VERIFIED WRITTEN STATEMENT OF AMVAC
EXPERT WITNESS ELAINE FREEMAN, MS DABT

BUSINESS CONFIDENTIAL INFORMATION REDACTED

Information claimed confidential has been redacted and a complete copy of the document containing the information claimed confidential has been filed with the Office of Administrative Law Judges.

EPA OALJ Docket No. FIFRA-HQ-2022-0002

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
BEFORE THE ADMINISTRATOR

In re FIFRA Section 3(c)(2)(B) Notice of Intent to Suspend Dimethyl Tetrachloroterephthalate (DCPA) Technical Registration	)	
AMVAC Chemical Corporation; Grower-Shipper Association of Central California; Sunheaven Farms, LLC; J&D Produce; Ratto Bros., Inc.; and Huntington Farms, **Petitioners.**	)	**Docket No. FIFRA-HQ-2022-0002**

VERIFIED WRITTEN STATEMENT OF AMVAC EXPERT WITNESS ELAINE FREEMAN, MS DABT

I, Elaine Freeman, declare and state as follows:

1. The following statement sets forth my expert opinions based on my training, experience, and my review of certain materials as described in more detail below.

Background and Curriculum Vitae

2. I am Managing Scientist with Exponent.

3. I have a Master of Science degree in Pharmacology/Toxicology from Duquesne University and a Bachelor of Science degree in Microbiology from the University of Pittsburgh. I am a Diplomat of the American Board of Toxicology (DABT) since 2006.

4. I have been with Exponent, Inc. for 10 years, starting in September 2011. My area of expertise is Regulatory Toxicology. In this role, I focus on pesticides, industrial chemicals, consumer products, and animal health toxicology as well as human health risk evaluations. My work includes, but is not limited to, monitoring toxicological testing programs including study placement, protocol development, the review of toxicological data and reports; conducting toxicology laboratory audits; and preparing data evaluation reports and study summaries. I prepare weight of the evidence-based assessments of toxicological data incorporating both hazard and risk. I have expertise regarding endocrine (including thyroid) and carcinogenic modes of action (MoAs), including in the design and monitoring of studies, the review of studies, and the evaluation of data packages to identify the relevant MoA for effects and their relevance to humans.

5. My full C.V. is attached as Exhibit A to this Statement.

Summary of Materials Reviewed

6. My opinions as set forth below relate to a comparative thyroid toxicity study that AMVAC Chemical Corp. ("AMVAC") performed in response to a Data Call-In ("DCI") issued

for Dimethyl Tetrachloroterephthalate ("DCPA") Technical (EPA Reg. No. 5481-495) by EPA on January 31, 2013.

7. I base the opinions set forth below on my review of the documents listed below:

a. Draft Audited Definitive CTA Study Report (including approved protocol) as provided to me by AMVAC on June 14, 2022.

b. Guidance for Thyroid Assays in Pregnant Animals, Fetuses and Postnatal Animals, and Adult Animals EPA 2005. Joint Exhibit ("JX") 81.

c. EPA 2011 Human Health Assessment Scoping Document, Regulations.gov Doc. ID. EPA-HQ-OPP-2011-0374-0004.

d. The Verified Witness Statement of AMVAC employee Ann Jonynas filed in this matter.

e. AMVAC's Request for Hearing and Objections filed in this matter (including the exhibits referenced within it).

Scope of Expertise

8. Based on my educational background and work experience as described above, I am an expert in the field of toxicology and in the design and review of United States Environmental Protection Agency (EPA) guideline and non-guideline (mechanistic) toxicology studies, hazard assessments, dose-response assessments, and the selection of points of departure for human health risk evaluations related to thyroid effects and thyroid toxicity MoA. In addition, I have expertise with comparative thyroid studies as I have reviewed completed studies and evaluated the results from two other studies for unrelated chemicals that have been submitted to EPA.

Statement of Expert Opinions

Regarding the Validity of the Data Obtained in the DCPA: Main Pre and Post Natal Developmental Comparative Thyroid Study in CD Rats by Oral Administration

9. Based on my review of the Audited Draft Report DCPA: Main Pre and Post Natal Developmental Comparative Thyroid Study in CD Rats by Oral Administration, dated June 14, 2022 ("Audited Draft Report"), provided to me by AMVAC on June 14, 2022, I conclude that the Audited Draft Final Report should be determined to be "Acceptable, Non-Guideline" by EPA.

10. In assessing the Audited Draft Report and the study it describes, I referred to EPA's guidance dated in 2005 concerning CTA studies noted above (the "EPA CTA Guidance"), the Good Laboratory Practice (GLP) Standards Regulations [40 CFR Part 160]; and the September 9, 2021, final CTA study protocol included in the Audited Draft Report.

11. According to the EPA CTA Guidance, the CTA assay is conducted to address uncertainty in the sensitivity of fetuses and offspring to thyroid effects. The study evaluates thyroid hormone levels (triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH)) in maternal animals, fetuses, and offspring, gross pathological and histopathological effects in maternal animals, fetuses, and offspring, and thyroid organ weight in maternal animals. In the study, the maternal animals are administered the test material from gestation day (GD) 6 through GD 20 for Phase I animals and GD 6 through lactation day (LD) 21 for Phase II animals. Fetal animals are exposed in utero in Phase I and offspring are exposed in utero and via lactation in Phase II. Thyroid hormone levels are evaluated in Phase I maternal animals and fetuses on GD 20, in offspring on post-natal day (PND) 4, and in maternal animals and offspring on PND 21 in the Phase II.

12. The Audited Draft Report provided the information required by the EPA CTA Guidance including T3, T4 and TSH hormone levels for GD 20 maternal animals and GD20 fetal animals, thyroid organ weight (absolute and relative to body weight) for GD 20 maternal animals, and thyroid histopathology for GD 20 maternal animals and GD20 fetal animals, T3, T4 and TSH hormone levels for PND 4 offspring, PND 21 offspring, and LD 21 maternal animals, thyroid organ weight in LD 21 maternal animals, and thyroid histopathology for PND 4 offspring, PND 21 offspring, and LD 21 maternal animals.

13. No GLP deviations were identified following my review or by the Quality Assurance unit reported in the Audited Draft Report.

Commercially Sensitive Information Regarding Study Protocols [redacted]

Commercially Sensitive Information Regarding Study Protocols [redacted]

Commercially Sensitive Information Regarding Study Protocols [redacted]

16. The Audited Draft Report provides information necessary for EPA to evaluate the sensitivity of fetuses and offspring to thyroid effects compared to maternal animals. The study provides NOAELs and LOAELs for each subgroup, including GD20 maternal animals, GD20 fetuses, PND 4 offspring, LD21 maternal animals, and PND 21 offspring.

Regarding the Utility of the Data obtained in the DCPA: Main Pre and Post Natal Developmental Comparative Thyroid Study in CD Rats by Oral Administration for Risk Assessment

17. Based on my review of the Audited Draft Report it is my opinion that the study described therein should be determined to be "Acceptable, Non-Guideline" by the EPA. The study will enable EPA to evaluate the sensitivity of fetuses and offspring compared to maternal animals to thyroid effects. The study provides NOAELs and LOAELs, which the Agency can use in their weight of the evidence evaluation to select point of departure (PODs) for use in human health risk evaluations.

18. The Audited Draft Report provides the information required by the EPA CTA Guidance to evaluate the sensitivity of fetal animals and offspring compared to maternal animals to thyroid effects. The information available in the study includes T3, T4 and TSH hormone levels for GD 20 maternal animals and GD20 fetal animals, thyroid organ weight (absolute and relative to body weight) for GD 20 maternal animals, and thyroid histopathology for GD 20 maternal animals and GD20 fetal animals, T3, T4 and TSH hormone levels for PND 4 offspring, PND 21 offspring, and LD 21 maternal animals, thyroid organ weight in LD 21 maternal

animals, and thyroid histopathology for PND 4 offspring, PND 21 offspring, and LD 21 maternal animals.

19. In my professional opinion there are no missing data in the Audited Draft Report dated June 14, 2022 that would be cause for EPA not to find the study acceptable.

20. The data generated by the CTA study conducted by AMVAC to meet the DCI will provide EPA with NOAEL and LOAEL values for the fetal animals, offspring, and maternal animals.

21. The NOAEL and LOAEL values can be then used by EPA in their weight of the evidence evaluation for the selection of PODs for human health risk assessment.

Regarding the Duration of Time Needed to Meet the CTA Data Requirement

22. When reviewing the DCI, I noted that EPA had initially provided a "Time Frame" of 24 months to complete the "comparative thyroid toxicity study." JX 4 (PDF page 33). Based on the need for a range-finding study, a milk transfer study, and the definitive CTA study as required by the EPA CTA Guidance, it was foreseeable that the proposed timeframe of 2 years was not adequate.

23. In addition, EPA requested that the protocols for the range-finding study as well as the definitive CTA study be submitted, reviewed, and approved by EPA, all of which takes considerable time. In my experience, EPA reviews of protocols require at least 3 months from the time of submission. Based on my review of the Ann Jonynas's Verified Witness Statement, it appears that, in the case of DCPA, the protocol review process took much longer because AMVAC was required to get EPA review and approval of protocols for two range-finding studies and the definitive study. As such, the total timeframe for the protocol review process was approximately 40 months. It took approximately 24 months for review and approval of the 1st

range finding study; 11 months for the 2nd range finding study; and 4 months for the definitive CTA study.

24. As the CTA is a non-guideline, special study, EPA does not have an official Guideline for the conduct of this study. Rather, EPA has provided a general guidance document –the EPA (2005) Guidance referenced above, but it does not constitute a specific study guideline. The 2011 Human Health Scoping Document for DCPA and the 2013 Data Call-In for DCPA, did not reference any specific guidance or guideline for conducting the CTA assay.

25. Even though the 2005 Guidance is now publicly available, I understand, based on review of the Ann Jonynas Witness Statement, that AMVAC was not aware of it and did not receive it from EPA until October 21, 2014. I do not recall precisely when I became aware of the EPA (2005) Guidance for the first time, but to the best of my recollection, it was in 2017.

26. A limited number of CTA assays have been conducted to date. To my knowledge, as of 2018, less than 10 CTA studies had been submitted to EPA. Therefore, at the time of the Data Call-In for DCPA (2013), contract research organizations (CROs) did not have significant experience with the CTA study design or with the challenges of analyzing the picogram to nanogram levels of thyroid hormones typical of rat fetuses and offspring.

27. CTA studies are inherently complex and require that preliminary studies be conducted first for dose selection and methods development. The laboratory must develop an analytical method to determine the homogeneity, stability, and concentration of the test material in the dosing vehicle. In addition, transfer of the test material via lactation must be experimentally demonstrated or the pups must be directly dosed with the test material via gavage. The laboratory also must be adept at analyzing a range of thyroid hormone concentrations, which commonly fall in the picogram to nanogram range in fetuses and PND 4

pups. Finally, a dose-range finding study using a smaller number of animals than required in the definitive CTA study is required to ensure that the doses selected for the definitive assay will provide a no observed adverse effect level (NOAEL) and a lowest observed adverse effect level (LOAEL). These preliminary studies must be completed before the definitive CTA study can be conducted.

28. Based on my review of the available relevant information, it is my expert opinion that AMVAC took all actions necessary to conduct the comparative thyroid assay. AMVAC consistently worked with both EPA and the CRO throughout the time period after the DCI to ensure the appropriate design and conduct of the comparative thyroid study. Based on the totality of the evidence presented, I conclude that it was not unreasonable that it took the amount of time that it did to complete the CTA study.

I, Elaine Freeman, declare under penalty of perjury under the laws of the United States that the statements above are true and correct to the best of my knowledge. Executed this 17th day of June 2022.

/s/ *Elaine Freeman*
Elaine Freeman

CERTIFICATE OF SERVICE

I hereby certify that the foregoing **Verified Written Statement of AMVAC Expert Witness Elaine Freeman**, was served on the following parties today, June 17, 2022, as indicated below.

/s/ *Hume M. Ross*
Hume M. Ross

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