RESPONDENT'S EXHIBIT 4

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

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: May 27, 2011

SUBJECT: **DCPA. (Chlorthal Dimethyl).** Human Health Assessment Scoping Document in Support of Registration Review.

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Petition No.: Not Applicable
Risk Assessment Type: Not Applicable
T**XR No.:** Not Applicable
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Executive Summary

The Health Effects Division (HED) DCPA (dimethyl tetrachlorophthalate) Registration Review Team has evaluated the most recent human health assessments and database for the herbicide DCPA to determine the scope of work necessary to support the established tolerances and existing registrations. The risk assessment used to support the 1998 Reregistration Eligibility Decision (RED) and a risk assessment to support new tolerances of DCPA (Dole, 2004) were the primary sources for this evaluation. DCPA is registered for use on several vegetable crops and some ornamental plants. Most residential uses have been cancelled and are no longer supported by the primary registrant.

Liver and thyroid effects are observed in many DCPA toxicity studies. The acute toxicity of DCPA is low. Toxicity in longer term studies with DCPA included thyroid toxicity as shown by decreased levels of thyroid hormone, microscopic thyroid changes, and increased thyroid weight. Liver toxicity included increased liver weight, elevated liver enzyme activity, increased cholesterol, and liver hypertrophy. It is believed that the liver effects are precursor events to the thyroid effects, with increased metabolism of thyroid hormone by the liver resulting in a compensatory stimulation of the thyroid. Effects on the kidney have also been observed. There were no mutagenicity concerns for DCPA, but thyroid follicular cell adenomas/carcinomas, hepatocellular adenomas/carcinomas, and hepatocholangiocarcinomas were found in rats; hepatic adenomas were found in mice. DCPA is classified a Group C, possible human carcinogen with a cancer potency factor based on the three combined liver tumors in female rats. DCPA has not been identified as a member of a common mechanism group for cumulative risk assessment.

The previous risk assessment identified a 28-day inhalation toxicity study and a comparative thyroid toxicity study as data gaps. These studies are still required. The test guidelines have been updated since the 2002 assessment and additional studies are now required, including immunotoxicity and acute and subchronic neurotoxicity studies. The endpoints and the FQPA safety factor will be re-evaluated after these studies have been completed and reviewed.

The most recent dietary, residential, aggregate, and occupational risk assessments did not identify risk estimates of concern. It is noted that DCPA and its environmental degradates are often found in groundwater monitoring studies. Additional residue chemistry studies are needed to support the registration review of DCPA including rotational crop field trials, sample storage information from prior crop field trials, a ruminant feeding study, a poultry metabolism study, and a livestock method validation. These studies had been previously requested in the RED and in response to new tolerances established in 2004. A new poultry feeding study is reserved pending results of the metabolism study. Once these studies have been received and reviewed, a new dietary assessment will be conducted to support the registration review of DCPA. Since the residential uses are no longer supported a new residential assessment will not be needed. However several studies have been identified in the literature that describe off-target movement of DCPA into residential settings, particularly in agricultural areas. The Agency will evaluate these studies during registration review to determine if a quantitative assessment of risk to residents in agricultural areas is needed. Should new points of departure for dermal and inhalation routes of exposure be identified once the new toxicity studies are received, a revised occupational assessment may be required.

There are impurities of toxicity concern in DCPA formulations. Prior assessments have estimated risks from exposure to these contaminants, and have determined them to be negligible. During registration review the registrants should certify that the impurities in current formulations are at similar levels or below the levels previously assessed. If not, then a new assessment may be required.

Introduction

DCPA (dimethyl tetrachlorophthalate) is also commonly referred to as dacthal, chlorthal dimethyl or chlorthal methyl. DCPA is a chlorinated benzoic acid herbicide which inhibits cell division of root tips in target plants. It controls many annual grasses and broadleaf weeds in a variety of agricultural crops and ornamental varieties (e.g., broccoli, onions, tomatoes, cabbage, cauliflower, dogwood, azalea). Annual agricultural use from 1998 through 2008 averaged approximately 500,000 pounds over 100,000 acres with broccoli and onions accounting for 79 percent of that use (Ratnayake, 2011). Information also suggests that on average 50 percent of broccoli is treated and 15 percent of onions (SLUA). It was also reported that use for ornamental crops in nurseries is low at around 2,600 pounds in 2006. California usage data exhibit similar trends for the years 2006-2008 (CA Usage reference). Most uses in residential settings have been cancelled and the remaining residential uses are not supported, so will eventually be removed (personal communication, J. Bloom, 3/3/11).

Tolerances are established in 40 CFR § 180.185 for residues of DCPA, which address direct treatment of crops as well as inadvertent residues of DCPA from off-target movement and carry-over of residues to rotational crops. The metabolites monomethyltetrachloroterephthalate (MTP) and tetrachloroterephthalic acid (TCP or TPA) are included in the tolerance expression for DCPA. Codex has not established maximum residue limits (MRLs) but MRLs are established in Canada for several commodities.

The HED DCPA Registration Review Team evaluated the most recent human health assessments and database for DCPA to determine the scope of work necessary to support Registration Review. In addition, HED has conducted a screening literature search for studies that could contribute to the assessment. The Reregistration Eligibility Decision (RED) and associated chapters as well as a risk assessment to support new tolerances were the primary sources for this document. It should also be noted that previous assessments assessed risks from trace contaminant materials in DCPA products.

Hazard Identification/Toxicology

Toxicity of DCPA: The database for DCPA is extensive. Previous risk assessments considered subchronic and chronic oral studies in rats, subchronic and chronic oral studies in mice, developmental studies in rats and rabbits, a 2-generation reproduction study in rats, a dermal toxicity study in rats, metabolism studies, a dermal absorption study, and a battery of mutagenicity studies with DCPA. Since the previous risk assessment, the registrant has conducted subchronic rat and dog studies and a chronic dog study with DCPA. These studies have been reviewed and will not result in changes to previously selected endpoints for DCPA.

The previous risk assessment identified an inhalation toxicity study and a comparative thyroid study as data gaps. These studies are still required. The test guidelines have been updated since the 2002 assessment and additional studies are now required, including immunotoxicity and acute and subchronic neurotoxicity studies.

The acute toxicity of DCPA is low. DCPA is in acute toxicity category III for the oral route of exposure and is in toxicity category IV for dermal and inhalation routes of exposure. It is a mild irritant to the eyes and skin and it is not a skin sensitizer.

Toxicity in longer term studies with DCPA included thyroid toxicity as shown by decreased levels of thyroid hormone, microscopic thyroid changes, and increased thyroid weight. Liver toxicity included increased liver weight, elevated liver enzyme activity, increased cholesterol, and liver hypertrophy. It is believed that the liver effects are precursor events to the thyroid effects, with increased metabolism of thyroid hormone by the liver resulting in a compensatory stimulation of the thyroid. Other toxicity included anemia, pneumonitis, and kidney toxicity (increased kidney weight, increased incidences of chronic nephropathy, and changes in clinical pathology). A PubMed search was conducted and no new toxicity information which would result in changes to the previous risk assessment was found.

There were no mutagenicity concerns for DCPA. Thyroid follicular cell adenomas/carcinomas, hepatocellular adenomas/carcinomas, and hepatocholangiocarcinomas were found in rats; hepatic adenomas were found in mice. DCPA was classified a Group C, possible human carcinogen, with a cancer potency factor based on the three combined liver tumors in female rats of 1.5×10^{-3} $(mg/kg/day)^{-1}$.

FQPA Assessment: There were acceptable rat and rabbit developmental toxicity studies and an acceptable 2-generation reproduction study. No quantitative or qualitative susceptibility occurred in these studies and no neurotoxicity was noted in any of the studies. The FQPA safety factor for DCPA was reduced to 1X in the most recent risk assessment. Considering current policy for FQPA database uncertainty factors, the FQPA factor would likely be retained at 10x for the lack of a comparative thyroid study. The most recent risk assessment showed very low risk estimates, so retaining the 10x factor would not likely result in these estimates exceeding the level of concern.

Toxicity Endpoints: The chronic dietary endpoint for DCPA was thyroid toxicity with a NOAEL of 1 mg/kg/day and a LOAEL of 10 mg/kg/day from a chronic rat study. The endpoint for incidental oral exposure and for inhalation exposure was hepatocellular hypertrophy with a NOAEL of 50 mg/kg/day and a LOAEL of 100 mg/kg/day from a subchronic rat study. No appropriate endpoint for acute dietary exposure was identified in any of the toxicity studies. Quantitation of dermal exposure was not required because no systemic toxicity occurred in the dermal toxicity study at the high dose of 1000 mg/kg/day. There were no concerns for developmental or reproductive toxicity by the dermal route of exposure because no developmental toxicity occurred in the developmental studies and parental and offspring effects in the reproduction study (decreased body weight) occurred at the same dose. Although the thyroid was not evaluated in this study, no liver effects were noted and liver hypertrophy is believed to be a precursor event for thyroid changes. The endpoints and the FQPA safety factor will be re-evaluated after completion of the inhalation, neurotoxicity, comparative thyroid toxicity, and immunotoxicity studies.

Toxicity of Metabolites and Degradates: Also evaluated in previous risk assessments were subchronic oral studies, a developmental rat study, and mutagenicity studies with TPA, a

degradate found in water. The only effects occurring in these studies were irritation from the acid moiety on this compound. Since the previous risk assessment, the registrant has conducted a mutagenicity study with MTP, which is a rat metabolite and environmental degradate. This study has been reviewed and will not result in changes to conclusions in the previous risk assessment.

Conclusions: Additional toxicity data are required, including a comparative thyroid toxicity study, an immunotoxicity study, and acute and subchronic neurotoxicity studies. Once these studies have been received and reviewed the Agency will evaluate the need for modifying endpoints for risk assessment and associated safety factors.

Dietary Exposure

DCPA is registered for use on several vegetable crops; according to the use profile prepared by BEAD the predominant uses are on broccoli and onions. The residue chemistry data was most recently reviewed in association with tolerances in/on several herbs (Hazel, 2002). Adequate plant metabolism, analytical method, crop field trial, and processing studies are available to support the existing uses. However, the following residue data gaps were identified in the most recent discussion of the residue database: (i) rotational crop field trials and labeling proposals, including crops to be rotated and plant-back intervals (PBIs); (ii) sample storage temperature and duration to confirm the stability of residues in samples collected and analyzed as part of certain field trials conducted prior to 1995; (iii) a ruminant feeding study; (iv) a poultry metabolism study; and (v) livestock method validation. Rotational crop field trials and storage stability data remain outstanding; the specific studies requiring stability data are listed in the W. Hazel memo of 2002. The acceptability of the existing poultry feeding study will be addressed once the poultry metabolism study has been submitted and evaluated.

It is noted that the previous technical registrant attempted to address some of these deficiencies in 2002 in MRIDs 43340401, 42713501, and 43938901. However, these studies were resubmissions of existing data and did not fully address the requirements.

There is some concern for inadvertent residues of DCPA due to off-site movement that appears to be largely due to wind-blown soil particles to which DCPA residues have adsorbed.

HED has updated the maximum reasonable dietary burden for livestock in accordance with the guidance published in 2008. The maximum reasonable dietary burden (MRDB) for dairy cattle is 8 ppm; residues in edible livestock commodities are likely, so the requirement for the ruminant feeding study remains outstanding. An adequate poultry metabolism study is not available, and the existing feeding study for poultry has numerous deficiencies. Therefore, the previously required poultry metabolism study is still needed to assess potential exposure to DCPA residues in poultry commodities. A method validation for the livestock residue analytical method remains outstanding. An updated summary of the MRDB may be found in Table 3 of this document.

PDP data are available for residues of DCPA on numerous commodities. Over the last several years, quantifiable residues were found in/on broccoli, cantaloupe, cauliflower, green beans, green onions, collards, kale, lettuce, onion, potatoes, summer squash, and bell peppers. In

addition, residues have been detected occasionally on commodities where no tolerances have been established. For example, during 2007 and 2008 5% of celery samples analyzed had detectable residues of DCPA *per se* at an average residue of 2.5 ppb, with residues ranging from 1.2 to 12 ppb (lowest LOD is 0.7 ppb). In addition in the years 2003, 2006, and 2008 2% of spinach samples have detectable residues of DCPA *per se* at average residue of 5.5 ppb, with residues ranging from 1.2 to 43 ppb (lowest LOD is 0.7 ppb). No tolerances have been established on celery and spinach.

There are a large number of studies and data available on DCPA and degradate residues in air, surface water, drinking water, ground water, rain, and snow. The most recent review of monitoring data was completed in May 2008 by the Office of Water (EPA, 2008), and reported in detail in the 2009 California Red-legged Frog risk assessment of DCPA. Monitoring data indicate widespread occurrence of DCPA in surface water, ground water, drinking water, and air. DCPA and TPA are among the most commonly found pesticides/degradates found in water samples (U.S. EPA, 2008). DCPA is typically detected at low concentrations in remote areas where it is not used and at higher concentrations near where it is used. DCPA's degradates, TPA and MTP are more commonly detected in ground water samples than DCPA. TPA is typically found at higher concentrations. TPA was the most commonly detected pesticide-derived compound in the National Survey of Pesticides in Drinking Water Wells Survey (U.S. EPA, 1998).

The estimated chronic risk from residues of DCPA in food was well below the level of concern in the most recent risk assessment, with the highest population estimated at 1% of the cPAD. Cancer risk estimates were in the range of 10^{-7}. Prior assessments did not directly include drinking water, but estimated environmental concentrations were well below the drinking water level of comparison indicating that no human health risk estimates of concern exist.

HED has also assessed dietary risks for the impurities of concern. Further discussion may be found in the appendix to this document.

Conclusions. The following studies remain outstanding: (i) rotational crop field trials and labeling proposals (crops to be rotated and PBIs); (ii) sample storage temperature and duration to confirm the stability of residues in samples collected and analyzed as part of certain field trials conducted prior to 1995; (iii) a ruminant feeding study; (iv) a poultry metabolism study; and (v) livestock method validation. The rationale for requiring these studies is attached to this document. Once these studies have been received and reviewed a new dietary risk assessment should be conducted. In addition, the registrants should certify that the impurity levels previously assessed in dietary risk assessment have remained the same or decreased.

Residential Exposure

Residential risks from DCPA use were considered in the previous assessments and the risk estimates that were calculated were not of concern for the uses at the time and given the policies used to define them. A turf transferable residue study for DCPA and its impurities was used in this assessment. Since the existing assessments were completed, most residential uses have been

deleted from most DCPA labels and the remaining residential uses are not supported, so will eventually be removed (personal communication, J. Bloom, 3/3/11).

It should be noted, however, that the Agency is considering how to evaluate risks associated with exposures that can occur from the off-target movement of pesticide residues in agricultural areas. During the screening literature search EPA identified a few studies that quantify residues of DCPA in homes in agricultural areas (Bradman, Gunier, Harnley, etc.) so any future changes in risk assessment policies regarding these exposures may require updated DCPA risk assessments.

Conclusions: No residential data gaps were identified during the *Registration Review* scoping process for DCPA. At this time residential uses of DCPA are not supported, so assessments are not needed in registration review. However, an assessment may be needed to address changes in other risk assessment policies related to spray drift, and volatilization of pesticides. This is especially germane since data exist that quantify some level of off-target movement from treated areas into residential settings.

Aggregate Risk Assessment

The most recent risk assessment included aggregate assessments that considered exposure from food, drinking water, and residential uses. All risk estimates were below the level of concern. Risk estimates from the impurities were also considered, and were below the level of concern. A new assessment will likely be needed that considers the required new toxicity and residue data as well as changes in residential uses. In addition, the new assessment may need to consider changes that consider off-target movement of pesticides into residential settings.

Cumulative Risk Assessment

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to DCPA and any other substances. For the purposes of this registration review assessment of data needs EPA has not assumed that DCPA has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

Occupational Exposure

DCPA controls many annual grasses and broadleaf weeds in a variety of agricultural crops and ornamental varieties (e.g., broccoli, onions, tomatoes, cabbage, cauliflower, dogwood, azalea). DCPA formulations include flowable concentrates and wettable powders. In agriculture, groundboom and aerial applications would be typical but DCPA can also be applied via chemigation and using handheld equipment, especially associated with the production of ornamental and nursery crops. Application rates can be as high as 10.5 pounds DCPA per acre. DCPA is marketed in typical containers that would allow open mixing activities (e.g., bottle).

Applications can be made prior to planting, as a pre-emergent, and as a layby treatment over existing crops. Concurrent cultivation practices are also recommended by labels to ensure efficacy of DCPA and reduce the potential for off-site movement (e.g., soil incorporation, banding applications, and proper irrigation timing).

Occupational risk estimates from DCPA use were considered in the previous assessments. Current labels require the use of normal work clothing for handlers with gloves and dust/mist respirators. The current Restricted-Entry Interval is 12 hours. Prior assessments were based on chemical-specific dislodgeable foliar residue studies. For all scenarios assessed, occupational risks were not of concern if these required label risk management elements were followed.

A revised occupational risk assessment will be required because updated monitoring data are being developed for pertinent occupational handler exposures and additional handler exposure scenarios also need to be addressed that were not included in previous assessments. These include aerial application and handheld methods used for the production of nursery and ornamental crops. Additionally, a revised risk assessment may be needed to address possible exposure to workers doing activities in previously treated areas (i.e., post-application exposure). The existing policy on farmworker activities was recently revised and includes either updated values for quantitatively evaluating these exposures or it will provide a more definitive qualitative rationale for not conducting a quantitative assessment.

In the existing assessments a dermal noncancer endpoint was not identified for risk assessment purposes but cancer risks from dermal exposures were quantitatively assessed. Additionally, noncancer and cancer risks were quantified for occupational handler inhalation exposures. Finally, post-application cancer risks from dermal exposures were quantified. Any changes in risk assessment endpoints for DCPA would necessitate appropriate revisions to the risk assessment.

It should also be noted that there are trace contaminant materials in DCPA products which were addressed in existing risk assessments, but they may require further review and analysis as part of the registration review process.

Conclusions: No occupational data gaps were identified during the *Registration Review* scoping process for DCPA. Adequate data, including studies currently in progress by various task forces, are available to assess all of the occupational exposure scenarios for the registered uses of DCPA. It is noted that the primary registrants are members of the Agricultural Reentry Task Force (ARTF), the Agricultural Handlers Exposure Task Force (AHETF), and the Outdoor Residential Exposure Task Force (ORETF). It should also be noted that likely upcoming policy revisions such as anticipated modifications in the Agency policies for completing occupational exposures could cause elements of the current exposure assessments to be revised (e.g., possible changes in transfer coefficients for field workers and unit exposures for handlers). These changes could specifically occur based on the results of the ARTF, AHETF and ORETF. Also, additional scenarios may be needed to address changes in other risk assessment policies related to spray drift, worker protection and volatilization of pesticides.

Public Health and Pesticide Epidemiology Data
HED has reviewed the OPP Incident Data System (IDS) to determine if there were significant incidents related to DCPA and human health (Winfield, 2011). Based on the low frequency and severity of incident cases, there does not appear to be a concern at this time that would warrant further investigation of incidents involving DCPA. The Agency will continue to monitor the incident information and if a concern is triggered, additional analysis will be included in the risk assessment.

Tolerance Assessment and International Harmonization
The US has established tolerances crops with registered uses of DCPA as well as inadvertent residue tolerances resulting from indirect exposure to crops via carry-over in the soil and transport of residues through drift. A summary of US tolerances may be found in Table 2 attached to this document, along with a summary of Canadian Maximum Residue Limits (MRL). Codex has not established MRLs in/on any commodity, and Mexico generally adopts US tolerances and/or Codex MRLs for export purposes. Note that the MRL regulations for Canada do not include a separate entry for inadvertent residues. The US and Canada are not harmonized with respect to residue definition: the US includes two metabolites (MPA and TPA) in the residue definition, while the Canadian MRL includes only the parent. With respect to residue levels, for almost all commodities where both US and Canadian limits have been established, the values are the same, with the exception of the *Brassica* vegetables. Whereas the US has established a crop group tolerance at a level of 5 ppm, Canada has established limits for the individual commodities, ranging from 1 to 5 ppm.

Some of the entries for the section on inadvertent tolerances include crops with registered uses. The registrants should clearly indicate in their response to the Registration Review Preliminary Work Plan (PWP) those crops where direct applications will be supported, and those tolerances that will be supported as inadvertent tolerances. During registration review HED will re-evaluate the data supporting the tolerances, correct the entries in the tolerance regulation, and will attempt to harmonize with international MRLs to the extent possible. In addition the residue definition should be modified in accordance with current policy on tolerance definitions (S. Knizner, 5/27/09) as describe below:

> Tolerances are established for residues of the herbicide dimethyl tetrachloroterephthalate (DCPA), including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels specified below is to be determined by measuring only the sum of DCPA and its metabolites monomethyltetrachloroterephthalate (MTP) and tetrachloroterephthalic acid (TCP), calculated as the stoichiometric equivalent of DCPA, in or on the commodity.

Environmental Justice
Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations,"

http://www.epa.gov/environmentaljustice/resources/policy/exec_order_12898.pdf. The Office of Pesticide Programs (OPP) typically considers the highest potential exposures from the legal use of a pesticide when conducting human health risk assessments, including, but not limited to, people who obtain drinking water from sources near agricultural areas, the variability of diets within the U.S. (including different ages, regions, and ethnicities), and people who may be exposed when harvesting crops. Should these highest exposures indicate potential risks of concern, OPP further refines the risk assessments to ensure that the risk estimates are based on the best available information.

Human Studies

Past DCPA risk assessments relied in part on data in generic databases from studies in which adult human subjects were intentionally exposed to a pesticide to determine their dermal and inhalation exposure or similar studies from the literature. Many such studies, involving exposure to many different pesticides including DCPA, are included in generic pesticide exposure databases such as the Pesticide Handler Exposure Database (PHED), the Agricultural Reentry Task Force (ARTF), and the Outdoor Residential Exposure Task Force (ORETF). Also, there will be a reliance on the work of the Agricultural Handlers Exposure Task Force (AHETF) for revisions to the occupational handler risk assessments possibly needed in the future. These studies have been determined to require a review of their ethical conduct and have received the appropriate review.

Endocrine Disruption

As required by FIFRA and FFDCA, EPA reviews numerous studies to assess potential adverse outcomes from exposure to chemicals. Collectively, these studies include acute, subchronic and chronic toxicity, including assessments of carcinogenicity, neurotoxicity, developmental, reproductive, and general or systemic toxicity. These studies include endpoints which may be susceptible to endocrine influence, including effects on endocrine target organ histopathology, organ weights, estrus cyclicity, sexual maturation, fertility, pregnancy rates, reproductive loss, and sex ratios in offspring. For ecological hazard assessments, EPA evaluates acute tests and chronic studies that assess growth, developmental and reproductive effects in different taxonomic groups. As part of its reregistration decision, EPA reviewed these data and selected the most sensitive endpoints for relevant risk assessment scenarios from the existing hazard database. However, as required by FFDCA section 408(p), DCPA is subject to the endocrine screening part of the Endocrine Disruptor Screening Program (EDSP).

EPA has developed the EDSP to determine whether certain substances (including pesticide active and other ingredients) may have an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate". The EDSP employs a two-tiered approach to making the statutorily required determinations. Tier 1 consists of a battery of 11 screening assays to identify the potential of a chemical substance to interact with the estrogen, androgen, or thyroid (E, A, or T) hormonal systems. Chemicals that go through Tier 1 screening and are found to have the potential to interact with E, A, or T hormonal systems will proceed to the next stage of the EDSP where EPA will determine which, if any, of the Tier 2 tests are necessary based on

the available data. Tier 2 testing is designed to identify any adverse endocrine-related effects caused by the substance, and establish a dose-response relationship between the dose and the E, A, or T effect.

Under FFDCA section 408(p), the Agency must screen all pesticide chemicals. Between October 2009 and February 2010, EPA issued test orders/data call-ins for the first group of 67 chemicals, which contains 58 pesticide active ingredients and 9 inert ingredients. DCPA was included on that list and has been issued an order to conduct the Tier 1 testing. Once all required Tier 1 and Tier 2 data have been received and reviewed, the endpoints and safety factors used for risk assessment purposes will be examined and a new risk assessment performed if necessary. For further information on the status of the EDSP, the policies and procedures, the list of 67 chemicals, future lists, the test guidelines and the Tier 1 screening battery, please visit our website: http://www.epa.gov/endo/.

Data Requirements

The following studies are required to support the registration review of DCPA:

Toxicity studies

- 870.7800: Immunotoxicity
- 870.3700SS (Special Study): Comparative Thyroid Study
- 870.3465: Subchronic Inhalation Toxicity Study – 28 day
- 870.6200: Neurotoxicity Battery (Acute and Subchronic Studies)

Residue Chemistry Studies

- 860.1300: Nature of the Residue: Poultry
- 860.1340: Residue Analytical Method: Livestock Commodities
- 860.1380: Storage Stability
- 860:1480: Meat/Milk/Poultry/Eggs: Ruminants
- 860.1900: Field Accumulation in Rotational Crops

Tables describing the rationale for requiring these studies are attached to this document. In addition, once the rotational crop studies have been completed product labels should be modified to include appropriate plant-back intervals. The registrants should also certify that the levels of the impurities of concern have not changed since the most recent risk assessment that considered the cancer risk to these toxic impurities.

References

Bradman A, et al. 2007. Pesticides and their metabolites in the homes and urine of farmworker children living in the Salinas Valley, CA. J Expo Sci Environ Epidemiol 17:331-349.

FR Vol. 70 No. 143 (07/27/05) pp 43408-43410, DCPA; Order to Amend to Terminate Uses.

Gray, Jr. LE, et al. Perinatal Exposure to the Phthalates DEHP, BBP, and DINP, but Not DEP, DMP, or DOTP, Alters Sexual Differentiation of the Male Rat. Toxicol. Sci. (2000) 58(2): 350-365 doi:10.1093/toxsci/58.2.350

Gunier RB, et al. 2011. Determinants of Agricultural Pesticide Concentrations in Carpet Dust. Environ Health Perspect doi:10.1289/ehp.1002532 (accessed March 3, 2011)

Harnly ME, et al. 2009. Pesticides in dust from homes in an agricultural area. Environ Sci Technol 43:8767-8774.

Nuckols JR, et al. 2007. Linkage of the California Pesticide Use Reporting Database with spatial land use data for exposure assessment. Environ Health Perspect 115:684-689.

Nuckols JR, Riggs PD, Gunier RB, Ward MH 2008. Geographic-based prediction of agricultural pesticides in household carpet dust in the central valley of California. Epidemiology 19:S320.

U.S. EPA. 1998b. *Reregistration Eligibility Decision (RED): DCPA*. EPA 738-R-98-005. November 1998. Special Review and Reregistration Division, Office of Pesticide Programs. Washington, D.C. U.S.A. Available at: http://www.epa.gov/oppsrrd1/REDs/0270red.pdf (accessed January 28, 2011)

U.S. EPA. 2008a. *Health Effects Support Document for Dacthal Degradates: Tetrachloroterephthalic Acid (TPA) and Monomethyl Tetrachloroterephthalic Acid (MTP). EPA-822-R-08-005*. May, 2008. Health and Ecological Criteria Division. Office of Water. Washington, D.C. U.S.A. Available at: http://www.epa.gov/safewater/ccl/pdfs/reg_determine2/healtheffects_ccl2-reg2_dacthaldegradates.pdf (accessed February 28, 2011)

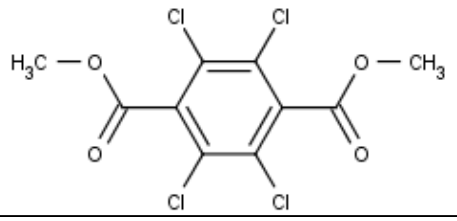
OPP Memoranda Citations

Author	DP Barcode/ Record No.	Date	Title
Winfield, S.	D386640	3/1/11	DCPA: Review of Human Incidents
Ratnayake, S., et al.	N/A	1/20/11	BEAD Chemical Profile for Registration Review: DCPA (07870I)
N/A	N/A	8/18/10	EPA Screening Level Estimate of Agricultural Uses (SLUA) (8/18/10)
N/A	N/A	8/10/10	EPA Analysis of California DPR Pesticide Usage Data (

Author	DP Barcode/ Record No.	Date	Title
Dole, T.	D303994	6/9/04	2nd Revised Drinking Water and Aggregate Human Health Risk Assessment for Chlorthal dimethyl (DCPA) and the metabolite tetrachloroterephthalic acid (TPA)
Farwell, K.	D303156	5/25/04	TPA (tetrachloroterephthalic acid) - metabolite of DCPA (Dacthal). Evaluation of Potential for Carcinogenicity.
Farwell, K. and Abdel-Saheb, I.	TXR No. 0052585	5/25/04	TPA (tetrachloroterephthalic acid) - metabolite of DCPA (Dacthal). Report of the Metabolism Assessment Review Committee
Dole, T., et. al.	D281320	7/8/02	HED Human Health Risk Assessment For DCPA to Support New Uses on California Parsley and Other Minor Crops (D281320, 7/8/02)
Hazel, W.	D280398	6/14/02	PP#0E3883 and PP#2E6442. IR-4 Petitions for Tolerances and Proposals. Review of Analytical Chemistry and Residue Data.
Dole, T.	D283509	6/10/02	Occupational and Residential Risk Assessment to Support Request for Establishment of Tolerance for Chlorthal-Dimethyl (DCPA) on Minor Crops.
Taylor, L., and Rinde, E.	TXR No. 0050123	2/10/95	Carcinogenicity Peer Review of DCPA (Dimethyl tetrachloroterephthalate or Dacthal)for meetings on June 29 and Nov. 16, 1994. Linda Taylor and Esther Rinde.

Attachments

Chemical Identity

Table 1. Chemical Identity	
Common Name	DCPA
Other Names	Chlorthal dimethyl; CAS Name: dimethyl 2,3,5,6-tetrachloro-1,4-benzenedicarboxylate; IUPAC Name: dimethyl tetrachloroterephthalate
PC Code	078701
	1861-32-1
Case No.	0720
Chemical Structure	
Metabolites/Degradates of Concern	
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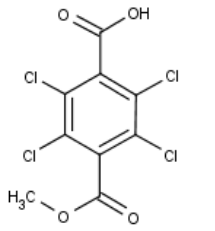
Chemical Structure	
Name	tetrachloroterephthalic acid (TCP or TPA)
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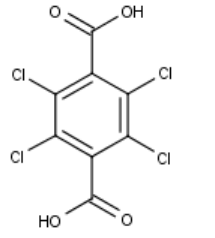
Chemical Structure	

Table 2. Summary of US and International Residue Limits				
***Commodity*[1]**	***Tolerance (ppm) /Maximum Residue Limit (mg/kg)***			
	US	**Canada**	**Mexico[2]**	**Codex**
180.185(a)				
Cantaloupe	1.0	1.0	None	None
Garlic	1.0	1.0	None	None
Ginseng	2.0	None	None	None
Horseradish	2.0	None	None	None

Table 2. Summary of US and International Residue Limits				
***Commodity*[1]**	***Tolerance (ppm) /Maximum Residue Limit (mg/kg)***			
	US	**Canada**	**Mexico[2]**	**Codex**
Muskmelon	1.0	Honeydew melon: 1.0	None	None
Onion, bulb	1.0	1.0	None	None
Onion, green	1.0	None	None	None
Strawberry	2.0	2.0	None	None
Tomato	1.0	1.0	None	None
Vegetable, brassica, leafy, group 5	5.0	Broccoli, Brussels Sprouts, Cabbages, Cauliflower: 1.0 Collards, Kale: 2 Mustard Greens: 5	None	None
Watermelon	1.0	1.0	None	None
180.185(c) (tolerances with regional registration)				
Radish, roots	2.0	None	None	None
Radish, tops	15.0	None	None	None
180.185(d) (inadvertent tolerances) [3]				
Basil, dried leaves	20.0	None	None	None
Basil, fresh leaves	5.0	None	None	None
Bean, dry	2.0	None	None	None
Bean, mung, seed	2.0	None	None	None
Bean, snap, succulent	2.0	2.0	None	None
Celeriac	2.0	None	None	None
Chicory, roots	2.0	None	None	None
Chicory, tops	5.0	None	None	None
Chive	5.0	None	None	None
Coriander, leaves	5.0	None	None	None
Corn, field, forage	0.4	None	None	None
Corn, field, grain	0.05	None	None	None
Corn, field, stover	0.4	None	None	None
Corn, pop, forage	0.4	None	None	None
Corn, pop, grain	0.05	None	None	None
Corn, pop, stover	0.4	None	None	None
Corn, sweet, forage	0.4	None	None	None
Corn, sweet, kernel plus cob with husks removed	0.05	None	None	None
Corn, sweet, stover	0.4	None	None	None
Cotton, undelinted seed	0.2	None	None	None
Cucumber	1.0	1.0	None	None
Dill	5.0	None	None	None
Eggplant	1.0	1.0	None	None
Lettuce	2.0	2.0	None	None
Marjoram	5.0	None	None	None
Parsley, dried leaves	20.0	None	None	None
Parsley, leaves	5.0	None	None	None
Pea, blackeyed, seed	2.0	2.0	None	None
Pepper	2.0	2.0	None	None
Pimento	2.0	2.0	None	None
Potato	2.0	2.0	None	None
Radicchio	5.0	None	None	None
Radish, oriental, roots	2.0	None	None	None

Table 2. Summary of US and International Residue Limits				
***Commodity*[1]**	***Tolerance (ppm) /Maximum Residue Limit (mg/kg)***			
	US	**Canada**	**Mexico[2]**	**Codex**
Radish, oriental, tops	2.0	None	None	None
Rutabaga	2.0	None	None	None
Soybean	2.0	None	None	None
Squash, summer	1.0	1.0	None	None
Squash, winter	1.0	None	None	None
Sweet potato	2.0	2.0	None	None
Turnip, roots	2.0	2	None	None
Turnip, tops	5.0	5	None	None
Yam, true, tuber	2.0	2	None	None

[1] Includes only commodities of interest for this action. Tolerance values should be the HED recommendations and not those proposed by the applicant.
[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.
[3]Canada does not distinguish maximum residue limits in their maximum residue limit regulations. Therefore the Canadian limits included in this section do not specifically refer to inadvertent residues.

Table 3. Summary of Revised Maximum Reasonable Dietary Burden for DCPA					
Feed Commodity	Feedstuff Type	% Dry Matter	Percent in Diet	Tolerance Level	Max Contribution
Beef Cattle (R=15%; CC=80%; PC=5%)					
Corn Forage	R	40	15	0.4	0.15
Corn Grain	CC	88	50	0.05	0.028
Processed Potato Waste	CC	15	30	2	4
Soybean Seed	PC	89	5	2	0.11
Total	NA	NA	100	NA	4.29
Dairy Cattle (R=45%; CC=45%; PC10%)					
Corn Forage	R	40	15	0.4	0.15
Turnip Tops	R	30	30	5	5
Turnip Roots	CC	15	10	2	1.33
Processed Potato Waste	CC	15	10	2	1.33
Corn Grain	CC	88	25	0.05	0.014
Soybean Seed	PC	89	10	2	0.22
Total	NA	NA	100	NA	8.06
Poultry (CC=75-80%; PC=20-25%)					
Corn Grain	CC	NA 0	80	0.05	0.04
Soybean Seed	PC		20	2	0.4
Total					0.44
Hogs (CC=80-85%; PC=15-20%)					
Corn Grain	CC	0	80	0.05	0.04
Soybean Seed	PC		20	2	0.4
Total	NA	NA	100	NA	0.44

Rationale for Requiring a Poultry Nature of the Residue Study

Guideline Number: 860.1300 **Study Title: Nature of the Residue, Livestock (Poultry)**
Rationale for Requiring the Data
This study provides essential information on the potential transfer and bioconcentration of residues in poultry meat and eggs for pesticides applied to feed items. Many pesticides undergo change during or after livestock consume treated feed. The composition of the terminal residue must be determined before complete residue detection methodology and residue quantification data can be developed. The study may help to validate the poultry magnitude of residue data previously submitted if no new residues of concern are identified. The requested poultry nature of the residue study will need supporting storage stability data for all DCPA residues of concern, unless the samples from the feeding study are analyzed within six months of collection.
Practical Utility of the Data
How did the Agency make its re-registration decision without these data? In order to make its reregistration decision, the Agency assumed poultry would have similar types of residues as cattle and goats. **How will the data be used?** The data will be used to provide a full characterization of the DCPA residue profile. The submission will provide the necessary data to set tolerances for livestock commodities. These data may also result in a change in how dietary risks are quantified.

Rationale for Requiring an Independent Laboratory Validation for a Livestock Residue Analytical Method

Guideline Number: 860.1340 **Study Title: Residue Analytical Methods (enforcement analytical method for livestock)**
Rationale for Requiring the Data
One of the analytical methods submitted by the registrant must be suitable for use by various Federal and State enforcement agencies. The Food and Drug Administration (FDA) collects these methods and then publishes them to be used for tolerance enforcement purposes. The registrant has submitted a method for determining residues of DCPA and its metabolites that may be suitable but must be tested by an independent laboratory to ensure that it is useful.
Practical Utility of the Data
How will the data be used? EPA would review the independent laboratory validation of the submitted method and determine its suitability as an enforcement method. If suitable, EPA would forward the method to FDA. The enforcement analytical methods are published by FDA and are available to all regulatory laboratories for use in monitoring the specific pesticide concentrations in foods and feeds. They are a necessary tool for tolerance enforcement and residue monitoring and, as such are essential in the efforts to ensure a safe food supply for the consumer.

Rationale for Requiring Cattle Magnitude of Residue Study

Guideline Number: 860.1480 **Study Title: Magnitude of the Residue** (Cattle Feeding Study)
Rationale for Requiring the Data
A new ruminant feeding study is required to determine whether tolerances are needed (and if so the appropriate tolerance levels) for milk and meat. The requested ruminant feeding study will need supporting storage stability data for all DCPA residues of concern, unless the samples from the feeding study are analyzed within 30 days of collection.
Practical Utility of the Data
How did the Agency make its re-registration decision without these data? The Agency has made conservative assumptions within the dietary assessment to account for the lack of magnitude of the residue (MOR) data from the cattle feeding studies. Residue estimates based on the metabolism studies were included to account for potential exposure to DCPA and it metabolites in meat and milk from ruminants. However, these data are needed to ensure that the correct assumptions were made. **How will the data be used?** The data will be used to provide a full characterization of the DCPA residue profile. The submission of livestock MOR data would provide the necessary data to determine if tolerances are needed for livestock commodities and if necessary, to set the appropriate tolerance levels. **How could the data impact the Agency's future decision-making?** The submission of MOR data would provide the necessary data to set tolerances for livestock commodities. These data may also result in a change in how dietary risks are quantified.

Rationale for Requiring Field Accumulation in Rotational Crops Study

Guideline Number: 860.1900
Study Title: Field Accumulation in Rotational Crops

Rationale for Requiring the Data

A rotational crop use is any field-vegetable crop use or any other site use on which it is reasonably foreseeable that any food or feed crop may be planted after harvest of a treated crop. The purpose of field accumulation in rotational crop studies is to determine the amount of pesticide residue uptake into rotational crops. The study uses a typical end-use product applied to a field plot. Results of these studies are used to determine whether residues occur in rotational crops grown under actual field conditions. Based on these data, appropriate crop rotation restrictions (time from application to planting of rotational crop) may be established and the need for tolerances on the rotated crops determined.

Carrot roots and tops, corn fodder and silage, oat forage, and turnip tops from plants sowed at a 1-year plantback interval in soil treated at half the maximum application rate bore quantifiable residues in one or more samples. These data indicate that tolerances are needed for residues of DCPA and metabolites in some crops if they are rotated to fields that have been treated at even half the maximum seasonal label rate. The petitioner/registrant has not proposed any restrictions that obviate the need for rotational crop tolerances.

Large-scale rotational crop field trials are required to determine the appropriate tolerance levels for rotated crop commodities. The scope of the required tests is dependent upon the petitioner's/registrant's intent with respect to the crops to be allowed in rotation and the desired plantback interval(s) for these crops. Any crop without a registered use, for which the petitioner/registrant wishes to allow rotation, requires field trial data to determine a suitable tolerance level. A crop group approach, requiring data on representative commodities, may be appropriate if several crops within a group are to be rotated. For individual crops, the standard number of trials needed to support direct crop treatment tolerances are required, e.g., 20 trials for wheat.

Practical Utility of the Data

How did the Agency make its re-registration decision without these data?
Since the data were lacking, the Agency was not able to evaluate risks for rotational crops.

How will the data be used?
The data will be used to provide a full characterization of the DCPA residue profile. The submission of these data would provide the necessary information to determine if tolerances are needed for rotated crops and if so, to set the appropriate tolerance levels. These data may also result in a change in how dietary risks are quantified.

How could the data impact the Agency's future decision-making?
The submission of these data would allow the Agency determine if tolerances are necessary for rotational crops and if so, to set the appropriate tolerances. The previously submitted confined and limited field rotational crop studies have shown potential residue uptake into rotated crops. If residues are detected in crops without established tolerances, these crops may be seized by the Food and Drug Administration (FDA). Accurate rotational crop tolerances protect farmers from inappropriate crop seizures.

Rationale for Requiring a 28-day Subchronic Toxicity Study

Guideline Number: 870.3465 **Study Title: Subchronic Inhalation Toxicity Study**
Rationale for Requiring the Data
This data requirement is conditionally required under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). This study is required for DCPA because workers can potentially be exposed to DCPA via the inhalation route of exposure. DCPA is in toxicity category IV for inhalation exposure and is a mild irritant to the eyes and skin and is not a skin sensitizer.
Practical Utility of the Data
How will the data be used? This study can be used to select endpoints and doses for use in exposure assessment for workers by the inhalation route of exposure. **How could the data impact the Agency's future decision-making?** This study will be used in a worker occupational exposure assessment. This study was requested in the previous risk assessment.

Rationale for Requiring a Comparative Thyroid Study

Guideline Number: 870.3700SS (Special Study) **Study Title: Comparative Thyroid Study**
Rationale for Requiring the Data
Thyroid toxicity with treatment with DCPA has been observed in studies with adult animals, but no such data exist for developmental effects of DCPA on the thyroid and thyroid hormones of young animals.
Practical Utility of the Data
How will the data be used? The thyroid and thyroid hormones are adversely affected by treatment with DCPA, but data are lacking with which to estimate developmental risks associated with this toxicity. The data may provide a dose and endpoint for use in the assessment of risks for children and will play a role in the registration review decision. **How could the data impact the Agency's future decision-making?** If the study indicates there is a special vulnerability to children from DCPA, a new toxicity endpoint will be incorporated into the risk assessment for children.

Rationale for Requiring The Neurotoxicity Battery

Guideline Number: 870.6200 **Study Title**: **Neurotoxicity Battery (Acute and Subchronic Studies)**
Rationale for Requiring the Data
The Neurotoxicity Screening Battery (OPPTS 870.6200) is designed to evaluate the potential adverse effects on the nervous system from exposure to pesticide chemicals. The Agency believes that the guideline studies are inadequate in their assessment of behavioral effects and do not use optimal methods to evaluate the potential toxicity to the nervous tissue structure and function. To detect and characterize these potential effects more fully, a battery of more sensitive testing is required. The objective of this neurotoxicity battery testing is to evaluate the incidence and severity of the functional and/or behavioral effects, the level of motor activity, and the histopathology of the nervous system. The acute neurotoxicity study is required to detect possible effects resulting from a single exposure. The subchronic neurotoxicity study is intended to detect possible effects resulting from repeated or long-term exposures. Neurotoxicity was not detected in the toxicity studies with DCPA.
Practical Utility of the Data
How will the data be used? The acute and subchronic neurotoxicity studies provide critical scientific information needed to characterize potential hazard to the human population on the nervous system from pesticide exposure. These studies can provide data on a wide range of functional tests for evaluating neurotoxicity including sensory effects, neuromuscular effects, learning and memory and histopathology of the nervous system and can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. **How could the data impact the Agency's future decision-making?** If the acute or subchronic neurotoxicity studies show that DCPA poses either a greater or a diminished risk than that given in the previous risk assessment, the risk assessment may need to be revised to reflect the magnitude of potential risk derived from the new data. If the Agency does not have these data, a 10X database uncertainty factor may be applied when conducting a risk assessment using the currently available studies.

Rationale for Requiring an Immunotoxicity Study

Guideline Number: 870.7800 **Study Title**: **Immunotoxicity**
Rationale for Requiring the Data
This is a new data requirement under 40 CFR Part 158 as a part of the data requirements for registration of a pesticide (food and non-food uses). The Immunotoxicity Test Guideline (OPPTS 870.7800) prescribes functional immunotoxicity testing and is designed to evaluate the potential of a repeated chemical exposure to produce adverse effects (i.e., suppression) on the immune system. Immunosuppression is a deficit in the ability of the immune system to respond to a challenge of bacterial or viral infections such as tuberculosis (TB), Severe Acquired Respiratory Syndrome (SARS), or neoplasia. Because the immune system is highly complex, studies assessing functional immunotoxic endpoints are helpful in fully characterizing a pesticide's potential immunotoxicity. These data will be used in combination with data from hematology, lymphoid organ weights, and histopathology in routine chronic or subchronic toxicity studies to characterize potential immunotoxic effects.
Practical Utility of the Data
How will the data be used? These animal studies can be used to select endpoints and doses for use in risk assessment of all exposure scenarios and are considered a primary data source for reliable reference dose calculation. For example, animal studies have demonstrated that immunotoxicity in rodents is one of the more sensitive manifestations of TCDD (2,3,7,8-tetrachlorodibenzo-p-dioxin) among developmental, reproductive, and endocrinologic toxicities. Additionally, the EPA has established an oral reference dose (RfD) for tributyltin oxide (TBTO) based on observed immunotoxicity in animal studies (IRIS, 1997). **How could the data impact the Agency's future decision-making?** If the immunotoxicity study shows that the test material poses either a greater or a diminished risk than that given in the interim decision's conclusion, the risk assessments for the test material may need to be revised to reflect the magnitude of potential risk derived from the new data. If the Agency does not have these data, a 10X database uncertainty factor may be applied for conducting a risk assessment from the available studies.

Discussion on Toxic Impurities

The manufacturing process of DCPA produces several contaminants known to be of significant toxicological concern, including hexachlorobenzene (HCB) and congeners (structurally related chemicals) of polyhalogenated dibenzo-p-dioxins/dibenzofurans (dioxins/furans). Carcinogenic risk was assessed for dietary exposure to HCB and dioxin/furans using cancer potency factors of 1.02 $(mg/kg/day)^{-1}$ and 1 x 10^5, respectively. Estimated dietary risks were negligible and below the level of concern. In addition, cancer risk from these contaminants was assessed for occupational exposure and was below the level of concern.