study Review and Quality Assessment

A total of 12 peer-reviewed epidemiologic publications were identified for OPP’s literature review and evaluation. Each publication was reviewed and relevant information was summarized on study design, results, conclusions, the strengths and weaknesses of each study per the epidemiology framework (US EPA, 2016), and recount details including the exposure measurement, outcome ascertainment, number of participants (n), number exposed/number of cases, number in reference (un-exposed/control) group, effect measure (e.g., odds ratio (OR), relative risk (RR), hazard ratio (HR)) and associated estimates of uncertainty and/or statistical significance (e.g., confidence interval (CI), p-value), confounders considered, and methods of analysis. OPP considered these elements in assessing the quality of each publication and its applicability to an overall assessment of the health effects associated with 1,3-D exposure.
The assessment of study quality followed the OPP Framework. As shown in Table 4, the study quality assessment considered aspects such as design, conduct, analysis, and interpretation of study results, including whether study publications incorporated a clearly articulated hypothesis; adequate assessment of exposure; critical health windows; valid and reliable outcome ascertainment; a sample representative of the target population; analysis of potential confounders; characterization of potential systematic biases; evaluation and reporting of statistical power; and, use of appropriate statistical modeling techniques.

Table 4. Epidemiology Study Quality Considerations (Adapted from Table 2 in US EPA, 2016)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure assessment</td>
<td>Exposure assessment includes information on 1,3-D or metabolite in the body, quantitative air sample data, or high-quality questionnaire on chemical-specific exposure assessment during relevant exposure window</td>
<td>Questionnaire based individual level information on 1,3-D</td>
<td>Low quality questionnaire-based exposure assessment, or ecologic exposure assessment, with or without validation</td>
</tr>
<tr>
<td>Outcome Assessment</td>
<td>Standardized tool, validated in study population; or, medical record review with trained staff</td>
<td>Standardized tool, not validated in population, or screening tool; or, medical record review, methods unstated</td>
<td>Subject report, without additional validation</td>
</tr>
<tr>
<td>Confounder control</td>
<td>Good control for important confounders relevant to 1,3-D study question, and standard confounders</td>
<td>Moderately good control of confounders, standard variables, not all variables for 1,3-D study question</td>
<td>Multi-variable analysis not performed, no adjustments</td>
</tr>
<tr>
<td>Statistical Analysis</td>
<td>Appropriate to study question and design, supported by adequate sample size, maximizing use of data, reported well (not selective)</td>
<td>Acceptable methods, questionable study power (esp. sub-analyses), analytic choices that lose information, not reported clearly</td>
<td>Minimal attention to statistical analyses, comparisons not performed or described clearly</td>
</tr>
<tr>
<td>Risk of (other) bias (selection, differential misclassification, other)</td>
<td>Major sources of other potential biases not likely present, present but analyzed, unlikely to influence magnitude and direction of the risk estimate</td>
<td>Other sources of bias present, acknowledged but not addressed in study, may influence magnitude but not direction of estimate</td>
<td>Major study biases present, unacknowledged or unaddressed in study, cannot exclude other explanations for study finding</td>
</tr>
</tbody>
</table>

Note: Overall study quality ranking based on comprehensive assessment across the parameters.

Study design influenced the assessment of study quality. Cohort studies, which enable researchers to assess the temporality of exposure in relation to health outcome and to consider multiple health outcomes, were generally considered higher quality than other study designs. Case-control studies, which are susceptible to recall bias, were generally considered to be of lower quality than nested case-control studies, which may be less susceptible to selection and recall bias. Cross-sectional studies cannot distinguish temporality for exposure in relation to health outcomes; therefore, cross-sectional studies were generally considered lower quality than cohort or case-control studies and were regarded as hypothesis-generating in the absence of additional studies supporting an observed association. The lowest quality study design considered was ecologic, due to an inability to extrapolate observed associations from the group level to the individual level (ecological fallacy) inherent in the ecologic study design. Ecologic studies were generally regarded as hypothesis-generating studies (US EPA, 2016).
Studies that characterized the exposure-response relationship (e.g., with a dose-response curve or trend statistic) were, in general, considered higher quality than studies that did not characterize exposure-response. Studies that specified temporality (i.e., those that determined exposure preceded a health outcome) and studies that specified and explored uncertainties in the analysis were, in general, considered higher quality than studies that failed to specify temporality and studies that lacked an examination of uncertainty. Consistent results between study groups (e.g., a significant and positive association seen for both farmers and commercial applicator study groups within a single study) bolstered the assessment of study quality.

Risk estimates (estimates of effect) reported in epidemiological studies were generally considered as follows:

- No evidence of a positive association between exposure and outcome (e.g., OR ≤ 1.00);  
- No evidence of a significant positive association (e.g., OR > 1.00 but not significant);  
- Evidence of a slight positive association (e.g., 1.00 < OR < 1.30 and significant);  
- Evidence of a positive association (e.g., 1.30 ≤ OR < 2.0 and significant);  
- Evidence of a moderately strong (e.g., 2.0 ≤ OR < 3.0 and significant) or strong (e.g., OR ≥ 3.0 and significant) positive association.\(^{15}\)

However, we recognize that results that fail to attain statistical significance may still indicate clinical, biological, and/or public health importance and may warrant further exploration (US EPA, 2016). We particularly noted large observed associations (e.g., OR ≥ ~2.5) even in the absence of significance, perhaps indicating a smaller than optimal sample size.

### 3.5.2. Categories of Evidence

The categories of evidence described in Table 5 are guided by several documents that have been developed by EPA and others. These include as a main reference a document developed by the Institute of Medicine (now the Academies of Science, Engineering, and Medicine)\(^ {16}\) which detailed various “Categories of Association” which describes guidance for drawing conclusions regarding the overall strength of the evidence that exists regarding any putative linkage between an exposure and a health effect (IOM, 1998). Also considered in developing OPP’s categories of evidence were the NTP’s OHAT document on systematic review and evidence integration (Woodruff and Sutton, 2014), OPP’s epidemiologic framework document (US EPA, 2016), and EPA’s Preamble to the Integrated Science

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\(^{15}\) For publications that reported ORs, RRs, and HRs, the confidence interval (CI) acted as a proxy for significance testing, with CIs that do not contain the null value (OR / RR / HR = 1.00) considered significant. P-value significance considered a critical value of \(\alpha = 0.05\) unless otherwise specified by the authors and noted in the summaries here.

Assessments which serve as a scientific foundation for the review of EPA’s National Ambient Air Quality Standards (US EPA, 2016).

In this memorandum, each category is assigned based on a case-by-case approach that considers the weight of the epidemiological evidence and expert judgement and not a binding or inflexible formulaic approach in deciding the number and/or quality of studies that would be necessary to assign a specific evidence category. When assigning a level of evidence category to an exposure and the body of evidence pertaining to that health effect, the level of quality of the studies available in the peer-reviewed literature for that health effect, the strength of the associations (effect sizes) and consistency of the association in magnitude and direction across available studies was considered, as described in OPP’s epidemiologic framework document.

Table 5. Tier II Epidemiology Studies Categories of Evidence

<table>
<thead>
<tr>
<th>Evidence Category</th>
<th>Description</th>
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</table>
| **Sufficient Epidemiological Evidence of a Clear Associative or Causal Relationship** | *Sufficient epidemiological evidence to suggest a clear associative or causal relationship between the exposure and the outcome.*  
There is high confidence in the available evidence to suggest that a clear associative or causal relationship exists between the exposure and the health outcome of interest. Studies are minimally influenced by chance, bias, and confounding. Further, additional epidemiological data, evidence, or investigations are unlikely to substantively affect the overall magnitude or direction of the observed association or result in a meaningful change with respect to any conclusions regarding this association.  
This level of evidence might be met, for example, if several high- or moderate-quality studies on different study populations, by different authors, in different settings, and/or using different epidemiological study designs that are likely to be minimally influenced by bias and confounding show a clear associative or causal relationship that is consistent among studies with respect to magnitude and direction of effect sizes. Such evidence is strengthened when one or more high- or moderate-quality studies also demonstrate dose-response trends with the range of these doses (exposures) considered sufficient to cover the range of expected human exposure levels (including the high end) and the evidence base consists of a least one high-quality prospective cohort study. |
| **Limited but Insufficient Epidemiological Evidence of an Association** | *Limited but insufficient epidemiological evidence to conclude that there is a clear associative or causal relationship between the exposure and the outcome.*  
There is some confidence that the available evidence accurately reflects a clear association between the exposure and the outcome, but the evidence is limited because the studies are of insufficient quantity, quality, (internal) validity, or consistency or because chance, bias, and confounding could not be ruled out with confidence. While the present body of evidence suggests that a relationship between exposure and disease outcome may possibly exist, additional high- or moderate-quality epidemiological data, evidence, or investigations could affect the overall magnitude or direction of the observed associations and might result in a meaningful change to this level of evidence category.  
This level of evidence category might be met, for example, if the body of evidence is: (1) based at least on one high-quality study suggesting a statistically significant relationship and the results of other high or moderate quality studies are mixed, contradictory, imprecise, ambiguous, or inconsistent; (2) based on several moderate-quality studies which show a relationship between exposure and outcome that is less pronounced than in (1); or (3) based on many studies (both moderate and possibly low-quality studies) showing a generally consistent direction and for which additional and more thorough analysis would be needed to make the determination of a relationship. |
<table>
<thead>
<tr>
<th>Evidence Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insufficient Epidemiological Evidence of an Association</td>
<td><em>Insufficient epidemiological evidence to conclude that there is a clear associative or causal relationship between the exposure and the outcome.</em>&lt;br&gt;There is minimal confidence in the available evidence that the findings accurately reflect an association between the exposure and the outcome because the studies are of insufficient quantity, quality, (internal) validity, consistency, or statistical power to permit a conclusion to be reached, and/or chance, bias, or confounding may play an important role and cannot be ruled out. Further, additional high- or moderate-quality epidemiological data, evidence, or investigations could substantively affect the overall magnitude or direction of any observed associations.&lt;br&gt;This level of evidence category might be met, for example, if the body of evidence is: (1) too small to permit conclusions, such as when there are no available studies to validate or corroborate the findings of a single moderate- or low-quality study; (2) based entirely on one or more studies judged to be of low-quality; or (3) based on multiple moderate- or low-quality studies, but the heterogeneity of exposures, outcomes, and methods leads to mixed, conflicting, imprecise, ambiguous, or contradictory conclusions.</td>
</tr>
<tr>
<td>No Epidemiological Evidence of an Association</td>
<td><em>No epidemiological evidence to conclude that there is a clear associative or causal relationship between the exposure and the outcome.</em>&lt;br&gt;There is no epidemiological evidence to suggest the presence of an association between an exposure and outcome.&lt;br&gt;This level of evidence category might be met, for example, if the body of evidence consists of high- or moderate-quality studies that show no evidence of a statistically significant association and generally appear to have small effect sizes, and/or for which chance, bias, or confounding may play an important role.</td>
</tr>
<tr>
<td>Sufficient Evidence of No Causal Relationship</td>
<td><em>Sufficient epidemiological evidence to suggest there is no causal relationship between the exposure and the outcome.</em>&lt;br&gt;There is high confidence in the available evidence to suggest there is no causal relationship between the exposure and the outcome. The studies are minimally influenced by chance, bias, and confounding, and it is unlikely that additional epidemiological data, evidence, or investigations would meaningfully affect the current overall magnitude, direction, or conclusions about the association.&lt;br&gt;This level of evidence category might be met, for example, if at least one high-quality study with adequate power (e.g., ≥80%) to detect a meaningful effect size determined to be of substantive importance fails to show an effect and no other high or moderate quality studies provide affirmative evidence against this null result. In addition, data would also exist that suggests no significant dose-response trends are present with the range of these doses (exposures) considered sufficient to cover the range of expected human exposure levels (including the high end) and the evidence base consists of a least one high-quality prospective cohort study.</td>
</tr>
</tbody>
</table>

### 3.6. Literature Review and Evaluation

This section presents a review and evaluation of the epidemiologic literature on the potential association between 1,3-D exposure and carcinogenic and non-carcinogenic adverse health outcomes. The review and evaluation is organized by carcinogenic and non-carcinogenic health outcomes. For each of the health outcome sections, individual study publications are summarized and then an overall evaluation of findings is characterized. **Appendix B** provides an additional tabular summary of all studies with respect to their design, methods, results, and study quality organized by health outcome.
3.6.1. Carcinogenic Health Outcomes

Two studies (Band et al., 2011; Clary and Ritz, 2003) were reviewed which investigated the relationship between 1,3-D exposure and carcinogenic effects including pancreatic cancer and prostate cancer and are described below.\(^{17}\)

Pancreatic Cancer

One study (Clary and Ritz, 2003) investigated the association between 1,3-D exposure and pancreatic cancer.

Clary and Ritz (2003) evaluated the potential association between pancreatic cancer and exposure to 1,3-D and several other pesticides. This semi-ecologic study used detailed 1,3-D use data from Kern, Fresno, and Tulane counties in California via the California Department of Pesticide Regulation (CA DPR) Pesticide Use Reporting (PUR) database to determine if the reported location of pesticide use during a specific time period (1972 – 1989) was within proximity to residents living in the same area, who were likely exposed and who died from pancreatic cancer. Eligible cases were identified through death certificates obtained from the electronic California Death Tape Files (California Vital Statistics), and cases included residents within the three California counties who died from pancreatic cancer between 1989 and 1996. Controls (~10 controls per case) were randomly selected and from all non-cancer deaths in the same three counties, within the same time period. In order to be included within this study, the decedent’s death certificate data had to indicate both race and education level. Exposure to 1,3-D was assessed using Geographic Information System (GIS) software to link the total tons of 1,3-D applied between 1972 and 1989 (PUR data) to the deceased resident’s home at the zip code level and duration of residency in the county (data from death certificates) since only the zip code level of residence information was included on each death certificate. Quartiles of 1,3-D pesticide use were created at the zip code level, and ORs were calculated for the highest quartile (≥ 75%), using the lower three quartiles (< 75%) as the referent group. Logistic regression was used to obtain an adjusted OR and corresponding 95% CI for the highest quartile of 1,3-D use, adjusting for age at death, year of death, sex, race, years of living in a county, urban residence (urban vs. rural), and education (< 12, 12, > 12 years) and all 17 other organochlorine pesticides in the study simultaneously. Among the 950 pancreatic cases and 9,435 controls residing within the three counties (a total of 102 zip codes), 130 of the cases were exposed to 1,3-D according to PUR data. No evidence of a significant positive association was reported between residential proximity to agricultural use of 1,3-D and those who died from pancreatic cancer among those in the highest exposure quartile (OR: 1.48; 95% CI: 0.95, 2.31).\(^{18}\) A further analysis stratified the data by years of living within a county (> 20 years) to determine if there was an association between long-term pesticide exposure and pancreatic cancer mortality. Of the total 697 cases and 6,259 controls who lived in any of the three counties for > 20 years, 107 of the cases reported exposure to 1,3-D, and evidence of a positive association was observed between pancreatic cancer mortality and 1,3-D exposure (highest quartile) among those who reported living in the area for more than 20 years (OR: 1.89; 95% CI: 1.13, 3.15), relative to the lower three quartiles. When individual pesticides were added singularly to the 1,3-D regression model, appreciable changes in risk estimates for 1,3-D were reported for 1,2-dibromo-3-

\(^{17}\) An additional publication (Markovitz & Crosby et al. 1984) reported on the potential association between 1,3-D exposure and hematologic malignancies through a series of three case reports. No statistical methods were conducted to assess the association between 1,3-D exposure and hematologic malignancies and no effect estimates (e.g., ORs, RRs) were reported. As a result, the EPA was unable to evaluate the association between 1,3-D exposure and hematologic malignancies at this time.

\(^{18}\) The reported OR was calculated based on the highest quartile of 1,3-D use, relative to the three lower quartiles. The study authors did not report any data for the three lower quartiles.
chloropropene (DBCP) and chloropicrin (widely used as a mixture in the product 1,3-D) (risk estimates not reported).

The quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. Study limitations included the semi-ecologic study design, the possible under-reporting of PUR data among farmers, the measurement of outcome using death certificate data without histological confirmation, and incomplete adjustment for possible confounding factors (e.g., smoking, the strongest established risk factor for this cancer). For the exposure estimation, the study relied on residential proximity to 1,3-D agricultural use determined from the California PUR database 1,3-D use reports mapped to zip code of patient residence rather than measuring direct exposure. Although farmers were mandated to report their restricted pesticide use as of 1970, some under-reporting may have occurred two years later in 1972, which was the start of the exposure assessment period for this study. Additionally, applications of 1,3-D in large amounts in this area did not begin until 1984 and the study mortality data did not end until 1996, allowing only a short latency period of no more than 12 years, and this may not have been long enough for all carcinogenic effects to become present. Furthermore, the pancreatic cancer cases were not histologically confirmed (only confirmed via death certificates) and errors in diagnosis may have led to incorrect cause of death information on the death certificate. Lastly, the study did not account for smoking as a potential confounder, and since smoking is a major risk factor for pancreatic cancer, smoking should have been considered. The quality of this study was ranked low due to the study limitations mentioned above.

**EPA Conclusion**

Overall, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between 1,3-D exposure and pancreatic cancer. There was one available study that examined pancreatic cancer (Clary and Ritz, 2003). The overall quality of the study was ranked low. Clary and Ritz (2003) reported no evidence overall of a significant positive association between residential proximity to agricultural use of 1,3-D and those who died from pancreatic cancer; however, when the data were further stratified by years of living within a county, evidence of a significant positive association was observed between pancreatic cancer mortality and 1,3-D exposure among those who reported living in the area for more than 20 years. Several study limitations were noted above including the study design, the indirect, semi-ecologic exposure measure, the possible under-reporting of PUR data among farmers, and the inadequate consideration of confounders, particularly smoking, thus deeming the study to be low quality.

**Prostate Cancer**

One study (Band et al., 2011) investigated the association between 1,3-D exposure and prostate cancer. Band et al. (2011) evaluated the potential association between prostate cancer and exposure to active ingredients in pesticides including 1,3-D by conducting a population-based case-control study among male cancer patients in British Columbia, Canada. Cases were ascertained from the British Columbia Cancer Registry (BCCR) and included males, aged ≥ 20 years old, who lived in British Columbia, Canada, and who were diagnosed with prostate cancer between 1983 and 1990. Prostate cancer cases were histologically confirmed. Controls were age-matched to cases by birth year and diagnosis year and included study subjects with a cancer diagnosis -- besides prostate, lung, and/or unknown primary site -- and were also ascertained from the BCCR. Lifetime occupational exposure was assessed using a self-

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reported questionnaire that was sent to all BCCR participants and was returned via mail within six weeks. The validated questionnaire also included questions on occupation and industry titles, time period and duration of work, education, smoking and alcohol consumption, and ethnic origin. Next-of-kin were used as proxy respondents for deceased subjects (for cases: 212 (18.4%) proxy respondents; for controls: 689 (17.2%) proxy respondents). In addition to the questionnaire, a job exposure matrix (JEM) was used to determine cumulative exposure from 1950 - 1998. Exposures from this JEM were developed in part from the North American Pesticide Handlers Exposure Database. Conditional logistic regression using an automated forward selection process was used to calculate adjusted ORs and 95% CIs for individual pesticide exposures (based on ever/never exposure). Prior to including the pesticide exposure in the final model, the authors implemented a forward selection approach with a cut-off p-value = 0.2 to select the potential confounding variables/covariates: marital status; education (<8 years; 8–11 years; high school; post-secondary); smoking (age started smoking, average number of cigarettes, pipes or cigars smoked per day, total years smoked, packyears); alcohol consumption (starting age at consuming alcohol; average number of bottles of beer, glasses of wine, ounces of spirits per day; total years of consuming alcohol); ethnicity; person who filled out the questionnaire (self or proxy). Among the 1,153 cases and 3,999 controls, six of the cases and 19 of the controls reported exposure to 1,3-D. No evidence of a positive association between 1,3-D exposure and prostate cancer in men was observed (OR = 0.90; 95% CI: 0.34, 2.38), based on ever/never use.

The quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. Study strengths included the case-control study design, case ascertainment using population-based cancer registry information, histological confirmation of prostate cancer, and the fact that differential recall bias potentially was decreased since cancer patients were used as well in the control group. Study limitations included use of forward selection approach to select the potential confounding variables/covariates to be included in the final model and the potential of overfitting the model (a total of only 25 subjects exposed to 1,3-D), the lack of consideration of family history since it is known risk factor for prostate cancer, potential inaccurate recall due to the use of proxy respondents (18.4% of the cases, 17.2% of the controls), and selection bias since cancer patients were selected for both the case and control groups. In addition, the number of exposed cases on which the odds ratio was based was small (n ≤ 6).

**EPA Conclusion**

Overall, there is no epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between 1,3-D occupational exposure and prostate cancer. There was one available study, Band et al. (2011), that evaluated the potential association between prostate cancer and occupational exposure to select pesticides, including 1,3-D, adjusting for smoking years (cigarettes, pipes, cigars), alcohol consumption, education level, and proxy respondent, and reported no evidence of a positive association between 1,3-D exposure and prostate cancer in men based on ever/never use of 1,3-D. The study quality was ranked low based on the study quality criteria provided in the OPP Framework. Study strengths included the case-control study design, the case ascertainment and histological confirmation, and the fact that differential recall bias potentially was decreased since cancer patients were

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used as well in the control group. Study limitations included the lack of consideration of family history, inaccurate recall due to the use of proxy respondents (18.4% of the cases, 17.2% of the controls), and selection bias since cancer patients were selected for both the case and control groups. In addition, the number of exposed cases was small (n ≤ 6).

3.6.2. Non-carcinogenic Health Effects

Kidney Function

Four studies (Osterloh et al., 1989 and Osterloh & Feldman, 1993; Brouwer et al. 1991; and Verplanke et al., 2000) investigated the association between 1,3-D exposure and kidney function.

- Osterloh & Feldman (1993) as a follow-up to Osterloh et al. (1989), investigated the association between occupational air exposure to 1,3-D (referred to as DCP in the study) and excretion of two proteins microalbumin (ALB) and retinol-binding proteins (RBP) as well as the renal enzyme, NAG among application workers using the archived urine samples collected by Osterloh et al. (1989). Briefly (described in Osterloh et al (1989)), the study population (n = 15) included male 1,3-D applicators who completed a study questionnaire detailing their current and past medical histories prior to the start of the study done under the guise of the Worker Health and Safety Branch of the California Department of Food and Agriculture. A total of five consecutive exposure intervals were recorded for each applicator over the course of one day (four applicators were studied on a second application) and consisted of a pre-exposure interval (morning), two exposure intervals during the day (morning and afternoon), and then two post-exposure (evening and overnight) intervals. Twelve of the applicators were studied at least 40 hours after any previous pesticide application to act as a “wash out” period and minimize any carry-over exposures from a previous work day. Male applicators donned air sampling devices prior to exposure during the second and third intervals to measure the exposure to 1,3-D (expressed as the exposure product of concentration of 1,3-D mg/m³ multiplied by the minutes of exposure), with operator breathing zone air samples collected into charcoal absorbent tubes that were changed after four hours, whenever there was an obvious change in work practice, and at change in interval. Tubes were stored on dry ice on day of collection and at -20°C until analysis. The amount of 1,3-D in tubes was measured using electron capture gas chromatography (sensitivity and precision was 0.10 µg per column). One applicator was excluded from additional analysis because air monitoring data were not collected uniformly. Air concentrations ranged from 0.26 - 9.39 mg/m³ (mean +/- standard deviation (SD): 2.56 +/- 2.40 mg/m³) (n = 22 samples) with exposure duration between 120-697 minutes (mean +/- SD: 424 +/- 228 min) (n = 14 applicators) and the 1,3-D air exposure product ranged from 62 - 3,780 mg*min/m³ (mean +/- SD: 990 +/- 916 mg*min/m³) (n = 14 applicators).

A morning urine sample was collected during the pre-exposure interval and again at the end of each of the remaining four exposure intervals that lasted ~6 – 8 hours each. Urine samples were also collected at change in air monitoring tubes and were stored in polyethylene tubes on dry ice on the day of collection, and then at -70°C until for the known 1,3-D metabolite, N-acetyl-S-(cis-3-chloroprop-2-enyl)-cysteine (3CNAC), using gas chromatography-mass spectrometry. Four years later, the stored urine samples were slowly warmed to 37°C over one hour and their polyethylene vials (known to absorb proteins less than polystyrene or glass) were slowly rotated to promote thawing prior to the NAG, ALB, and RBP analysis. The study authors indicated that renal enzymes can remain stable in the urine for several years assuming proper urine storage.22 Urine samples were

tested for the renal tubular enzyme, NAG, using the fluorometric method to measure the hydrolysis of 4-methylumbelliferyl-β-D-glucosaminide. Urinary concentrations for ALB and RBP were determined with a SLT 340 microplate reader, using competitive enzyme-linked immunosorbent assay (ELISA) to measure ALB, and direct ELISA to measure RBP, with all samples run in triplicate. For the statistical analysis, a Mann-Whitney U test was conducted to evaluate the associations between daily excretions of the 3CNAC metabolite (dichotomized as high if excretion > 1.5 mg/24 hours and low if excretion < 1.5 mg/24 hours) and each of NAG, ALB, and RBP excretion values. Regression analyses were also conducted to determine whether excretion of 3CNAC was correlated to renal protein excretion for NAG, RBP, and ALB at each interval (concentrations, amounts, and creatinine corrected) and 24-hour cumulatively (amounts). The 24-hour cumulative data included data of only 14 workers (two workers were missing some interval data). For the dichotomous comparisons between low and high 3CNAC excretion groups, evidence of a statistically significant difference was reported as follows: for NAG, Low – 3,458 ± 677 mU/day; High – 6740 ± 2067 mU/day; p = 0.0040; and for RBP, Low – 29.92 ± 13.88 µg/day; High – 61.9 ± 34.01 µg/day; p = 0.0476; no evidence of a statistically significant difference was observed for ALB (Low – 3.53 ± 1.51 mg/day; High – 5.14 ± 3.01 mg/day; p = 0.4822). For the regression analyses, significant associations between 3CNAC excretion and renal protein NAG, ALB, and RBP excretion were observed in the interval regressions (either by concentration or amount, 0.0001 ≤ p ≤ 0.0081), and in the cumulative regression for ALB and RBP but not for NAG (daily, 24-hour interval) (for ALB and RBP: 0.0271 ≤ p ≤ 0.0403; for NAG p = 0.086). For the interval regression analyses with creatinine correction, 3CNAC was significantly associated with only ALB (p=0.007) but neither with NAG nor RBP (p = 0.125 and 0.442, respectively).

The overall quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. Study limitations included the inappropriate statistical methods used in the analyses of interval data (failing to account for the correlation between the repeated measures data of the same worker). Urine samples were four years old when analyzed for ALB and RBP and the long-term storage may have resulted in loss of protein due to absorption into the storage vial; however, authors suspected minimal loss due to type of storage vial used and storage temperature. All participants were exposed to 1,3-D but the study would have benefited from including unexposed participants to compare differences in kidney function. The study also reported a small sample size (n=16).

- Brouwer et al. (1991) investigated effects on kidney and liver function among commercial applicators in the Netherlands in a study similar to a case-crossover design. The study population consisted of all 14 workers applying the racemic mixture 1,3-D as a soil fumigant in the flower bulb cultivation area between Leiden and Haarlem in the Netherlands. To assess 1,3-D exposure, workers were asked at the end of the season to estimate the number of hours and days spent working in soil fumigation. Among the 14 workers, the total number of working hours for each participant varied from 26 to 300 hours (median: 142 hours) over four to 37 days (median: 27 days). A questionnaire that collected information on age, smoking and drinking habits, medications, and current and past diseases was administered in July on the first day of blood and urine sampling. Workers ranged between 33 and 60 years old (mean: 42 years, median 40 years), five smoked, 13 drank alcohol, two were taking an anticoagulant (phenprocoumon) and none of the workers reported having liver or kidney disease. The outcome, kidney function, was assessed through measurements of several parameters in blood serum and urine samples that were collected before the season in July and after the season for all 14 workers (liver function parameters were also tested and are presented in the Liver Function section). Kidney function parameters included glomerular function indicators β2-microglobulin in serum (β2-M-S), creatinine in serum (Creat-S), and albumin in urine (Alb-U). Proximal tubular function was assessed by measurement of the excretion of β2-microglobulin in urine (β2-M-U), RBP in urine, β-galactosidase (β-Gal) in urine, and alanine aminopeptidase (AAP) in urine. Since the resorption of RBP and β2-M-U proteins by proximal tubular cells of the kidney is almost complete under normal
kidney function, the presence of these proteins in urine is a sensitive indicator of impaired proximal tubular function. Excretion of Alb-U in the urine is also an indicator of reduced tubular resorption. Blood samples were collected and transported within two hours to the laboratory in a cool box. Concentrations of β2-M in urine and serum were measured with a commercial radioimmunoassay. Urine samples used to measure Alb-U and RBP concentrations and AAP and β-Gal activity, were cooled and transported on ice to a different laboratory, prepared the same day, and analyzed within one week using various methods including latex immunoassay (Alb-U and RBP) and colorimetric assay (β-Gal). Data were adjusted for urinary density in this analysis. The association between 1,3-D exposure and kidney function was measured using matched pair analysis with a Wilcoxon non-parametric signed rank test. Data were excluded for β2-M-U values with pH < 5.5 (eight samples) and β-Gal values with pH > 7.0 due to instability. Data were analyzed with and without adjustment for urinary density in this analysis. The Friedman test (2-way non-parametric ANOVA) was used to test equality of values of both kidney and liver function parameters simultaneously.

For the glomerular function parameters tested, a significant decrease in the concentration between samples collected before and after the season was reported for Creat-S (Before – 93.0 µmol/l, n=13; After – 87.5µmol/l, n=14; p-value = 0.045) and a significant increase was reported for Alb-U (Before – 5.2mg/l, n=14; After – 7.6mg/l, n=14; p-value = 0.013). Among the tubular function parameters, RBP concentration was significantly increased in the after period compared to before: Before – 20.0µg/l, n=14; After – 26.9µg/l, n=14; p-value = 0.036. No evidence of a significant increase was reported for β2-M-U concentration in urine (Before – 76.4µg/l, n=8; – 109.0µg/l, n=12; p-value = 0.208) and for β2-M-S concentration in serum (Before – 1.3µg/l, n=14; After – 1.4µg/l, n=14; p-value = 0.563). Similarly, no evidence of a significant decrease in AAP activity in urine (Before – 9.7U/l, n=12; – 8.3U, n=13; p-value = 0.754) was reported and no evidence of a significant increase in median β-Gal activity in urine (Before – 1.9U/l, n=11; After – 2.4U, n=12; p-value = 0.308). The overall study quality was ranked low based on the study quality criteria provided in the OPP Framework. The study assessed the change in kidney function from the start of the 1,3-D application season to the end of the season among 1,3-D applicators using a study similar to a case-crossover design. Demographic and lifestyle information, health status and blood and urine samples were collected at the start of the season, and blood and urine samples were collected again at the end of the season for measured outcomes. Exposure to 1,3-D was assessed through individual recall of number of hours and days worked over the course of the season and this data was not collected until the end of the study. The exposure assessment relied entirely on the commercial applicators’ memory and ability to estimate at the end of the season how many hours and days they worked in soil fumigation throughout the season, and no attempt at validation or comparison with application records appears to have been made. Further, there is no comparison to unexposed persons to compare difference in renal function and prior exposure to 1,3-D was not considered. In addition, seven different kidney enzyme analyses were performed, of which only two reached statistical (but not necessarily practical, given that they remained in the normal range) significance and no adjustments for multiple comparisons were made. The use of nonparametric methods was not able to quantify the percent of changes in the parameters. Finally, the study also reported a small sample size. Specifically, only 14 men were included in the study.

• Verplanke et al. (2000) investigated the association between occupational exposure to cis-1,3-D and kidney function among pesticide application workers in the starch potato growing region of the Netherlands, in a prospective cohort study. The study population (n = 31) included exposed pesticide application workers (n = 13) and non-exposed lorry drivers (n = 22) who transported potatoes from farms sprayed by pesticide applicators to three, separate processing plants in the northern area of the Netherlands. Lorry drivers were age-matched to pesticide applicators. Study participants were excluded based on the following criteria: a) current medications with nephrotoxic or hepatotoxic side effects; b) liver disease, diabetes, hypertension, kidney disease, or bile disorder within the last five
years; and, c) application workers who expected to fumigate for ≤ five days throughout the season. 23 Exposure to cis-1,3-D was assessed in applicators through biomonitoring on all fumigation days. The concentration of creatinine corrected mercapturic acid metabolite N-acetyl-S-(cis-3-chloro-2-propenyl)-L-cysteine (cis-1,3-D-MA) was measured in urine samples collected within three hours after the fumigation period. Inhalation exposure was assessed by personal air sampling on a representative sample of fumigation days, and real-time air monitoring in tractor cabins to obtain peak exposures. 24 Overnight urine samples were collected eight separate times from the study participants before, during, and after the fumigation season (August – December, Weeks 32 – 50, ~117 exposure days) on either Tuesdays, Wednesdays, or Thursdays. Additionally, five separate blood serum samples were obtained from study participants during this time. A total of 104 urine and 65 serum samples were collected from the exposed group and 171 urine and 106 serum samples were collected from the non-exposed group. 25 To determine renal effects, the following parameters were measured in the collected urine and serum samples in random order and in duplicate, using the EPOS 5060 automated analyzer: AAP, NAG, RBP and ALB in the urine, and creatinine (Creat-S) and β2-microglobulin (β2M-S) in the serum. The limit of detection (LOD) was determined to be 10 µg/L for RBP (n = 4 samples below the LOD), and 0.66 mg/l for Albumin (n = 17 samples below the LOD). For statistical evaluation, samples with activity or concentration below the LOD were assigned a value of half of the LOD. To adjust for dilution of the urine samples, the activities or concentrations of the urinary renal effect parameters were divided by the concentration of creatinine in urine (Creat-U). QA/QC laboratory procedures were conducted and included within and between run precision determinations using quality control samples. For the statistical analysis, non-normal distributions for variables AAP, NAG, RBP, and ALB were log-transformed and two-sided t-tests were used to determine the mean differences between the exposed application workers and non-exposed lorry drivers on each of all collection days. Repeated measures analysis of variance was conducted using a general linear model to determine if a dose-response was present for renal effects relative to exposure.

An average baseline of renal parameter activity was calculated from results from urine samples collected during weeks 32 and 33 and renal variables in samples collected during subsequent weeks were compared to the baseline results. The 13 applicators fumigated on 117 days during the season, mean (SD) daily exposure time was 521 (230) minutes, and the geometric mean (range) of 1,3-D exposure of 2.7 mg/m³ (0.1 – 9.5 mg/m³) for eight hours (time weighted average)/day was estimated from the relation between the personal air sampling data and the biological monitoring data. No evidence of a statistically significant difference (p ≥ 0.05) was observed among workers occupationally exposed to cis-1,3-D during fumigation season for the following renal parameters in the urine and serum samples, relative to the lorry drivers who were not exposed: AAP, NAG, RBP, ALB, Creat-S, and β2M-S. For the dose-response analysis, repeated measurement testing ascertained that renal effects were not related to 1,3-D exposure.

The overall quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. Study strengths included the cohort study design and the laboratory QA/QC procedures. As a result, the exposure estimates for cis-1,3-D may not have been as precise since cis-

23 Lorry drivers who transported potatoes to one of the three factories were excluded for logistical reasons and three lorry drivers were excluded to better match for age with pesticide application workers. (Verplanke et al., 2000)
25 Urine (n = 4) and serum (n = 4) samples from non-exposed lorry drivers were missing.
1,3-D is known to have a short half-life (5.3 hours). While the authors used repeated measures analysis of variance (ANOVA) to analyze the repeated measures data, the authors inappropriately used the t-test to compare the variables between the groups on each of all collection days and failed to adjust for the difference between the groups at baseline in all the comparisons. The study also reported a small sample size. Specifically, only 13 exposed and 22 non-exposed were included in the final study population.

**EPA Conclusion**

Overall, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between workers occupationally exposed to 1,3-D and renal effects. Four studies (Osterloh & Feldman, 1993 partially citing Osterloh et al., 1989; Brouwer et al., 1991; and Verplanke et al., 2000) investigated the association between occupational exposure to 1,3-D and kidney function among application workers. Osterloh et al. (1989) and Osterloh & Feldman (1993) investigated the association between occupational air exposure to 1,3-D (the metabolite 3CNAC) and excretion of renal proteins (NAG, ALB, and RBP) among application workers in California, United States. Osterloh & Feldman (1993) reported evidence of a statistically significant difference for the high and low daily 3CNAC urinary excretions relative to urinary NAG and RBP excreted, and no evidence of a statistically significant difference for ALB. Both studies had several study limitations including the inappropriate statistical methods used in the analyses of interval data (failing to account for the correlation between the repeated measures data of same worker). Additionally, the small sample size (n ≤ 16) was noted in both studies. Brouwer et al. (1991) evaluated the effects on kidney function of commercial applicators in the Netherlands, and for the glomerular function parameters tested, a significant decrease in median concentration between samples collected before and after the season was reported for Creat-S and a significant increase was reported for Alb-U. Among the tubular function parameters, median RBP concentration was significantly increased. No evidence of a significant increase was reported for median β2-M concentration in urine and for median β2-M concentration in serum. Similarly, no evidence of a significant decrease in AAP activity in urine was reported and no evidence of a significant increase in median β-Gal activity in urine. The overall quality of the study was ranked low due to several study limitations including the timing of when the exposure data were collected (e.g., at the end of the study), potential inaccurate recall stemming from the exposure assessment relying solely on the commercial applicators’ memory and their ability to estimate at the end of the season how many hours and days they worked in soil fumigation throughout the season with no attempt at validation or comparison with application records, no comparison to unexposed persons to compare difference in kidney function and prior exposure to 1,3-D, and the nonparametric methods that were used were not able to quantify the percent of changes in the parameters. The study also reported a small sample size. With respect to this latter limitation, only 14 men were included in the study and several kidney function measurements included fewer than 14 in the analysis. Verplanke et al. (2000) investigated the association between occupational exposure to cis-1,3-D and kidney function among exposed application workers and non-exposed lorry drives in the starch potato growing region of the Netherlands. Verplanke et al. (2000) reported no evidence of a statistically significant difference among application workers exposed to cis-1,3-D relative to lorry workers who were not exposed to cis-1,3-D, for the following renal parameters in the urine and serum samples: AAP, NAG, RBP, ALB, Creat-S, and β2M-S. No evidence of a dose-response was reported as well. Study strengths included the study design and the use of laboratory QA/QC procedures. Study limitations included the inappropriate use of the t-test to compare the variables between the groups on each of all collection days and the failure to adjust for the difference between the

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groups at baseline in all the comparisons. The study also reported a small sample size. Specifically, only 13 exposed and 22 non-exposed were included in the final study population. As a result, this study was considered low quality.

Liver Function

Two studies (Brouwer et al., 1991; Verplanke et al., 2000) investigated the association between 1,3-D exposure and liver function.

- Brouwer et al. (1991) investigated effects on kidney and liver function among commercial applicators in the Netherlands, using a design similar to a case-crossover study. The study population consisted of all fourteen workers applying 1,3-D as a soil fumigant in the flower bulb cultivation area between Leiden and Haarlem in the Netherlands. Study details and kidney function results are presented in the kidney section. To assess exposure, workers were asked at the end of the season to estimate the number of hours and days spent working in soil fumigation. Additional study details and kidney function results are reported above in the kidney function section. Liver function parameters included alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), lactate dehydrogenase (SLDH), \( \gamma \)-glutamyltransferase (GGT), alkaline phosphatase (ALP), and total bilirubin concentration (TBIL – called Bil-tot in the publication) in serum. Blood samples were collected then transported within two hours to the laboratory in a cool box. ALAT, ASAT, SLDH, GGT, and ALP activities, and TBIL and Creat-S concentrations in serum were measured within 24 hours using a SMAC multichannel analyzer. The association between 1,3-D exposure and liver function was measured using matched pair analysis with a Wilcoxon non-parametric signed rank test. The Friedman test was used to test equality of values of both kidney and liver function parameters simultaneously. Evidence of a significant decrease in concentration of TBIL was reported after the season from 9.5 \( \mu \text{mol/l} \) to 7.0 \( \mu \text{mol/l} \) (n = 14, p-value = 0.025) which is still within normal range. GGT activity increased from 12.5 U/l to 19.5 U/l after the season but did not reach significance (p-value = 0.099). Authors suggest that the significant decrease in TBIL concentration (although within normal range) along with the increase in GGT activity (though not significant) may indicate that 1,3-D might have properties that induce liver enzyme activities. No evidence of a significant difference was reported for any of the other liver function measures (n = 14, all p-values > 0.05).

The overall study quality was ranked low based on the study quality criteria provided in the OPP Framework. The study assessed the change in liver function from the start of the 1,3-D application season to the end of the season, using a study similar to a case-crossover design. Demographic and lifestyle information and health status were collected at the start of the season, urine and blood samples were collected at the beginning and end of the season for measured outcomes, and exposure data were collected at the end of the study. The exposure assessment relied entirely on the commercial applicators’ memory and ability to estimate at the end of the season how many hours and days they worked in soil fumigation throughout the season, and no attempt at validation or comparison with application records appears to have been made. Further, there is no comparison to unexposed persons to assess difference in liver function and prior exposure to 1,3-D was not considered. In addition, six different liver enzyme analyses were performed, of which only one reached statistical (but not necessarily practical, given that they remained in the normal range) significance and no adjustments for multiple comparisons were made. The use of nonparametric methods was not able to quantify the percent of changes in the parameters. Finally, the study also reported a small sample size. Specifically, only 14 men were included in the study.

- Verplanke et al. (2000) evaluated the association between occupational exposure to 1,3-D and liver function among application workers in the Netherlands, in a prospective cohort study. The study population (n = 31) included exposed application workers (n = 13) and non-exposed lorry drivers (n
in the northern area of the Netherlands, and participants were excluded based on one of the following criteria: a) current medications with nephrotoxic or hepatoxic side effects; b) applicator workers who fumigated for ≤ five days throughout the season; or c) had liver disease, diabetes, hypertension, kidney disease, or bile disorder within the last five years. The non-exposed included lorry drivers in the Netherlands (same region as the exposed workers, n = 47) who transported potatoes to three separate processing plants were matched to the exposed workers’ age, and were excluded if they met any of the following: had diabetes, hypertension, kidney disease, or bile disorder; or b) current medications with nephrotoxic or hepatoxic side effects. Additional study details and kidney function results are reported above in the kidney function section. Urine and blood samples were collected and assessed to estimate exposure and measure liver effects. Overnight urine samples were collected eight separate times from study participants before, during, and after the fumigation season (August – December, Weeks 32 – 50, ~117 exposure days) on either Tuesdays, Wednesdays, or Thursdays. Additionally, five separate blood serum samples were obtained from study participants during this time; a total of 171 urine and 106 serum samples were collected. To determine liver effects, the following parameters were measured in the collected urine and serum samples in random order and in duplicate: the urinary ratio of 6-β-OH-cortisol (βOHC) & free cortisol (COR), ALAT, ASAT, GGT, ALP, and TBIL. An enzyme immunoassay was used to measure βOHC, the COR was measured using high performance liquid chromatography, and a Hitachi 747 analyzer was used to determine ALAT, ASAT, GGT, ALP, and TBIL. The LOD for βOHC was 100 µg/L and 89 urine samples were below the LOD (two samples did not have enough sample material to be measured). Laboratory QA/QC procedures were conducted including duplicate precision measurements and between run precision determined by one quality control sample analyzed in each run. For the statistical analysis, non-normal distributions for variables for ALAT, GGT, βOHC/COR were log-transformed and two-sided t-tests were used to determine the mean differences between the exposed workers and non-exposed drivers on each of all collection days. Repeated measures analysis of variance was conducted using a general linear model to determine if a dose-response was present for liver effects relative to 1,3-D exposure. A total of 13 exposed and 22 non-exposed completed this study, with a geometric mean (range) cis-1,3-D exposure of 2.7 mg/m³ (0.1 – 9.5 mg/m³) for eight hours (time weighted average)/day. Evidence of a statistically significant difference was observed among workers occupationally exposed to cis-1,3-D for the urinary ratio βOHC/COR parameter during Week 32 (p < 0.05), Week 41 (p < 0.01), Week 47 (p < 0.05) and Week 50 (p < 0.01) of the fumigation period, relative to the unexposed group. No evidence of a statistically significant difference (p ≥ 0.05) was observed among workers occupationally exposed to cis-1,3-D during fumigation season for the following liver parameters in the urine and serum samples: ALAT, ASAT, GGT, ALP, and TBIL. For the dose-response analysis, repeated measurement testing ascertained that liver effects were not related to cis-1,3-D exposure.

The overall quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. Study strengths included the cohort study design and the use of laboratory QA/QC procedures. Limitations included the statistical approach that was used to analyze the data. While the authors used repeated measures ANOVA to analyze the repeated measures data, the authors inappropriately used the t-test to compare the variables between the groups on each of all collection days and failed to adjust for the difference between the groups at baseline in all the comparisons. Further, six different liver enzyme analyses were performed and no adjustments for multiple

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27 For the control group, the study authors mentioned that “for logistical reasons lorry drivers who transported potatoes to one of the three factories were excluded,” in addition to three controls (i.e. lorry drivers) who were excluded to better match for age. (Verplanke et al., 2000)
comparisons were made. The study also reported a small sample size. Specifically, only 13 cases and 22 non-cases were reported.

EPA Conclusion

Overall, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between workers occupationally exposed to 1,3-D during fumigation season and liver effects. Brouwer et al. (1991) and Verplanke et al. (2000) investigated the association between 1,3-D exposure and effects on liver function of commercial applicators in the Netherlands. In Brouwer et al. (1991), evidence of a significant decrease in concentration of TBIL was reported after the season from 9.5 µmol/l to 7.0 µmol/l and GGT activity increased from 12.5 U/l to 19.5 U/l after the season but did not reach significance. No evidence of a significant difference was reported for any of the other liver function measures. The overall quality of the study was ranked low due to several study limitations including the timing of when the exposure data were collected (i.e. at the end of the study) and no attempt at validation or comparison with application records, potential inaccurate recall of the exposure stemming from the exposure assessment relying solely on the commercial applicators’ memory and their ability to estimate at the end of the season how many hours and days they worked in soil fumigation throughout the season, no comparison to unexposed persons to compare difference in kidney function and prior exposure to 1,3-D, and the use of nonparametric methods were not able to quantify the percent of changes in the parameters. The study also reported a small sample size. Specifically, only 14 men were included in the study. Verplanke et al. (2000) reported evidence of a statistically significant difference for the urinary ratio $\beta$OHC/COR parameter during Week 32, Week 41, Week 47 and Week 50 of the fumigation period among workers occupationally exposed to $cis$-1,3-D, relative to the unexposed group. No evidence of a statistically significant difference was observed during any other weeks of the fumigation season for the urinary ratio $\beta$OHC/COR parameter. Additionally, for the other liver parameters measured -- ALAT, ASAT, GGT, ALP, and TBIL --, no evidence of a statistically significant difference was observed among workers occupationally exposed to $cis$-1,3-D during fumigation season. The overall quality of the study was ranked low due to several study limitations. Study strengths included the cohort study design and the use of laboratory QA/QC procedures. Study limitations included the weak and inappropriate statistical approach that was used to analyze the data. While the authors used repeated measures ANOVA to analyze the repeated measures data, the authors inappropriately used the t-test to compare the variables between the groups on each of all collection days and failed to adjust for the difference between the groups at baseline in all the comparisons. Further, six different liver enzyme analyses were performed, and no adjustments for multiple comparisons were made. The study also reported a small sample size. Specifically, only 13 exposed and 22 non-exposed were reported.

Neurodevelopmental Effects

Three studies (Kalkbrenner et al., 2010; Kalkbrenner et al., 2018; Gunier et al., 2017) examined the association between 1,3-D exposure and neurodevelopmental effects from exposure during the perinatal period including autism spectrum disorder (ASD) and intelligence quotient measures.

Autism Spectrum Disorder (ASD)

Two studies (Kalkbrenner et al., 2010; Kalkbrenner et al., 2018) investigated the association between 1,3-D exposure and ASD.

- Kalkbrenner et al. (2010) examined the association between perinatal exposure to hazardous ambient air pollutants, including 1,3-D, and ASD in a case-control study of children living in North Carolina and West Virginia. The study population included 8-year old children living in North Carolina in 2002 and 2004 (born in 1994 and 1996) and in West Virginia in 2000 and 2002 (born in 1992 and
1994). Cases with ASD and controls with speech and language impairment were identified using the Autism and Developmental Disabilities Monitoring Network (ADDM), a monitoring network that screens developmental records of children in health and education settings. Cases included all children with developmental records documenting characteristics and behaviors that met a standardized definition for ASD disorder (Diagnostic Statistical Manual of the American Psychiatric Association, DSM-IV-TR), regardless of previous diagnosis of ASD. Controls included children with a school designation of speech and language impairment without documentation of other developmental problems such as ASD or intellectual disabilities. Cases and controls were limited to children who resided in the study area at the time of birth and at eight years of age and who had a developmental evaluation through the ADDM. Participant address at time of birth and demographic characteristics were obtained from birth certificate data. In West Virginia, a random sample of 1/3 of the children identified with speech and language impairment were matched with birth certificate data to reduce the burden on the vital statistics department retrieving the data. Exposure was assessed using ambient hazardous air pollutant concentrations modeled by the National Air Toxics Assessment (NATA) program\textsuperscript{28} for the year 1996 and was assigned to patient address at birth using address from birth certificate, census tract data, and geocoding software. The NATA model assumes Gaussian air dispersion and predicts annual-average ambient concentration of hazardous chemicals for each census tract using overlapping special grids using National Emissions Inventory data and meteorological and secondary-pollutant formation data. The National Emissions inventory included the location and rate of release of pollutants from areas such as dry cleaners, gas stations, and motor vehicles as well as point sources such as manufacturing, power-generation, and waste facilities. No mention is made by the study authors with respect to agricultural sources of release of 1,3-D (e.g. field fumigation), and it is not clear how or the extent to which this was sizable, important, or accounted for. Data from 1990 and 1999 were also available; however, authors selected the 1996 data because it had improved data input and was closer in time to the birth-years of the study cohort. Total concentrations were obtained by adding modeled concentrations to an invariant clean background level (known only for a few hazardous air pollutants) and participants were assigned individual exposures using the modeled concentrations corresponding to census tract of the residential address from the birth certificate. Census tracts for year 2000 were translated to 1990 boundaries using census tract relationship files. The relationship between perinatal 1,3-D exposure and ASD was estimated using logistic regression to calculate ORs and 95% CIs, adjusting for surveillance year and state, race, maternal education, maternal age, smoking in pregnancy (yes, no), marital status, census tract median household income, and urbanicity. Selection of these confounders was based on directed acyclic graphs, and exposure during the perinatal period was selected to be of interest since this is the time period over which there is susceptibility to exogenous agents in ASD etiology. Odds ratios corresponded to the odds of ASD for high air pollutant concentrations (80\textsuperscript{th} percentile) to the odds of ASD for low concentrations (20\textsuperscript{th} percentile). Among the 3,177 children included in the sample, there were 374 cases of ASD (201 from North Carolina and 173 from West Virginia) and 2,803 controls (1,730 from North Carolina and 1,073 from West Virginia). Authors did not specify the number of cases and controls with exposure to 1,3-D. Children with ASD were more likely than controls (speech and language impairment) to be male, firstborn, have mothers with higher education and to reside in urban areas. The children from North Carolina all lived in urban or mixed-urbanicity census tracts while the children from West Virginia lived in rural or mixed census tracts and thus level of urbanicity and state were related in the sample. Authors did not report if these were significant differences. No evidence of a significant positive association was reported between 1,3-D exposure

and ASD in children at age eight years in West Virginia and North Carolina (OR = 1.90, 95% CI: 0.80, 4.80).

The overall quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. The study assessed the association between 1,3-D exposure during the perinatal period and ASD in 8-year-old children living in North Carolina and West Virginia using a case-control study design. A major study limitation included the exposure analysis which estimated the child’s exposure near the time of birth by combining the census tract of birth address and the modeled time-averaged NATA ambient air concentrations of 1,3-D measured in 1996 using a semi-Bayes model. The birth years included 1994 and 1996 for participants from North Carolina and 1992 and 1994 for West Virginia participants. The 1996 measurements were up to four years different for study participants born in 1992. Additionally, the study did not account for possible residential mobility of the study participants between pregnancy and childbirth with residency coded only for maternal address at delivery. The maternal residential addresses during the exposure period may have differed from the reported addresses at childbirth that were geocoded and used to determine prenatal exposure, possibly causing exposure misclassification. Nor did the study authors account for any exposures after birth through eight years old. Additionally, differences between the cases and controls with respect to gender, birth order, maternal education level, and urbanicity were reported. Further, the authors did not consider exposure sources other than ambient air exposure in their analysis including diet, tobacco smoke, indoor air environment and other factors potentially relevant to 1,3-D exposure. Regarding the statistical analysis, hazardous air pollutants are highly correlated (Spearman rank correlations of ≥ 0.50) and authors attempted to account for this by simultaneously adjusting for measured air pollutants and using complex semi-Bayes models. It is not clear how successful this adjustment might have been.

• Kalkbrenner et al. (2018) evaluated the association between perinatal exposure to air toxics including 1,3-D and ASD in children using data from a family-based cohort study conducted within the United States. The study population included a subset of families who are part of the Autism Genetic Resource Exchange (AGRE), a voluntary research repository that maintained ASD phenotype and biomaterials collected from families in which at least two or more siblings have been diagnosed with ASD. Inclusion criteria for this study included families who: a) had ≥ one birth(s) between 1994 – 2007 to correspond to the large amount of air quality data that was available during this time period; and b) ≥ five years of follow-up prior to the study start in 2012 for a potential ASD diagnosis. The following three outcomes were considered for this study: a) ASD diagnosis; b) a measure of the broader ASD phenotype, using the Social Responsiveness Scale (SRS) to determine ASD traits of children aged 4 – 18 years old including non-affected siblings; and, c) a measure of the severity of ASD symptoms using the Calibrated Severity Score (CSS) for those who met the ASD criteria only. All ASD diagnoses were based on the parent-based interview Autism Diagnostic Interview Revised (ADI-R), and following scoring, participants were categorized as Autism, Not Quite Autism (NQA), Broad Spectrum, or Not Met. For the degree of ASD severity analysis, a scoring system based on direct observation, the Autism Diagnostic Observation Schedule (ADOS), was used. The ADOS raw scores were then mapped to the Calibrated Severity Score (CSS) using an algorithm, and the CSS

29 In this study, the total t-score for the SRS was used once completed by a parent of an index participant who met the recommended age range of 4 – 18 years.

30 The AGRE defines the following categories as such: NQA as “no more than one point away from meeting autism criteria on any or all of the three ‘content’ domains (i.e., social, communication, and/or repetitive behavior) and meeting criteria on the ‘age of onset’ domain; or, individuals who meet criteria on all three ‘content’ domains, but do not meet criteria on the ‘age of onset’ domain”; Broad Spectrum as “patterns of impairment along the spectrum of pervasive developmental disorders”; and Not Met as not having an ASD diagnosis. (Kalkbrenner et al. 2018)
scores were used to indicate the severity of ASD; CSS scores ranged from 1 - 10, with ten being the most severe form of ASD. For the exposure assessment, air concentrations including 1,3-D were geocoded to the family residential address or addresses during pregnancy. Self-reported addresses were obtained from a residential history questionnaire in addition to using LexisNexis software \(^{31}\) as a supplemental source, and participants with no home address during the specific time period of one year prior to the child’s birth through two years after the birth were removed from the study. The date of birth for the child was used to assign exposure to air toxics including 1,3-D. Air concentrations were determined by the U. S. EPA NATA model (as described more fully earlier under Kalkbrenner (2010)), using inputs from the National Emissions Inventory. The NATA models were run every three years to determine census-tract estimates for the year, and in this study, the NATA model was then linked to the closest birth year of each study participant to estimate exposure. \(^{32}\) Logistic regression was used to determine if an association existed between 1,3-D air concentrations at birth and ASD diagnosis participants relative to siblings who did not have an ASD diagnosis, using an odds ratio and corresponding 95% confidence interval. Linear regression models were run for the second and third outcomes (change in SRS total t-score and change in ASD CSS). All three models contained the single log-transformed air toxic, were mixed models with a random effect for family, and were adjusted for birth year, mean air toxic level in the family, education level, the census block group population density, and median rent. For the ASD diagnosis outcome, a total of 1,540 cases and 477 non-cases (1,006 families) were reported, for change in SRS score, 1,272 cases (678 families) were reported, and for change in CSS score, 1,380 cases (845 families) were reported. No evidence of a positive association was observed between 1,3-D air concentrations at birth and ASD diagnosis among sibling study participants, relative to siblings who did not have an ASD diagnosis (OR: 1.00; 95% CI: 0.95, 1.05). For changes in SRS and CSS scores relative to 1,3-D air concentrations, no evidence of a significant increase was observed (change in SRS score – OR: 0.20; 95% CI: -0.44, 0.84; change in CSS score – OR: 0.02; 95% CI: -0.03, 0.07).

In an additional analysis, that examined the association between log-transformed 1,3-D exposure and ASD diagnosis for all participants restricted by birth year with a random effect for family, and adjusted for the mean air toxic level in the family, birth year, and the census block group population density, education level, and median rent, no evidence of a significant positive association was reported (OR = 1.08; 95% CI: 0.99, 1.17; n = ~60% of the full sample). \(^{33}\) Similarly, when the association between log-transformed 1,3-D exposure and ASD diagnosis was stratified by child sex, (with a random effect for family, adjusted for the mean air toxic level in the family, birth year, and the census block group population density, education level, and median rent) no evidence of a positive association was reported for either male or female children (male – OR: 1.00; 95% CI: 0.94, 1.07; female – OR: 0.99; 95% CI: 0.93, 1.05; p-value = 0.63).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the cohort study design, and the sound statistical analyses (mixed model method, appropriate sensitivity analyses). A major limitation of this study included the indirect measure of exposure to 1,3-D. The study relied on modeled air toxic concentrations of 1,3-D as a proxy to measuring direct exposure, using NATA model data that was

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31 The LexisNexis software sources data from consumer and public records and can often be used to determine residential addresses.


33 Birth years are years where the pregnancy may have overlapped years of NATA air toxic models- years 1996, 1997, 1999, 2000, 2002, 2003, 2005, and 2006. The difference in odds ratios was calculated as the OR for restricted birth years – the OR for all birth years.
obtained every three years. Additionally, the study authors did not provide information on maternal occupational exposures or the location of the maternal workplace during pregnancy. Furthermore, the study did not account for potential residential mobility during pregnancy. Since the NATA model estimates for a specified year are developed every three years, exposure measurement error was likely in this study for children who were born up to two years earlier or later than the measurement year, in comparison to those children whose birth year aligned with the year the NATA model estimates were released. When the population was restricted to those children with birth years corresponding with NATA measurement years, the magnitude of the association between 1,3-D and ASD diagnosis increased but did not reach significance suggesting that exposure estimates for non-NATA years might be underestimated.

**EPA Conclusion**

Overall, there is no epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between 1,3-D exposure and ASD in children. There were two available studies that examined ASD. Kalkbrenner et al. (2010) was a case-control study that reported no evidence of a significant positive association with ASD, following perinatal exposure to hazardous ambient air pollutants, including 1,3-D among children. The overall quality of the study was ranked low. Kalkbrenner et al. (2018) reported no evidence of a positive association between 1,3-D air concentrations and ASD diagnosis among sibling study participants relative to siblings who did not have an ASD diagnosis. For changes in SRS and CSS scores relative to 1,3-D air concentrations, no evidence of a significant increase was observed. Similarly, when the study population was limited to those children born in the same years as the NATA model data, no evidence of a significant positive association was reported between 1,3-D exposure and ASD diagnosis. The overall quality of the study was ranked moderate. Study strengths included the cohort study design. The main limitation of both studies included the reliance on NATA model census-tract estimates as opposed to direct measurement of prenatal air toxic exposure.

**Neurodevelopmental Effects**

One study investigated the association between prenatal maternal exposure to 1,3-D and neurodevelopmental effects in children (Gunier et al., 2017).

Gunier et al. (2017) conducted a prospective cohort study to investigate the associations between prenatal and postnatal residential proximity to agricultural use of fumigants, including 1,3-D and neurodevelopment in 7-year-old children who were participants in the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) birth cohort. The study population consisted of children born to mothers who were recruited and enrolled between October 1999 and October 2000 from health clinics serving low-income residents of Salinas, California. Of the 601 pregnant women enrolled, 537 of their children were live born, singleton and, without medical conditions that could affect their neurodevelopment assessment. Though 336 children were followed through age seven years and completed all components of the neurodevelopmental assessment at seven years old, children were included for the present analysis only if maternal residence was known for at least 80% of the time during the prenatal period from pregnancy to birth (n = 285) and during the postnatal period from birth to the 7-year neurodevelopmental assessment (n = 255), and if they had prenatal dialkyl phosphate (DAP)

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34 Specific fumigants investigated included methyl bromide, chloropicrin, metam sodium, and 1,3-D, as the study authors mentioned these fumigants were the most commonly used agricultural fumigants between 1999 – 2008 (the study period) in Monterey County, CA (location of the study).

35 Inclusion criteria for mothers included the following: ≥ 18 years of age, < 20 weeks gestation, eligible for Medi-Cal, English or Spanish speaking, and planning to deliver at the county hospital.
metabolites of organophosphate pesticides measurements. Potential exposure to 1,3-D was estimated using global positioning system (GPS), GIS, and CA DPR PUR data from 1999 – 2008. The amount (kg) of 1,3-D applied per 2.56 square-km section within 3-, 5-, and 8- km radii buffers of maternal residence during the prenatal and postnatal time periods. As all buffers contained more than one 2.56 square-km section, the amount of pesticide applied in each section was weighted by the proportion of land area included in each buffer based on the CA DPR PUR data. The amount of 1,3-D used in each section was also weighted by the proportion of time the residence was downwind of sections where 1,3-D was applied based on wind direction seven days subsequent to application extracted from meteorological records maintained by California Department of Water Resources. Authors reported that buffer distances of 3-, 5-, and 8-km were selected for this analysis because these distances best captured the spatial scale of fumigant use most strongly correlated with measured fumigant concentrations in outdoor air samples (CA CDP, 2015; Li et al., 2005). Neurodevelopment measures were based on the (i) Wechsler Intelligence Scale for Children, 4th edition (WISC-IV) to estimate participants’ Full-Scale Intelligence Quotient (Full-Scale-IQ) as well as domain-specific IQ (Working Memory, Processing Speed, Perceptual Reasoning, and Verbal Comprehension) at age seven; and (ii) the Behavior Assessment System for Children 2 (BASC-2) to assess children’s behavior at age seven at home by maternal report (interviewer-administered due to low literacy) and at school by teacher report (self-administered). Assessments were administered in each participant’s dominant language (68% completed the WISC-IV in Spanish; 32% completed the assessment in English), with a single bilingual psychometrician who was trained and supervised by a pediatric neuropsychologist administering the WISC-IV. Raw WISC-IV scores were standardized against U.S. population-based norms for English- and Spanish-speaking children. Interviews of mothers conducted by bilingual interviewers during pregnancy (~13 weeks and 26 weeks gestation), after delivery, and when their children were : 1-, 2-, 3.5-, 5-, and 7- years old was the source of demographic data including maternal age, education, marital status, paternal education, number of years lived in the United States, country of birth, and family income. Maternal verbal intelligence was determined by the Peabody Picture Vocabulary Test and Spanish version for Spanish speakers at 6th the month visit, and a Home Observation for Measurement of the Environment (HOME) inventory was completed at the 7-year visit. Home visits were also performed by trained personnel shortly after enrollment (~16 weeks gestation) and when their children were 6 months and 1-, 2-, 3.5-, and 5- years old where latitude and longitude coordinates of participant’s home were determined using handheld GPS device. For the statistical analysis, continuous prenatal and postnatal fumigant use (kg/yr) was log-transformed and one kg/yr was added to use prior to transformation so that minimum log10 of use would be zero and all values positive. Generalized additive models of 7-year IQ (Full Scale and domain-specific) were used and authors evaluated departures from linearity using spline functions (though observed none). Regression coefficients from multivariable linear regression models for 1,3-D were presented as mean change (β coefficients) in cognition or behavior scores for each ten-fold increase in fumigant use, along with corresponding 95% CIs and p-values and adjusted for covariates.36

For the analysis that considered 1,3-D use within 3-, 5-, and 8- km distance of pregnant mother’s residence and child’s 7-year IQ scores, no evidence of a significant association was reported for Full-Scale IQ as well as domain-specific IQ scores of Processing Speed, Verbal Comprehension, Working Memory, Perceptual Reasoning, and Processing Speed relative to a ten-fold increase in wind-adjusted 1,3-

36 Covariates were selected both a priori and if found to be empirically associated with child neurodevelopment, and included child’s age at assessment, sex, language of assessment, maternal age at assessment, maternal education, maternal intelligence, maternal country of birth, maternal depression at the 7-year visit, maternal work status, HOME score at the 7-year visit, household poverty level at the 7-year visit, presence of father in the home, location of neurodevelopmental assessment (field office or home), season of assessment, house density (number of persons per room), prenatal urinary DAP concentration, and agricultural organophosphate use within 1 km of the residence during pregnancy.
D use within 3-, 5-, or 8-km of the pregnant mother’s home (0.10 \( \leq \beta \leq 1.00 \); all CIs encompassed the null value of 0, with n = 257 – 285/category and p values \( \geq 0.05 \)). Similarly, no evidence of a significant association was reported at any distance of 1,3-D use from postnatal residence \(^{37}\) (within 3-, 5-, or 8-km) and child’s Full-Scale IQ or domain-specific IQ scores at seven years old (-3.90 \( \leq \beta \leq 1.00 \); all CIs encompassed the null value of 0, with n = 228 – 255/category and p values \( \geq 0.05 \)). For the analysis of 1,3-D and child neurodevelopmental behaviors (BASC-2 Hyperactivity and Attention Problems) at seven years of age, no evidence of a significant association was similarly reported for a ten-fold increase in wind-adjusted 1,3-D use at any distance from prenatal or postnatal residence (3-, 5-, and 8-km radii) and children’s hyperactivity or attention problems for either maternal or teacher report on child’s behavior assessment (-1.10 \( \leq \beta \leq 0.90 \); all CIs encompassed the null value of 0, with n = 255 – 284 for the maternal report pre- and postnatal, n = 211 – 234 for the teacher report pre- and postnatal; p-values \( \geq 0.05 \)). Correlation analyses were conducted using Pearson correlations of log-transformed 1,3-D use by time period, distance, and active ingredient. For the correlation between fumigants analyses, specifically for 1,3-D use during the postnatal time period within an 8-km radius of the maternal residence, a statistically significant association existed (p < 0.001, n = 255) with a moderate correlation for methyl bromide (r = 0.68), chloropicrin (r = 0.73), and metam sodium (r = 0.56).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. This study had several strengths including the cohort study design, the cognitive assessment used to determine intelligence in children, and the use of maternal residence at multiple timepoints during and after the pregnancy to estimate exposure throughout pregnancy and early childhood years, as well as a sound statistical analyses (generalized additive model to test nonlinearity prior to the selection of multivariable linear regression models, appropriate data transformations to address heteroscedasticity and the influence of outliers, and appropriate sensitivity analyses. Additionally, although follow-up was not mentioned extensively by the study authors, the loss to follow-up was minimal, with a large number of mothers and children completing the neurobehavioral testing and maternal reporting at 7-years of age. The primary limitation of the study was in the exposure estimation, which relied on residential proximity to agricultural 1,3-D use determined from a combination of GPS, GIS, CA DPR PUR data, and wind measurement/direction data as an exposure proxy rather than measuring direct exposure. Furthermore, this method does not capture exposures away from the residence such as use near schools or workplaces where mothers and children might spend a significant amount of time outside of the home.

**EPA Conclusion**

Overall, there is no epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between 1,3-D maternal exposure and neurodevelopmental effects in children. A single study, Gunier et al. (2017), reported no evidence of a significant association during prenatal and postnatal maternal residential proximity to agricultural use of 1,3-D (3-, 5-, or 8-km) and neurodevelopmental effects including attention, IQ and hyperactivity in 7-year-old children. The overall quality of the study was ranked moderate. Study strengths included the comprehensive statistical analyses performed and the prospective cohort study design. The main limitation included the indirect measurement of the exposure, and the use of residential proximity to agricultural 1,3-D use determined from a combination of GPS, GIS, the California PUR database, and weather/wind direction data instead which was not validated for its use of distance as a proxy for exposure.

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\(^{37}\) Postnatal residence in this study was defined as residence from birth until seven years old.
One study (Brouwer et al., 2017) evaluated the association between residential exposure to 1,3-D and Parkinson’s disease (PD).

Brouwer et al. (2017) investigated the association of environmental exposure to pesticides and Parkinson’s disease (PD) in a large hospital-based case-control study. Cases and controls were recruited from five separate hospitals within the Netherlands during 2010 – 2012, and cases included patients diagnosed with PD during January 2006 – December 2011 with confirmed PD diagnosis (a neurologist reviewed their medical files). Controls included patients who visited the same neurology departments during the same time period for non-neurodegenerative symptoms. The participation rate among eligible cases was 45% and was 35% among controls resulting in 444 cases and 876 controls. Participants were excluded if they were missing > 50% of their residential history or if employed in a high pesticide exposure occupation (n = 201) according to a JEM assignment. A total of 352 cases and 607 individually matched controls based on hospital, visiting date (within three years), sex, and age were included in the analysis. Pesticide exposure was assessed using a GIS-based spatio-temporal model that relied on residential address information and land-use data on crops in the Netherlands. Land-use datasets from each year since 1961 were combined with both agricultural census data and expert-generated historical crop use estimates of probability and frequency of use to estimate the area likely treated with 1,3-D and other pesticides within circular rings around the residential addresses. Higher quality agricultural land-use data were available from 1990 on. Residential addresses of the current study were geocoded to building coordinates of the cadastral Registry of Addresses and Buildings (n=3779, 83%) or -- if unsuccessful -- were geocoded to the corresponding 6-digit (n = 248, 5%), 5-digit (n = 313, 7%), or 4-digit (n = 61, 1%) postal code level (addresses for n = 150 (1%) could not be geocoded). For each residential address and each pesticide, the estimated crop area present within 100 m of the residence (split into two distance categories: 0 - 50 m and within > 50 - 100 m) and the estimated probability and frequency of pesticide use were used to estimate the total surface area in hectares (ha) treated with the pesticide during the specific year. These estimates were summed across years (from 1961 up to year preceding case-diagnosis) to obtain an estimate of cases’ cumulative environmental exposures (ha-years). For control subjects, cumulative environmental exposures were calculated through the year preceding the diagnosis year of the matched case. Responses to a telephone-based questionnaire given by trained interviewers that collected demographic data served as a data sources for covariates and exclusion criteria including: medical history, diet, smoking, alcohol consumption, residential pesticide use, and occupational and residential history. A median Spearman correlation coefficient of 0.63 (range 0.36-1.00) for the 21 pesticides that were examined in their primary analysis indicated high correlation. Conditional logistic regression was used to determine ORs and 95% CIs, adjusting for smoking (pack years), time since smoking cessation, home pesticide use, neighborhood income, family history of PD, low occupational pesticide exposure in the JEM, and occupational attainment. Participants unexposed to 1,3-D in the distance category analyzed (0 – 100m, 0 – 50m, > 50 – 100m) served as the reference category, though could have been exposed to other pesticides. Based on this approach, for the association between 1,3-D environmental exposure within 0 - 100 m of residence and PD, evidence of a moderately strong

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38 Residential addresses for cases and controls were determined through a telephone-based questionnaire administered by trained interviewers and included all addresses where a participant lived for over a year and the first and last year the participant inhabited each address. Participants missing > 50% of their residential history were excluded (n = 17).

39 Pesticide exposure originating from crop cultivation for this study was determined to be most relevant at 100m from the residence in terms of exposure probability and intensity because pesticide treatment in the Netherlands is predominantly done using ground-based sprayers and drift of pesticides is highest within the first few meters of the field and decreases exponentially from there.
association was reported when comparing subjects ever exposed to not exposed to 1,3-D (OR: 2.01; 95% CI: 1.09, 3.70; with n = 29 PD cases, 32 controls). When the 1,3-D use within distance of residence was stratified, evidence of a positive association was observed for 1,3-D use at > 50 – 100 m distance, (OR: 1.97; 95% CI: 1.06, 3.65; with n = 28 PD cases, 32 controls). No evidence of a significant positive association was reported for 1,3-D use within 0 – 50 m of the residence (OR: 1.54; 95% CI: 0.61, 3.87; with n = 11 PD cases, 16 controls).

In a further analysis of cumulative exposure (ha-year), based on tertiles of the exposure distribution among the control participants, no evidence of a significant positive association was reported among exposed relative to those not exposed, in any tertile, for the 0 – 100 m distance, (1.48 ≤ OR ≤ 3.33; all CIs encompassed the null value of 1; n = 8 - 13 cases/tertile, 10 – 11 controls/tertile). A test of trend among the tertiles was statistically significant (p = 0.02). An elevated but not significant positive association was reported for the highest tertile at the 0 – 100 m distance (OR = 3.33; 95% CI: 0.97, 11.46; with n = 8 cases, 10 controls). For cumulative exposure of 1,3-D at the 0 - 50 m distance from residence, in the highest tertile, evidence of a strong association was reported (OR: 4.95; 95% CI: 1.20, 20.46; with n = 7 cases, 5 controls). A test of trend among the tertiles was not statistically significant (p = 0.09). Due to the small number of cases reported and the very large confidence intervals for the highest exposure tertile, we place less emphasis on this finding. No evidence of a significant positive association was reported among 1,3-D exposed subjects relative to those not exposed in any tertile (1.37 ≤ OR ≤ 3.33; all CIs encompassed the null value of 1; n = 7 - 13 cases/tertile, 10 – 11 controls/tertile). A test of trend among the tertiles was statistically significant (p = 0.03). An elevated but not significant positive association among a small number of cases was reported for the highest tertile at the > 50 – 100 m distance (OR = 3.33; 95% CI: 0.97, 11.46; with n = 8 cases, 10 controls).

The authors also conducted a lagged analysis that measured the association between 1,3-D exposure within 100 m of the residence and PD based on a lag period of 1,3-D exposure occurring 5-, 10- or 15-years prior to the year before the case-diagnosis. In this analysis, evidence of a moderately strong association was observed for the 5-year, 10-year, and 15-year lagged analyses based on ever/never exposure (5-year – OR: 2.01; 95% CI: 1.09, 3.70; with n = 29 cases, 32 controls; 10-year – OR: 2.12; 95% CI: 1.13, 3.96; with n = 27 cases, 28 controls; 15-year – OR: 2.47; 95% CI: 1.01, 6.05; with n = 13 cases and controls).40 In a final investigation conducted by the study authors, analysis was restricted to environmental exposure data for 1,3-D use from 1990 onward and limited to within 100m of the residence, the same results were reported for use data from 1961 onward, and evidence of a moderately strong positive association was reported (OR = 2.01; 95% CI: 1.09, 3.70; with 29 cases, 32 controls), based on ever use. No evidence was reported for any of the tertiles for cumulative exposure for 1,3-D use.

40 The study authors also performed further analysis by stratifying by exposure tertiles to assess cumulative exposure with lag time at 15 years, evidence of a strong association was reported in the highest tertile only for the 15-year lag-time (OR = 5.27; 95% CI: 1.52, 18.26; with n = 8 cases, 5 controls). A test of trend among the tertiles was statistically significant (p = 0.02). However, due to the small number of cases and controls, and wide confidence interval, we do not have confidence in this finding. There were too few cases (n < 5) to calculate the cumulative OR for the two lower tertiles. No evidence of a significant positive association was observed for the 5- and 10-year lagged time periods (although statistically significant (p<0.02) trends among the tertiles were reported), or in any tertile for 1,3-D use within 100m of the residence (1.37 ≤ OR ≤ 3.04; all CIs encompassed the null value of 1; n = 6 - 14 cases/tertile, 9 – 11 controls/tertile). Although elevated but not significant positive associations were reported for the high exposure tertile for the 5-year lagged analysis (OR = 3.04; 95% CI: 0.91, 10.08; with n = 8 cases, 11 controls) and at both the lowest and highest tertiles of exposure for 10 year lagged time period (TT – OR = 2.21; 95% CI: 0.92, 5.34; with n = 14 cases, 10 controls; T3 – OR = 2.99; 95% CI: 0.96, 9.31; with n = 7 cases, 9 controls), the number of exposed cases were similarly small and the confidence intervals quite wide.
from 1990 onward, at the 100m distance from the residence (1.48 < ORs < 3.33; all CIs encompassed the null value of 1.0, with n = 8 - 13 cases/tertile, 10 – 11 controls/tertile, p-trend = 0.02) An elevated but not significant positive association was reported for the highest tertile at the 0 – 100m distance for use from 1990 onwards (OR = 3.33; 95% CI: 0.97, 11.46; with n = 8 cases, 10 controls).

The overall quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included utilizing a dataset from a hospital-based case-control study that recruited cases and controls from the same hospital neurology departments. While this recruitment approach was a strength of the study, participation was relatively low, with 45% of eligible cases and 35% of eligible controls participating. In addition, Brouwer et al. (2017) assessed potential environmental 1,3-D exposure by linking residential address to land-use data. This approach relied on expert judgement to assign 1,3-D usage to specific crop types and may be subject to misclassification. Too, the GIS-based exposure approach used in Brouwer et al. (2017) lacked land-use data on pesticide application and instead estimated exposure more generically using spatial crop information and expert judgement on the frequency/probability of specific pesticide use of these crops. Additionally, the GIS based exposure estimate method lacks validation. This approach may be limited in assessing exposure to 1,3-D specifically if there is a strong degree of correlation across pesticides. The investigators did not adjust for pesticide co-exposure in their statistical analysis but reported a median Spearman correlation coefficient of 0.63 (range 0.36-1.00) for the 21 pesticides that were examined in their primary analysis. For 1,3-D specifically, the median Spearman correlation coefficient was 0.57 (range 0.28, 1.0), based on values reported in Figure A1 of Appendix A of Brouwer et al (2017), suggesting correlation across pesticides was present in their study. Finally, the authors’ primary analysis focused on four a priori selected pesticides (paraquat, maneb, lindane, and benomyl). The analysis of 1,3-D was part of a secondary, hypothesis-generating analysis that investigated a total of 153 pesticides for which exposure data was available based on the agricultural census and expert judgement of historical crop-specific pesticide use. This secondary analysis included a large number of statistical comparisons, which were further stratified by tertiles of exposure, residence distance, and exposure lag, so the authors concluded that they could not exclude the possibility that the observed associations were false positives.

EPA Conclusion

Overall, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between 1,3-D exposure and PD. One study, Brouwer et al. (2017), reported evidence of a moderately strong association when comparing subjects ever exposed and not exposed to 1,3-D within the 0 – 100 m distance and PD, and when further stratified by distance, at the > 50 – 100 m use from residence distance, evidence of a positive association was observed; no evidence of a significant positive association was reported for use of 1,3-D use within the 0 – 50 m distance of the residence. In the lagged analyses, evidence of a moderately strong association was observed for 5, 10 and 15 years prior to the year before the case based on ever/never exposure. When the data were further stratified by tertiles, evidence of an association in the highest tertile only for the 15-year lag-time was observed; however, due to the small number of cases and controls, and the wide confidence intervals, we do not place much emphasis on this finding. No evidence of a significant positive association was observed for the 5-yr and 10-yr lagged time-periods, in any tertile. The overall quality of the study was ranked moderate. Study strengths included the hospital-based case-control study design, and the outcome assessment using medical record review to verify PD diagnosis. Study limitations included low participation rates among the eligible population, possible exposure misclassification resulting from the spatio-temporal GIS based approach of estimating pesticide exposure using residential address and agricultural land-use data that did not include actual pesticide application data, and the large number of statistical comparisons, which were further stratified by tertiles of exposure, residence distance, and exposure lag.
Two studies (Gunier et al., 2018; Gharibi et al., 2019) investigated the association between fumigant exposure to 1,3-D and respiratory effects including lung function and asthma among children and adults. Study details are provided below.

- Gunier et al. (2018) conducted a prospective cohort study to investigate the associations between prenatal and postnatal residential proximity to agricultural use of fumigants including 1,3-D and respiratory effects in 7-year-old children who are part of the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) birth cohort. The study population consisted of children born to mothers recruited and enrolled between October 1999 and October 2000 from health clinics serving low-income residents of the Salinas Valley, California. Inclusion criteria for mothers included the following: ≥ 18 years of age; < 20 weeks of gestation; were eligible for MediCal; spoke English or Spanish; and, were planning to deliver at the county hospital. Of the 601 mothers enrolled, 537 were followed to delivery. Although information on respiratory symptoms and use of asthma medication were available for 347 participating children through age seven and spirometry was performed on 279 of these, children were included for the prenatal analysis only if maternal residence during pregnancy for ≥ 80% of their pregnancy was known to the investigators and included for the postnatal analysis only if ≥ 80% of the child’s residential history was known from birth through seven years old at the time of assessment. A total of 294 participants were part of either the prenatal or postnatal analysis. For the prenatal and postnatal periods, 257 children with and 276 children provided covariate data with further details regarding asthma medications and respiratory symptoms obtained during the postnatal period. Maternal questionnaire data collected from two interviews conducted during pregnancy (1st interview (M ± SD): 13.4 ± 4.7 weeks gestation, 2nd interview: 26.5 ± 2.6 weeks gestation), after pregnancy and when their children were 0.5-, 1-, 2-, 3.5-, 5-, and 7-years old provided demographic information and prenatal and postnatal lifestyle behaviors and were used as covariates. Prenatal and delivery medical records data were abstracted by registered nurses, and home visits were performed by trained personnel during pregnancy (~13 weeks gestation) and when children were 0.5-, 1-, 2-, 3.5-, and 5- years old. At the 7-year visit, mothers were interviewed about their child’s respiratory symptoms using questions adapted from the International Study of Asthma and Allergies in Childhood questionnaire and were asked if their child had been prescribed medications for asthma or wheezing/chest tightness. Respiratory symptoms in the past year was considered a binary outcome (yes/no); and was defined as a positive response to at least one of a series of questions. Children’s lung function was also assessed using spirometry to determine forced expiratory volume in one second (FEV₁), forced vital capacity (FVC), and forced expiratory flow 25-75% (FEF₂₅₋₇₅%), and the best spirometric measurements for each component (FEV₁, FVC, and FEF₂₅₋₇₅%) were recorded for each child. One technician conducted 92% of the tests, three identical spirometers were used and calibrated every morning, two physicians experienced in pediatric spirometry reviewed the expiratory flow-volume curves obtained from the spirometry software, and inadequate data were excluded from the statistical analysis. Investigators used GPS data (latitudes and longitudes).

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41 Specific fumigants investigated included methyl bromide, chloropicrin, metam sodium, and 1,3-D.
42 A positive response to any of the following questions indicated respiratory symptoms in children in the past year: (i) wheezing, whistling, or shortness of breath so severe the child could not complete a sentence; (ii) whistling or wheezing in the chest; (iii) trouble going to sleep or awakening due to whistling, wheezing, or shortness of breath, or coughing when child did not have a cold; (iv) having to stop running or playing active games due to whistling, wheezing, shortness of breath, or coughing when the child did not have a cold; or (v) asthma medication use even in the absence of the above symptoms reported by the mother.
43 In this study, children were allowed up to eight expiratory maneuvers, and a maximum of three best acceptable tests were saved and recorded per child.
longitudes) of participants residences (obtained during home visits at ~13 weeks gestation, and 0.5-, 1-, 2-, 3.5-, and 5- years, and verbally at the 7-year visit), GIS, and CA DPR PUR data to estimate to 1,3-D use within 3-, 5-, and 8-km radii of maternal residences during specific time periods including: prenatal during pregnancy, postnatal from birth to the 7-year follow-up visit, and the year before the 7-year visit. Authors reported that distances of 3-, 5-, and 8-km were selected because they best captured the spatial scale most strongly correlated with concentrations of methyl bromide and 1,3-D in air.\textsuperscript{44} PUR data include all agricultural pesticide applications in California including date and location and quantity of active ingredient applied, acres and crop treated within 1-square-mile sections defined by the Public Land Survey System (PLSS). The amount (kg) of pesticide active ingredient applied within each PLSS 2.56 square-km within each buffer distance at various time points was weighted based on the proportion of each square-mile PLSS that was within each buffer surrounding a residence. Additionally, the downwind transport of fumigants was accounted for by determining the wind frequency, which was then used to calculate the wind-weighted amount of each fumigant applied within the buffer areas and the corresponding time periods of the child’s residence. Logistic regression models were used to determine the association for respiratory symptoms and asthma medications among children at seven years of age relative to the child’s residential proximity to fumigants, including 1,3-D, during prenatal and postnatal exposure periods using ORs and corresponding 95% CIs. Covariates, selected both \textit{a priori} and if found to be empirically associated with respiratory function and/or asthma medication, included: signs of moderate or extensive mold noted during either home visit; maternal smoking during pregnancy; season of birth; and, runny nose without a cold in previous 12 months reported at 7-year visit (a proxy for allergy). Adjusted results were presented as a 10-fold increase in wind-weighted fumigant exposures including 1,3-D within 3-, 5- and 8-km buffer distances of the child’s residence during prenatal and postnatal periods, with respiratory symptoms and asthma medication use in children aged 7-years as the outcome. For lung function, after verifying the deviation from linearity was not significant by the generalized additive model, a multivariable linear regression model was used to regress the mean change in lung function with the log_{10}-tranform of continuous fumigant use. Separate regression models were run for each combination of potential outcome (FEV\textsubscript{1}, FVC, FEF\textsubscript{25-75}), time period, and buffer distance.

Covariates, selected both \textit{a priori} and found to be empirically associated with lung function, included child’s height, age, sex, maternal smoking during pregnancy, season of birth, technician performing the test, mean daily PM\textsubscript{2.5} concentration during the first three months of life, breast feeding duration, distance from highway (≤ 150 m) during the first year of life, furry pets at home, signs of moderate/extensive mold during the home visit, household food insecurity score (seven years), prenatal exposure to fumigant (postnatal exposure models only), and runny nose without a cold at 7-year visit (proxy for allergy). Adjusted results were presented as mean changes (regression coefficients) in lung function measurements (highest FEV\textsubscript{1}, FVC, FEF\textsubscript{25-75}) in children at seven years of age for every 10-fold increase in wind-weighted 1,3-D exposure within 3-, 5-, and 8-km buffer distances during prenatal and postnatal exposure periods, along with corresponding 95% CIs and p-values.

For the respiratory symptoms analysis, no evidence of a significant positive association was reported among children at 7-years of age relative to a 10-fold increase in wind-weighted fumigant exposures to 1,3-D use within 3-, 5-, or 8-km radii of the residence during prenatal and postnatal exposure periods (1.00 ≤ ORs ≤ 1.60; all CIs encompassed the null value of 1.00, with n = 257 – 276

participants during both periods and all p-values ≥ 0.05). Similarly for asthma medication usage analysis, no evidence of a significant positive association was reported among children at 7-years of age relative to a 10-fold increase in wind-weighted fumigant exposures for 1,3-D within a 3-, 5-, or 8-km proximity to the residence during prenatal and postnatal periods (1.20 ≤ ORs ≤ 1.70; all CIs encompassed the null value of 1.00, with n = 257 – 276 participants during both periods and all p-values ≥ 0.05).

Similarly for asthma medication usage analysis, no evidence of a significant positive association was reported among children at 7-years of age relative to a 10-fold increase in wind-weighted fumigant exposures for 1,3-D within a 3-, 5-, or 8-km proximity to the residence during prenatal and postnatal periods (1.20 ≤ ORs ≤ 1.70; all CIs encompassed the null value of 1.00, with n = 257 – 276 participants during both periods and all p-values ≥ 0.05).

For lung function analysis during prenatal exposure, for a 10-fold increase in wind-weighted fumigant exposures including 1,3-D use within a 3-, 5-, or 8-km distance to the residence, no evidence of a statistically significant decrease in lung function in children at seven years of age was observed for highest FEV\(_1\), FVC, and FEF\(_{25-75}\) (-0.09 ≤ β ≤ -0.02; all CIs encompassed the null value of 0; with n = 208 – 229 participants, all p-values ≥ 0.05). For lung function analysis during the postnatal exposure period, for a 10-fold increase in wind-weighted fumigant exposures for 1,3-D use within a 3-, 5-, or 8-km buffer distance, no evidence of a significant association in lung function in children at 7-years of age was observed for highest FEV\(_1\), FVC, and FEF\(_{25-75}\) (-0.02 ≤ β ≤ 0.04; all CIs encompassed the null value of 0; with n = 193 – 212 participants, all p-values ≥ 0.05). And similarly, no evidence of a significant association was reported between 1,3-D exposure at 3-, 5-, or 8-km buffers distance during the year prior to assessment and lung function assessment at seven years of age (-0.06 ≤ β ≤ 0.03; all CIs encompassed the null value of 0; with n = 194 – 214 participants, all p-values ≥ 0.05).

The quality of the study was ranked moderate based on the study quality criteria provided in the OPP Framework. Study strengths included the prospective cohort study design, the sound statistical analyses (generalized additive model to test nonlinearity prior the selection of multivariable linear regression models, appropriate data transformations to address heteroscedasticity and the influence of outliers, appropriate sensitivity analyses), and the large amount of information on covariates selected within this study. The spirometry tests used to determine lung function in children was also a strength due to the multiple spirometry samples that were collected for each child participant and the routine quality control procedures implemented. Daily calibrations of the three spirometers used to test lung function were carried out, and the quality of the expiratory flow-volume curves from each child was reviewed by two physicians before being deemed acceptable to be part of the statistical analyses for this study. Additionally, although follow-up was not mentioned extensively by the study authors, the loss to follow-up was minimal, with a large number of children involved in the lung function test at 7-years of age (n = 193 – 212 children of the total 294 maternal study participants involved in either the prenatal or postnatal analyses). A major limitation of this study is the lack of direct measurement of exposure to the fumigant. Instead, the study relied on residential proximity to fumigant applications including 1,3-D, as a proxy to measuring direct exposure, using California PUR data. The study authors also did not provide information on maternal occupational exposures or the location of the maternal workplace or the location of the child’s school which may have helped define the exposure but alternatively, contributed to potential exposure misclassification. In addition, authors reported a correlation between prenatal 1,3-D and metam sodium use at 8-km radius (Pearson correlation r = 0.70, p < 0.001) making it difficult to separate associations of 1,3-D from associations with metam sodium in this study.

- Gharibi et al. (2019) conducted a case-crossover study (bidirectional-symmetric) to investigate the association between short-term 1,3-D exposure and emergency department (ED) visits due to asthma exacerbation in central and southern California. ED visits due to asthma were identified from a dataset acquired by the California Office of Statewide Health Planning and Development (OSHPD), and cases included ED patients (any age) in central and southern California from October through
February of 2005 through 2011, whose primary diagnosis was documented as an ‘asthma-related visit’ according to the International Classification of Diseases 9th Revision (ICD-9) code. Pesticide exposure was measured using air quality data monitored by the Environmental Protection Agency Outdoor Air Exposure database, and the daily-average of one-day air samples was recorded every two weeks. Measured 1,3-D concentrations were then assigned to each asthmatic ED case based on the residential proximity of the cases to the sampling stations responsible for measuring the pesticide exposures, using patient geocoded zip codes. For each ED asthma case, two referent days (two weeks apart) prior to and two referent days (two weeks apart) after the ED visit were applied as controls to compare exposure of patients on the day of the ED visit to the four referent days. A conditional logistic regression was used to determine the association between the daily-average of 1,3-D and asthma ED cases, adjusting for concomitantly present pollutants including fine particulate matter (PM$_{2.5}$) and nitrous oxide (NO$_2$), as well as relative humidity and temperature. Results were based on incremental increases of 0.01 ppb of 1,3-D air concentrations. Among the total number of ED patients in central and southern California between 2005 – 2011 (n = 35,876), 3,878 of these patient visits were asthma-related and corresponded to days with ambient pesticide concentrations. Of the 3,878 asthma ED patients, 46.0% were female and 54.0% were male, and percentages of visits by age group included: age 2 – 5 years (11.6%), age 6 – 18 years (22.7%), age 19 – 40 years (31.3%), age 41 – 64 (23.9%), and age ≥ 65 years (6.6%), respectively. Evidence of a slight positive association between exposures within and asthma ED visits in central and southern California between 2005 – 2011 were observed (OR: 1.14; 95% CI: 1.12, 1.15) when adjusted for concomitantly present pollutants, suggesting that a 0.01 ppb increase in 1,3-D air concentrations increases the odds of asthma ED visits in central and southern California by 13.5%. When the data was further stratified by sex, race, and age the following ORs were reported (Table 6).

Table 6. The association between 1,3-D ambient air concentration and ED visits for asthma exacerbation in central and southern California between 2005 and 2011, stratified by sex, race, and age.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>1,3-D (ppb) OR (95% CI)</th>
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<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
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<tr>
<td>Female</td>
<td>1.069 (1.035, 1.103)</td>
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<tr>
<td>Male</td>
<td>1.081 (1.042, 1.123)</td>
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<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic White</td>
<td>1.003 (0.921, 1.079)</td>
</tr>
<tr>
<td>Non-Hispanic Black</td>
<td>1.095 (1.035, 1.155)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1.121 (1.064, 1.179)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>2 – 5 years</td>
<td>1.065 (1.020, 1.113)</td>
</tr>
<tr>
<td>6 – 18 years</td>
<td>1.142 (1.086, 1.196)</td>
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<tr>
<td>19 – 40 years</td>
<td>1.044 (1.015, 1.073)</td>
</tr>
<tr>
<td>41 – 64 years</td>
<td>0.991 (0.977, 1.012)</td>
</tr>
<tr>
<td>≥ 65 years</td>
<td>1.081 (0.991, 1.162)</td>
</tr>
</tbody>
</table>

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45 This time period was selected since the largest ambient concentration of 1,3-D was recorded during this time in 2005 – 2011.
46 [https://www.cdc.gov/nchs/icd/icd9cm.htm](https://www.cdc.gov/nchs/icd/icd9cm.htm)
47 Residential proximity was defined as the residence located within a 5-km radius of the sampling station.
48 The number of cases were not reported by the study authors for any of the corresponding ORs and 95% CIs mentioned in this study.
The quality of the study was ranked low based on the study quality criteria provided in the OPP Framework. Study strengths included the study design and the extensive amount of data collected using the government databases. Study limitations included the lack of case reporting (only the total number of cases was reported by the study authors not case numbers when stratified by sex, race, or age), the residential proximity to sampling stations (~within a 5-km radius) that collected air quality samples for 1,3-D as a proxy of measuring exposure, no QA/QC procedures mentioned in measuring the exposure (i.e., for the air quality data collected), use of zip code vs. actual geocoded patient address, and the reporting system’s inability to differentiate between first-time asthma ED cases and those cases who have had multiple asthma ED visits. For the outcome, this study relied upon the first ICD-9 diagnosis code entered into the medical record for each case, unlike other studies that also considered the second and third ICD-9 coded diagnoses in an effort to further confirm the suspected outcome and potentially rule out other outcomes. Additionally, the ED data collection system used in this study did not contain personally identifiable information, so the system was unable to longitudinally determine if a single case had multiple visits to the ED, or if the ED patient was a first-time asthma case. As a result, the total number of asthma ED cases reported may have included multiple visits by a single person and may have been inflated.

EPA Conclusion

Overall, there is insufficient epidemiological evidence at this time to conclude that there is a clear associative or causal relationship between 1,3-D exposure and respiratory effects in children and adults. Two studies, Gunier et al., 2018 and Gharibi et al., 2019 were ranked moderate and low quality, respectively, based on the study quality criteria provided in the OPP Framework. In Gunier et al. (2018), no significant positive association was observed between maternal residential proximity to 1,3-D applications (at 3-, 5-, or 8-km radii) during prenatal and postnatal periods and respiratory health outcomes in children at 7 years of age. For Gharibi et al. (2019), although evidence of a slight positive association was observed between 1,3-D exposures within the air and asthma ED visits in central and southern California between 2005 – 2011, the quality of the study was ranked low due to study limitations including indirect measurement of the exposure and the reporting system’s inability to differentiate a single person with multiple asthma-related ED visits. Additionally, the study relied solely on the first ICD-9 diagnosis code entered into the medical record for each case and did not consider the second and third ICD-9 coded diagnoses to further confirm that the ED visit was asthma-related.

3.7. Epidemiology Conclusion

OPP performed a systematic review of the epidemiologic literature on 1,3-D exposure and identified 12 publications that investigated carcinogenic and non-carcinogenic health outcomes including pancreatic cancer, prostate cancer, kidney function, liver function, Parkinson’s disease, respiratory effects, and neurodevelopmental effects in children. OPP’s conclusions on the available evidence for these outcomes are summarized below.

Pancreatic Cancer

- For pancreatic cancer, there is insufficient evidence at this time to conclude that there is a clear associative or causal relationship with 1,3-D exposure. In a semi-ecological study, Clary and Ritz (2003) reported no evidence overall of a significant positive association between residential proximity to agricultural use of 1,3-D and those who died from pancreatic cancer; however, when the data was further stratified by years of living within a county, evidence of a positive association was observed between pancreatic cancer mortality and 1,3-D exposure among those who reported living in the area for more than 20 years. Several study limitations were noted, and the quality of the study was ranked...
low. The study was determined to be low quality and had several limitations, including its study design, the indirect, semi-ecologic exposure measure, the possible under-reporting of PUR data among farmers, and the inadequate consideration of confounders (i.e., smoking).

**Prostate Cancer**

- For **prostate cancer**, there is no evidence at this time to conclude that there is a clear associative or causal relationship with 1,3-D exposure. A single population-based case-control study, Band et al. (2011), evaluated the potential association between prostate cancer and occupational exposure to select pesticides including 1,3-D, and reported no evidence of a positive association between 1,3-D exposure and prostate cancer in men based on ever/never use. Several study limitations were identified and the study was of low quality.

**Kidney Function**

- For **kidney function**, there is insufficient evidence at this time to conclude that there is a clear associative or causal relationship between workers occupationally exposed to 1,3-D and renal effects. Three studies (Osterloh et al., 1989/Osterloh & Feldman, 1993; Brouwer et al., 1991; Verplanke et al., 2000) investigated the association between occupational exposure to 1,3-D and kidney function among 1,3-D application workers, and two of the three studies reported statistically significant results (Osterloh et al., 1989/Osterloh & Feldman, 1993; Brouwer et al., 1991). While significant associations were reported, the two studies were considered to be of low quality due to major study limitations including the use of inappropriate statistical methods and/or the lack of adjustments made for multiple comparisons (Brouwer et al., 1991), as well as the exposure assessment relying entirely on the commercial applicators’ memory and ability to estimate at the end of the season how many hours and days they worked in soil fumigation throughout the season; no attempt at validation or comparison with application records was made. The studies included a small number of cases (n ≤ 16), and as a result, the reported estimates in these studies lack precision and are unreliable. The third study, Verplanke et al. (2000), reported no evidence of an association for renal parameters relative to cis-1,3-D. No evidence of a dose-response was reported as well. This study used a prospective cohort study design; however, the study was considered low quality and had several limitations and used inappropriate statistical methods.

**Liver Function**

- For **liver function**, there is insufficient evidence at this time to conclude that there is a clear associative or causal relationship between workers occupationally exposed to 1,3-D and liver effects. Both Brouwer et al. (1991) and Verplanke et al. (2000) investigated the association between 1,3-D exposure and effects on liver function of commercial applicators in the Netherlands. While significant associations were reported for effects on liver function for both studies, each study was considered to be of low quality due to several study limitations. In Verplanke et al. (2000), study limitations included the inappropriate statistical methods used for the t-test and lack of adjustments for multiple comparisons when several different liver enzymes analyses were performed. In Brouwer et al. (1991), study limitations included the exposure assessment relying on the commercial applicators’ memory and ability to estimate at the end of the season how many hours and days they worked in soil fumigation throughout the season; no attempt at validation or comparison with application records was made. Authors did not consider prior exposure to 1,3-D and no adjustments for multiple comparisons were made. A small number of cases (n ≤ 14) were included in both studies, and as a result, the reported estimates in these studies lack precision and are unreliable.
Neurodevelopmental Effects

Neurodevelopmental effects in children including autism spectrum disorder (ASD) following perinatal exposure to 1,3-D, and effects on full-scale and domain-specific IQ following prenatal exposure to 1,3-D were assessed.

For ASD, there is no evidence at this time to conclude that there is a clear associative or causal relationship relative to 1,3-D perinatal exposure. This determination was based on two studies (Kalkbrenner et al., 2010; Kalkbrenner et al., 2018) that reported no evidence of a significant positive association between 1,3-D, using a case-control study design in one study and a family-based cohort study design in the second study. A main limitation of both studies included the reliance on the NATA model census-tract estimates as opposed to direct measurement of perinatal air toxic exposure. Kalkbrenner et al. (2010) was ranked low and Kalkbrenner et al. (2018) was ranked moderate.

• For full-scale IQ and domain-specific IQ, there is no evidence at this time to conclude that there is a clear associative or causal relationship between child IQ and 1,3-D prenatal exposure. One prospective cohort study, Gunier et al. (2017), reported no evidence of a significant association between prenatal exposure to agricultural use of 1,3-D at 3-, 5-, or 8-km proximity to maternal residence (prenatal) and neurodevelopmental effects including attention, IQ and hyperactivity in 7-year-old children. Study limitations were noted. The overall quality of the study was ranked moderate.

Parkinson’s disease

• For Parkinson’s disease (PD), there is insufficient evidence at this time to conclude that there is a clear associative or causal relationship between 1,3-D exposure and Parkinson’s disease. A single study, Brouwer et al. (2017), reported evidence of a moderately strong association between 1,3-D environmental exposure within 0 - 100 m of the residence and PD, when comparing exposed to unexposed. When distance was further stratified (0 – 50 m vs. > 50 – 100 m), no evidence of a significant positive association was reported within the 0 – 50 m distance, but evidence of a positive association was observed within the > 50 – 100 m distance. The overall quality of the study was ranked moderate based on the study quality criteria in the OPP Framework. The study was a hospital-based case-control study design; however, several study limitations were noted, including low participation rates among the study population, exposure misclassification from linking residential address to land-use data, and the GIS-based approach used to measure exposure lacked pesticide application land-use data. The analysis of 1,3-D was also part of a secondary, hypothesis-generating analysis that investigated a total of 153 pesticides for which exposure data was available based on the agricultural census and expert judgement of historical crop-specific pesticide use. This secondary analysis included a large number of statistical comparisons, which were further stratified by tertiles of exposure, residence distance, and exposure lag, so the authors concluded that they could not exclude the possibility that the observed associations were false positives.

Respiratory Effects - Lung Function and Asthma

• For respiratory effects, there is insufficient evidence at this time to conclude that there is a clear associative or causal relationship between 1,3-D exposure and respiratory effects in children and adults. This determination was based on two studies that were ranked moderate and low quality, respectively. In Gunier et al. (2018), no significant positive association was observed between maternal residential proximity to 1,3-D application (3-, 5-, or 8-km radii) during prenatal and postnatal periods and respiratory health outcomes in children at seven years of age. The study was a prospective cohort study; however, several study limitations were noted. Gharibi et al. (2019)
reported evidence of a slight positive association between 1,3-D exposures and asthma ED visits in central and southern California between 2005 – 2011. The quality of the study was ranked low due to study limitations including the residential proximity to the sampling stations as a proxy of measuring exposure and potential misclassification of the outcome.

4. **OVERALL CONCLUSION**

For this 1,3-Dichloropropene (1,3-D) Tier II Incident and Epidemiology Report, HED found the majority of incidents involving 1,3-D were low in severity (82% in IDS and 89% in SENSOR-Pesticides). Most of the incidents reviewed for this memorandum reported that individuals experienced minor symptoms such as burning eyes and coughing. These are symptoms, which were minimally traumatic and resolved rapidly, and are likely the result of chloropicrin exposure. Chloropicrin is used as a warning agent with other more toxic active ingredients, such as 1,3-D, because it has a strong odor and causes respiratory and eye irritation. In IDS (71%), SENSOR-Pesticides (83%), and CA PISP (96%) exposure from drift/volatilization was responsible for the most reported 1,3-D incidents. These incident events, often involving multiple cases, resulted from off-target drift or volatilization of the a 1,3-D product onto nearby farms, fields and residential areas. These events exposed workers and residents of neighboring communities.

Epidemiological studies investigating the association between 1,3-D and health outcomes available in the open literature were reviewed. Overall, there was insufficient evidence to suggest a clear associative or causal relationship exists between 1,3-D exposure and the carcinogenic and non-carcinogenic health outcomes investigated in the studies reported here. The Agency will continue to monitor the epidemiology data, and -- if a concern is triggered -- additional analysis will be conducted.

5. **REFERENCES**


## 6. Appendix A: 1,3-D Incidents Reported to Main IDS from January 1, 2014 to September 17, 2019

<table>
<thead>
<tr>
<th>Incident Package Report</th>
<th>Incident Date</th>
<th>Location</th>
<th>Reg Number</th>
<th>Product Name</th>
<th>PC Code</th>
<th>Ingredient Name</th>
<th>Exposure Severity</th>
<th>Incident Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>027329 - 00001</td>
<td>10/22/2014</td>
<td>INDIANTOWN, FL</td>
<td>008536-00008-087994</td>
<td>PIC-CLOR 60</td>
<td>081501, 029001</td>
<td>Chloropicrin, 1,3-D,</td>
<td>Minor</td>
<td>An adult male worker was exposed to the product after a forklift operator accidentally hit a rig which split the valve fitting and released a small amount of fumigant from an injection line. He was wearing a respirator but momentarily adjusted it to remove hair caught in the mask and was exposed to the fumes from the spill. He experienced sensory irritation.</td>
</tr>
<tr>
<td>028401 - 00021</td>
<td>7/31/2015</td>
<td>CA</td>
<td>058266-00002-011220, 062719-00032</td>
<td>TRI-CLOR, 1,3-D II</td>
<td>081501, 029001</td>
<td>Chloropicrin, 1,3-D</td>
<td>Moderate</td>
<td>A pest control operator made an aerial pesticide (Reg. No. 70310-5) application by helicopter to an organic lettuce field. A farm labor contractor (FLC) crew consisting of 28 employees, was working approximately 600 feet from the application site. A FLC crew member complained of feeling sick and experiencing symptoms. The FLC transported the entire work crew to El Centro Regional Medical Center for decontamination. It was determined that 7 workers out of 26 reported to hospital staff of having symptoms of dizziness, cough, ocular irritation/pain.</td>
</tr>
<tr>
<td>028977 - 00001</td>
<td>7/21/2015</td>
<td>OROVILLE, CA</td>
<td>062719-00032, 058266-00002-011220</td>
<td>1,3-D II, TRI-CLOR</td>
<td>029001, 081501</td>
<td>1,3-D, Chloropicrin</td>
<td>Moderate</td>
<td>A 4.9-acre agricultural field was treated with a combination of Tri-Clor and 1,3-D II via the deep non-tarped shank application method. The application rate was 183lbs/acre of Tri-Clor and 33.9</td>
</tr>
<tr>
<td>Incident Package Report</td>
<td>Incident Date</td>
<td>Location</td>
<td>Reg Number</td>
<td>Product Name</td>
<td>PC Code</td>
<td>Ingredient Name</td>
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<tr>
<td>028934 - 00003</td>
<td>5/21/2016</td>
<td>SANTA MARIA, CA</td>
<td>008536-00043-011220, 007969-00302, 062719-00545</td>
<td>PIC-CLOR 60 EC, ZAMPRO FUNGICIDE, RADIANT SC INSECTICIDE, INDUCE (CANADA 5909-50091)</td>
<td>081501, 029001, 119210, 268800, 110007</td>
<td>Chloropicrin, 1,3-D, Ametocradin, Dimethomorph, Spinetoram (amixture of spinetoram-J and spinetoram-L), Adjuvant</td>
<td>Moderate</td>
<td>Gal/acre of 1,3-D II. Two out of three residents located approximately 375' from the fumigation experienced sensory irritation and called 911. The mother and teenage daughter reported symptoms while the father did not. Paramedics arrived onsite and evaluated the mother and daughter. None of the paramedics experienced sensory irritation while onsite. The mother and daughter then took themselves to the hospital, where they were examined and released.</td>
</tr>
<tr>
<td>A registered Aerial Pest Control Company performed a helicopter pesticide application. The pilot treated a total of 12.7 acres using Radiant SC and Zamp-o (R) Fungicide. The helicopter passes were from south to north and was approximately 1150 feet west of the Strawberry field where the field workers were planting strawberries and experienced illness symptoms. The crew was planting strawberries and noticed the helicopter spraying and four of the eleven members began feeling ill. The foreman informed his supervisor who was instructed to evacuate the area to a safer location and to drive the entire crew to Marian Regional Medical Center in Santa Maria. All eleven workers were decontaminated and four of them reported illness symptoms of nausea, headache, and dizziness. Another two crew members who had symptoms and were working among others, harvesting zucchini at approximately 1415 feet north east of the</td>
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<tr>
<td>029622 - 00005</td>
<td>11/24/2016</td>
<td>RIDGE SPRING, SC</td>
<td>062719-00032</td>
<td>1,3-D II</td>
<td>029001</td>
<td>1,3-D</td>
<td>Moderate</td>
<td>aerial application. The two harvesters reported symptoms of dizziness and nausea after witnessing the aerial application but did not seek medical attention. The site of fumigation is approximately 1447.5 feet from the squash harvesting crew and 1626 feet from the Strawberry planting crew and on the opposite direction of the lettuce field.</td>
</tr>
<tr>
<td>030307 - 00001</td>
<td>8/26/2017</td>
<td>CA</td>
<td>011220-00035</td>
<td>TRI-FORM 80 EC</td>
<td>029001, 081501</td>
<td>1,3-D, Chloropicrin,</td>
<td>Minor</td>
<td>An adult male farm worker had some of the product spill onto the top of his boot. Initially, no treatment was done. Later, the patient noticed some redness on the top of his foot, in the area and washed his skin. He continued to wear the contaminated boots. A week later, his foot was very red and swollen. He was sent to the doctor who diagnosed a burn (degree unknown).</td>
</tr>
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<td></td>
<td>Between 6:00am and 10:30am a licensed pest control business injected Tri-Form 80 EC into tarped strawberry beds in Salinas, California. At approximately 9:40, a Monterey County Agricultural inspector was driving by the fumigated strawberry beds and he observed 10 field workers pruning raspberry canes in hoop houses adjacent to the strawberry beds. The workers were inadvertently entering the 30-foot fumigation buffer zone. Eight employees were interviewed, and seven have stated they had eye irritation. This investigation is ongoing.</td>
</tr>
<tr>
<td>Incident Package Report</td>
<td>Incident Date</td>
<td>Location</td>
<td>Reg Number</td>
<td>Product Name</td>
<td>PC Code</td>
<td>Ingredient Name</td>
<td>Exposure Severity</td>
<td>Incident Description</td>
</tr>
<tr>
<td>-------------------------</td>
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</tr>
<tr>
<td>032207 - 00001</td>
<td>6/4/2019</td>
<td>LOS OLIVOS, CA</td>
<td>062719-00032</td>
<td>1,3-D II</td>
<td>029001</td>
<td>1,3-D</td>
<td>Minor</td>
<td>On Thursday, June 6, 2019, the Santa Barbara County Agricultural Commissioner's Office (SB CAC) was notified by Firestone Winery in Los Olivos that 6 employees experienced symptoms of light headache and sore throat after a 1,3-D II application on the property, but did not seek medical attention. On June 4, a registered pest control business, applied 1,3-D II (EPA Reg number 62719-32) with deep shank method to 11 acres of grapes.</td>
</tr>
</tbody>
</table>
### 7. Appendix B: Summary of Epidemiologic Studies and Study Quality Assessment

#### Table B-1: Summary of Epidemiologic Studies on Cancer

<table>
<thead>
<tr>
<th>First Author (Pub Year)</th>
<th>Study Period</th>
<th>Description of study population</th>
<th>Study Design</th>
<th>Exposure Measurement</th>
<th>Outcome Measurement</th>
<th>Primary 1,3-D Results</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Band et al. (2011)</td>
<td>1950-1998</td>
<td>Farm workers in British Columbia, Canada</td>
<td>Population-based case-control study Males only \n( n = 1,153 ) cases and 3,999 controls</td>
<td>Self-reported questionnaires and job exposure matrix (JEM)</td>
<td>Cancer registry with histopathological verification</td>
<td>No evidence of a positive association between 1,3-D exposure and prostate cancer in men, based on ever/never use.</td>
<td>Low</td>
</tr>
<tr>
<td>Clary &amp; Ritz (2003)</td>
<td>1972-1996</td>
<td>Kern, Fresno, &amp; Tulane counties, California (CA)</td>
<td>Semi-ecologic study \n( n = 130 ) cases</td>
<td>California PUR database and GIS software</td>
<td>Death certificates</td>
<td>No evidence overall of a significant positive association for residential proximity to agricultural use and those who died from pancreatic cancer.</td>
<td>Low</td>
</tr>
</tbody>
</table>

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49 For additional reported results including risk measures, number of cases/non-cases, and p-values, refer to the individual study summaries written above.
<table>
<thead>
<tr>
<th>First Author (Pub Year)</th>
<th>Study Period</th>
<th>Description of study population</th>
<th>Study Design</th>
<th>Exposure Measurement</th>
<th>Outcome Measurement</th>
<th>Primary 1,3-D Results(^5^0)</th>
<th>Study Quality</th>
</tr>
</thead>
</table>
| Brouwer et al. (1991)  | July – October, year not reported | The Netherlands | Similar to a case-crossover study  
\(n = 14\) males only | Self-report via personal interview – number of hours and days worked in soil fumigation. | Urine samples were measured Alb-U, \(\beta\)-M-U, RBP, \(\beta\)-Gal, and AAP.  
Serum samples were measured \(\beta\)-M-S and Creat-S to assess glomerular function. | Evidence of a significant decrease in concentration of median Creat-S and evidence of a significant increase in Alb-U and RBP between samples collected before and after the season.  
No evidence of a significant increase in concentration of median \(\beta\)-M-U and median \(\beta\)-M-S concentration before and after the season.  
No evidence of a significant decrease in AAP activity in urine and no evidence of a significant increase in median \(\beta\)-Gal activity in urine before and after the season. | Low |
| Osterloh & Feldman (1993) | Not stated | CA | Similar to a case-crossover study  
\(n = 16\) male applicators | Air sampling device, questionnaire, and urine samples were measured for the 1,3-D metabolite 3CNAC. | Urine samples were measured for NAG, ALB, and RBP enzymes. | Evidence of statistically significant difference between the low and high 3CNAC urinary excretion relative to urinary NAG and RBP.  
No evidence of a statistically significant difference between low and high 3CNAC excretion relative to ALB.  
For the regression analysis, significant associations between 3CNAC excretion and renal proteins NAG, ALB, and RBP excretion in the interval regression, and in the cumulative regression for ALB and RBP. | Low |

\(^5^0\) For additional reported results including risk measures, number of cases/non-cases, and p-values, refer to the individual study summaries written above.
<table>
<thead>
<tr>
<th>First Author (Pub Year)</th>
<th>Study Period</th>
<th>Description of study population</th>
<th>Study Design</th>
<th>Exposure Measurement</th>
<th>Outcome Measurement</th>
<th>Primary 1,3-D Results</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vereplank et al. (2000)</td>
<td>Not stated</td>
<td>The Netherlands</td>
<td>Prospective cohort n = 13 exposed applicators, 22 unexposed lorry drivers</td>
<td>Urine samples were measured for mercapturic acid metabolite N-acetyl-S-(cis-3-chloro-2-propenyl)-L-cysteine (cis-1,3-D-MA). Inhalation exposure was assessed by personal air sampling on a representative sample of fumigation days, and real-time air monitoring in tractor cabins to obtain peak exposures.</td>
<td>Urine samples were measured for AAP, NAG, RBP, and ALB and serum samples were measured for Creat-S, and β2M-S.</td>
<td>No evidence of a statistically significant difference (p ≥ 0.05) among workers occupationally exposed to cis-1,3-D during fumigation season relative to unexposed lorry drivers for the following renal parameters in urine and serum samples: AAP, NAG, RBP, ALB, Creat-S, and β2M-S</td>
<td>Low</td>
</tr>
</tbody>
</table>

Table B-3: Summary of Epidemiologic Studies on Liver Function

<table>
<thead>
<tr>
<th>First Author (Pub Year)</th>
<th>Study Period</th>
<th>Description of study population</th>
<th>Study Design</th>
<th>Exposure Measurement</th>
<th>Outcome Measurement</th>
<th>Primary 1,3-D Results</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brouwer et al. (1991)</td>
<td>July – October, year not reported</td>
<td>The Netherlands</td>
<td>Similar to a case-crossover study n = 14 males only</td>
<td>Self-report via personal interview – number of hours and days worked in soil fumigation.</td>
<td>Urine and serum samples were measured for the following liver parameters: ALAT, ASAT, SLDH, GGT, ALP, and TBIL.</td>
<td>For liver function, evidence of a significant decrease in concentration of TBIL was reported after the season. No evidence of a significant difference was reported for any of the other liver function measures.</td>
<td>Low</td>
</tr>
</tbody>
</table>

51 For additional reported results including risk measures, number of cases/non-cases, and p-values, refer to the individual study summaries written above.
<table>
<thead>
<tr>
<th>Study</th>
<th>Region</th>
<th>Cohort Details</th>
<th>Methodology</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verplanke et al. (2000)</td>
<td>The Netherlands</td>
<td>Prospective cohort (n = 13 exposed applicators, 22 unexposed lorry drivers)</td>
<td>Urine samples were measured for mercapturic acid metabolite N-acetyl-S-(cis-3-chloro-2-propenyl)-L-cysteine (cis-1,3-D-MA). Inhalation exposure was assessed by personal air sampling on a representative sample of fumigation days, and real-time air monitoring in tractor cabins to obtain peak exposures.</td>
<td>No evidence of a statistically significant difference (p ≥ 0.05) between cis-1,3-D applicators relative to unexposed lorry drivers during fumigation season for ALAT, ASAT, GGT, ALP, TBIL; βOHC, and COR. Evidence of a statistically significant difference between workers cis-1,3-D applicators and unexposed lorry drivers for the urinary ratio βOHC/COR parameter during Week 32 (p &lt; 0.05), Week 41 (p &lt; 0.01), Week 47 (p &lt; 0.05) and Week 50 (p &lt; 0.01) of the fumigation period.</td>
</tr>
<tr>
<td>First Author (Pub Year)</td>
<td>Study Period</td>
<td>Description of study population</td>
<td>Study Design</td>
<td>Exposure Measurement</td>
</tr>
<tr>
<td>------------------------</td>
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</tr>
<tr>
<td>Gunier et al. (2017)</td>
<td>October 1999 – October 2000</td>
<td>Salinas Valley, CA</td>
<td>Cohort</td>
<td>Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) birth cohort n = 601 pregnant women, 537 of their children were liveborn</td>
</tr>
</tbody>
</table>

52 For additional reported results including risk measures, number of cases/non-cases, and p-values, refer to the individual study summaries written above.
<table>
<thead>
<tr>
<th>First Author (Pub Year)</th>
<th>Study Period</th>
<th>Description of study population</th>
<th>Study Design</th>
<th>Exposure Measurement</th>
<th>Outcome Measurement</th>
<th>Primary 1,3-D Results</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kalkbrenner et al. (2010)</td>
<td>2000 - 2004</td>
<td>West Virginia (WV) and North Carolina (NC)</td>
<td>Case-control</td>
<td>Ambient hazardous air pollutant concentrations modeled by the National Air Toxics Assessment program in 1996 and was assigned to patient address at birth using address from birth certificate, census tract data, and geocoding software.</td>
<td>Cases included all children with developmental records documenting characteristics and behaviors that met a standardized definition for autism disorder (Diagnostic Statistical Manual of the American Psychiatric Association, DSM-IV-TR), and were identified via the ADDM.</td>
<td>No evidence of a significant positive association between 1,3-D exposure and ASD in children at age eight in WV and NC.</td>
<td>Low</td>
</tr>
<tr>
<td>Kalkbrenner et al. (2018)</td>
<td>2012 (births occurred between 1994 – 1997, allowing a 5-year follow-up time)</td>
<td>United States</td>
<td>Family-based cohort</td>
<td>Air concentrations if 1,3-D geocoded to the family residential address during pregnancy. Self-reported addresses were obtained from a residential history questionnaire.</td>
<td>The following three outcomes were considered: a) ASD diagnosis; b) a measure of the broader autism phenotype, using the SRS to determine autism traits of children aged 4 – 18 years old including non-affected siblings; and, c) measuring the severity of autism symptoms using the CSS for those who met the ASD criteria only. All ASD diagnoses were based on the parent-based interview Autism Diagnostic Interview Revised (ADI-R), and following scoring, participants were categorized as Autism, Not Quite Autism (NQA), Broad Spectrum, or Not Met.</td>
<td>No evidence of a positive association between 1,3-D air concentrations at birth and ASD diagnosis among study participants, relative to siblings who did not have an ASD diagnosis. No evidence of a significant increase for changes in SRS and CSS scores relative to 1,3-D air concentrations.</td>
<td>Moderate</td>
</tr>
<tr>
<td>First Author (Pub Year)</td>
<td>Study Period</td>
<td>Description of study population</td>
<td>Study Design</td>
<td>Exposure Measurement</td>
<td>Outcome Measurement</td>
<td>Primary 1,3-D Results</td>
<td>Study Quality</td>
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</tr>
<tr>
<td>Brouwer et al. (2017)</td>
<td>2010 - 2012</td>
<td>The Netherlands PD study</td>
<td>Case-control study</td>
<td>Spatio-temporal model (based on agricultural crops around residential addresses from 1961 to 2010)</td>
<td>Medical files reviewed by a neurologist to confirm case diagnosis</td>
<td>Evidence of a moderately strong association when comparing subjects ever exposed and not exposed within the 100 m distance.</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lung Function and Asthma</th>
<th>Study Period</th>
<th>Description of study population</th>
<th>Study Design</th>
<th>Exposure Measurement</th>
<th>Outcome Measurement</th>
<th>Primary 1,3-D Results</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gharbi et al. (2019)</td>
<td>2005 – 2011</td>
<td>Central and southern CA (October through February)</td>
<td>Case-crossover study (bidirectional-symmetric)</td>
<td>US EPA Outdoor Air Exposure Database of air quality data and GIS software mapped 1,3-D exposure within 5km of ED asthma patient’s zip code. Zip code retrieved from CA Office of Statewide Health Planning and Development (OSHPD) database of ED visits with asthma ICD-9 code.</td>
<td>CA OSHPD database of ED visits and Asthma ICD-9 code for primary diagnosis.</td>
<td>Evidence of a slight positive association between ambient 1,3-D exposure and asthma ED visits in central and southern CA between 2005 – 2011.</td>
<td>Low</td>
</tr>
</tbody>
</table>

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55 For additional reported results including risk measures, number of cases/non-cases, and p-values, refer to the individual study summaries written above.
<table>
<thead>
<tr>
<th>First Author (Pub Year)</th>
<th>Study Period</th>
<th>Description of study population</th>
<th>Study Design</th>
<th>Exposure Measurement</th>
<th>Outcome Measurement</th>
<th>Primary 1,3-D Results</th>
<th>Study Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gunier et al. (2018)</td>
<td>October 1999 – October 2000</td>
<td>Salinas Valley, CA</td>
<td>Cohort Study</td>
<td>Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) birth cohort (n = 257 – 276 study participants for respiratory analysis); n = 193 – 229 study participants for lung function study analysis)</td>
<td>Prenatal pesticide exposure was estimated using maternal questionnaire data collected from two interviews conducted during and after pregnancy, and when their children were the following ages: 0.5, 1, 2, 3, 5, and 7 years old. Additionally, GPS, GIS, and CA DPR PUR data were used to estimate exposure within 3-, 5-, and 8-km distances during specific time periods including during and after pregnancy from birth to the 7-year follow-up visit, and the year before the 7-year visit.</td>
<td>Respiratory symptoms in children along with prescribed medication for asthma or wheezing/chest tightness were assessed using the International Study of Asthma and Allergies in Childhood questionnaire completed by the child’s mother at the 7-year visit; presence of respiratory symptoms was considered a binary outcome (yes/no). Lung function was assessed in children using spirometry to determine forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and forced expiratory flow 25-75% (FEF25-75).</td>
<td>No evidence of a significant positive association among respiratory effects or asthma medication use among 7-year-old children relative to a 10-fold increase in wind-weighted 1,3-D exposure within a 3-, 5-, or 8-km radius of the residence during prenatal and postnatal periods. No evidence of a statistically significant decrease in lung function (highest FEV1, FVC, and FEF25-75) in 7-year-old children for a 10-fold increase in wind-weighted prenatal 1,3-D exposure within a 3-, 5-, or 8-km radius of the prenatal maternal residence. No evidence of a statistically significant decrease in lung function (highest FEV1, FVC, and FEF25-75) in 7-year-old children for a 10-fold increase in wind-weighted postnatal 1,3-D exposure within a 3-, 5-, or 8-km radius of the postnatal maternal residence.</td>
</tr>
</tbody>
</table>