Potential Designated Chemicals:
Organophosphorus Pesticides

Materials for July 20, 2017 Meeting of the Scientific Guidance Panel for Biomonitoring California[1]

Introduction

At the July 2016 meeting of the Scientific Guidance Panel (SGP), the Office of Environmental Health Hazard Assessment (OEHHA) presented a preliminary screen of pesticide classes for possible future consideration as designated chemicals for Biomonitoring California (OEHHA, 2016). The SGP recommended that OEHHA prepare a potential designated chemical document on organophosphorus pesticides.

Organophosphorus pesticides are broadly defined here as a structure-based class, i.e., phosphorus-containing organic compounds used as pesticides. Subclasses include organophosphates, organophosphinates, and organophosphonates.

Some organophosphate insecticides are currently on the list of designated chemicals (see Attachment A). This set of organophosphates was designated based on their inclusion in the National Reports on Human Exposure to Environmental Chemicals program of the Centers for Disease Control and Prevention (CDC). In March 2009, the SGP recommended that this set of organophosphate insecticides be added as priority chemicals.

There is a fairly extensive body of literature on organophosphorus pesticides. This summary provides a brief overview of recent information relevant to the criteria for considering this class as potential designated chemicals. We specifically highlight available findings for organophosphorus pesticides currently used in California that are not already included as designated chemicals: bensulide, ethephon, ethoprop, fosetyl-aluminum, glufosinate-ammonium, glyphosate, and S,S,S-tributyl phosphorotrithioate (tribufos).

If the Panel were to recommend adding organophosphorus pesticides as a class to the list of designated chemicals, Biomonitoring California would have the flexibility to choose appropriate analytes in response to market shifts in pesticide use. For example, supply chain issues resulted in significantly decreased agricultural use of glufosinate-ammonium in California during 2012 and 2013, leading to increased use of alternate herbicides (California Department of Pesticide Regulation [DPR], 2012; 2013). The emergence of glyphosate-resistant weeds is another example of a factor that can affect herbicide selection (Bain et al., 2017; Green, 2016; Wechsler et al., 2017). Regulatory pressures can also determine pesticide availability and introduction of substitutes. For

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[1] California Environmental Contaminant Biomonitoring Program, codified at Health and Safety Code section 105440 *et seq*.

example, chlorpyrifos was formerly widely used in homes for termite and ant control, but those uses have been dramatically restricted, with concomitant increases in the use of pyrethroids (which are already on the list of designated chemicals as a class). By considering the group of organophosphorus pesticides, we capture structurally similar substitutes that may increase in use or be newly introduced in the future.

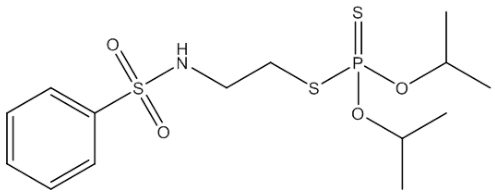
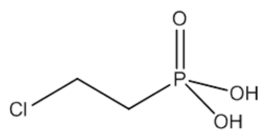
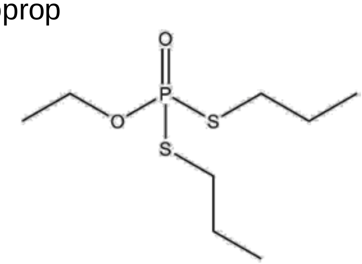
Chemical identity and use information

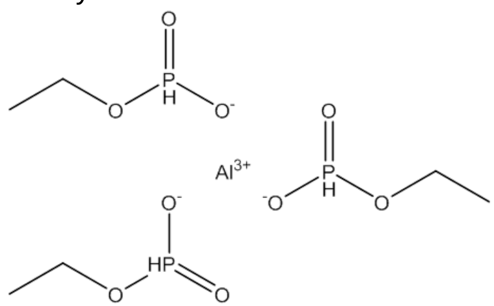
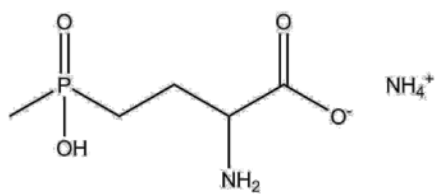
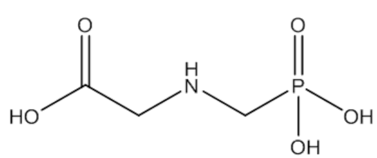
Several members of the class of organophosphorus pesticides that are already on Biomonitoring California's designated list are among the top 100 pesticides used agriculturally statewide in 2015, including acephate, chlorpyrifos, dimethoate, malathion, and naled (DPR, 2015a). Of these, chlorpyrifos was the most highly used (1,108,386 pounds, rank 26). Chlorpyrifos is commonly used agriculturally on such crops as tree nuts, oranges, and alfalfa (DPR, 2015b). DPR (2015c) extended existing federal restrictions on chlorpyrifos to make it a "state-restricted material[2] when labeled for the production of an agricultural commodity" in July 2015. Ant and roach baits in child-resistant packaging are the only residential chlorpyrifos products permitted in the state (DPR, 2015c). Other organophosphorus pesticides on the designated list that are used residentially, and for which we identified retail products, include acephate (ant killer products), and malathion (insect spray concentrates). Prescription medication containing malathion may be used to treat head lice, and tetrachlorvinphos is in some pet products for flea and tick control.

Table 1 (on pages 3-5) provides chemical structures and use information for seven organophosphorus pesticides that are in current use in California but are not on the list of designated chemicals. Five of these are in the top 100 pesticides used agriculturally in the state (DPR, 2015a).

[2] Restricted materials in California are pesticides deemed to have a higher potential to cause harm to public health, farm workers, domestic animals, honeybees, the environment, wildlife, or other crops compared to other pesticides. With certain exceptions, restricted materials may be purchased and used only by or under the supervision of a certified commercial or private applicator under a permit issued by the County Agricultural Commissioner. See http://www.cdpr.ca.gov/docs/enforce/permitting.htm for more information.

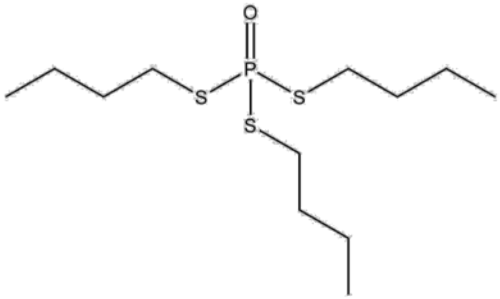
Table 1. Summary of California use information on highlighted organophosphorus pesticides not on designated list

Organophosphorus pesticide	Type and uses[1,2,3]	Rank in top 100 pesticides used statewide in 2015[4]	Pounds applied in CA (2011-2015)[5]	Pounds sold in CA (2011-2015)[6]
Bensulide 	Type: Herbicide Example crops: Lettuce, broccoli Other uses: Landscape maintenance (e.g., golf courses) Registered products: 10 Retail products identified: Yes	57	2015: 345,261 2014: 318,705 2013: 284,152 2012: 267,262 2011: 288,344	2015: 399,053 2014: 372,092 2013: 331,862 2012: 280,663 2011: 325,580
Ethephon 	Type: Plant growth regulator Example crops: Cotton, walnuts Other uses: Landscape maintenance Registered products: 29 Retail products identified: Yes	58	2015: 320,938 2014: 346,796 2013: 396,665 2012: 483,676 2011: 548,802	2015: 467,917 2014: 448,865 2013: 488,621 2012: 590,301 2011: 768,861
Ethoprop 	Type: Insecticide Crops: Cabbage, sweet potato Other uses: Outdoor-grown transplants Registered products: 3 Retail products identified: No[7]	--	2015: 1,751 2014: 1,228 2013: 2,434 2012: 2,077 2011: 7,475	2015: 6,287 2014: 2,100 2013: 654 2012: 8,248 2011: 11,944

Organophosphorus pesticide	Type and uses[1,2,3]	Rank in top 100 pesticides used statewide in 2015[4]	Pounds applied in CA (2011-2015)[5]	Pounds sold in CA (2011-2015)[6]
Fosetyl-aluminum 	Type: Fungicide Example crops: Lettuce, spinach Other uses: Landscape maintenance Registered products: 10 Retail products identified: Yes	77	2015: 216,136 2014: 230,655 2013: 235,194 2012: 280,414 2011: 285,185	2015: 652,562 2014: 276,289 2013: 217,531 2012: 352,950 2011: 348,020
Glufosinate-ammonium 	Type: Herbicide Example crops: Grapes, tree nuts Other uses: Rights-of-way Registered products: 15 Retail products identified: Yes	33	2015: 716,463 2014: 139,368 2013: 48,004 2012: 234,390 2011: 740,327	2015: 1,586,374 2014: 723,798 2013: 203,025 2012: 228,384 2011: 1,299,405
Glyphosate 	Type: Herbicide Example crops: Tree nuts, grapes, corn, cotton Other uses: Rights-of-way, landscape maintenance, forest timberland Registered products: 227 Retail products identified: Yes	7†	2015: 11,463,943‡ 2014: 10,605,865 2013: 10,370,148 2012: 10,473,329 2011: 10,745,583	2015: 24,487,089 2014: 22,524,790 2013: 21,480,479 2012: 22,086,272 2011: 21,016,705

† The potassium salt of glyphosate was rank 7; the isopropylamine salt was rank 8.

‡ For glyphosate, the values shown for pounds applied and pounds sold are for the parent compound and all its salts.

Organophosphorus pesticide	Type and uses[1,2,3]	Rank in top 100 pesticides used statewide in 2015[4]	Pounds applied in CA (2011-2015)[5]	Pounds sold in CA (2011-2015)[6]
Tribufos 	Type: Defoliant Crop: Cotton Other uses: -- Registered products: 4 Retail products identified: No[8]	--	2015: 6,472 2014: 11,683 2013: 19,077 2012: 21,960 2011: 30,745	2015: 31,417 2014: 9,821 2013: 34,070 2012: 23,596 2011: 51,792

[1] Information on crops and other uses was obtained from the DPR (2015b) Pesticide Use Report (available online: http://www.cdpr.ca.gov/docs/pur/pur15rep/chmrpt15.pdf). This report covers "agricultural use" of pesticides, which is broadly defined to include use on crops as well as landscape maintenance, for example. For further explanation, refer to pages 6-8 of this Pesticide Use Report.
[2] The DPR Product/Label database (available online: http://www.cdpr.ca.gov/docs/label/labelque.htm) lists all pesticide products registered for use in California, including pesticides for consumer home and garden use. The number of active products registered for use in California is shown in the table for each example organophosphorus pesticide.
[3] Several retail websites selling home, lawn, and garden supplies were scanned for commercially available products containing the selected organophosphorus pesticides. In instances where we did not locate retail products containing the pesticide, the category of "Retail products identified" is shown as "No".
[4] Ranks were obtained from the DPR list of the top 100 pesticides used in California in 2015 (available online: http://www.cdpr.ca.gov/docs/pur/pur15rep/top_100_ais_lbs_2015.pdf), based on pounds applied for "agricultural use" of pesticides (see footnote 1 above).
[5] DPR Summaries of Pesticide Use Report Data, Indexed by Chemical (available online: http://www.cdpr.ca.gov/docs/pur/purmain.htm) provide data on pounds of "agricultural use" of pesticides (see footnote 1 above).
[6] DPR Reports of Pesticides Sold in California (available online: http://www.cdpr.ca.gov/docs/mill/nopdsold.htm) contain self-reported data from pesticide registrants, pest control dealers, and pesticide brokers on the total pounds of each active ingredient they sell for any use in California (i.e., agricultural, institutional, and/or home use). Reporting is required for the first point of sale in the state by any seller registered with DPR, including, for example, retail stores and on-line purveyors. Because these data are self-reported, however, DPR cannot attest to their complete accuracy.
[7] The US Environmental Protection Agency (US EPA, 2016a) classifies some products containing ethoprop as restricted use products, which are not available for purchase or use by the general public. See https://www.epa.gov/sites/production/files/2016-02/documents/rupreport-sec3-update-jan2016.pdf.
[8] All active products registered in California containing tribufos are designated by DPR as restricted materials. See page 2, footnote 2.

Exposure or potential exposure to the public or specific subgroups

Organophosphorus pesticide exposure can occur through occupational use (Fenske et al., 1987; Jomichen et al., 2017; Lesmes-Fabian and Binder, 2013; Lotti et al., 1983; Suratman et al., 2015); living, working, or going to school near agricultural areas or other areas where pesticides are applied (Bradman et al., 1997; Fenske et al., 2000; Gibbs et al., 2017; Gunier et al., 2016; Salvatore et al., 2015; Smith et al., 2017; Whyatt et al., 2003); home use of some products (Deziel et al., 2015a); and diet (Bradman et al., 2015; Holme, et al., 2016; Lu et al., 2006). Take-home exposures by agricultural workers can lead to higher pesticide exposures for family members, particularly children (Deziel et al., 2015b; Hyland and Laribi, 2017). For example, some organophosphorus pesticides have been detected more frequently and at higher levels in dust samples collected from farm homes compared with dust samples from non-farm homes (Lu et al., 2000; Quirós-Alcalá et al., 2011; Simcox et al., 1995; Thompson et al., 2003).

Selected exposure studies on organophosphorus pesticides not already designated are discussed below; findings on already designated chemicals from these studies are also noted. We describe all of the recent California studies that we located in our literature search. We also review studies from other states and other countries, if relevant for illustrating potential exposure pathways; the specific findings of exposure studies from other locations may not apply to California.

Dust:

We did not identify California dust studies of the highlighted pesticides. Curwin et al. (2005) collected dust samples from home carpets and rugs, and surface wipes from the kitchen counter, top of the washing machine, various rooms with hard surface floors, and primary family vehicles. The study included both farm and non-farm homes in Iowa and samples were collected in 2001. Glyphosate was detected in 100% of dust samples from farm homes (n = 31 samples from 5 homes; range: 0.0081-2.7 ng/cm^2) and in 85% of samples from non-farm homes (n = 28 samples from 6 homes; range: 0.0012-13 ng/cm^2). It was not detected in any house or vehicle wipes. Glyphosate levels in dust were highest in samples collected from the child's bedroom in both farm (geometric mean [GM]: 1,500 ng/g) and non-farm (GM: 510 ng/g) homes. To put these dust findings in context, the study reported detections of chlorpyrifos in 84% of dust samples from farm homes (n = 116 samples from 20 homes; range: 0.00049-10 ng/cm^2) and in 81% of samples from non-farm homes (n = 114 samples from 19 homes; range: 0.00021-3.6 ng/cm^2).

Air:

As part of the Air Monitoring Network, DPR (2017a) included the highlighted pesticides bensulide and tribufos in their 2015 study of 155 air samples collected at three sites:

Salinas, Shafter, and Ripon. Bensulide was detected in one Salinas sample at a level below the limit of quantitation (LOQ) of 9.3 ng/m^3. Tribufos was not detected.

Majewski et al. (2014) collected air samples (n = 21) in 2007 from the Mississippi Delta agricultural region and reported detections of glyphosate (DF: 86%; median: 0.567 ng/m^3), aminomethylphosphonic acid (AMPA, the major breakdown product of glyphosate) (DF: 86%; median: 0.074 ng/m^3), and tribufos (DF: 10%; median: non-detect [ND]; maximum: 0.274 ng/m^3). This study also detected the already designated organophosphorus pesticides chlorpyrifos, dicrotophos, malathion, and methyl parathion in air samples.

Chang et al. (2011) measured glyphosate and AMPA in air samples collected from Iowa and Mississippi. Glyphosate was detected in 61% of Iowa air samples (n = 18; median: 0.08 ng/m^3) collected in 2007 and in 72% of samples (n = 18; median: 0.22 ng/m^3) collected in 2008. AMPA was detected in 56% of Iowa air samples (n = 18; median: 0.02 ng/m^3) collected in 2007 and in 61% (n = 18%; median: 0.04 ng/m^3) collected in 2008. Glyphosate was detected in 86% of Mississippi air samples (n = 22; median: 0.48 ng/m^3) collected in 2007 and in 100% of samples (n = 27; median: 0.24 ng/m^3) in 2008. AMPA was detected in 86% of Mississippi air samples (n = 22; median: 0.06 ng/m^3) collected in 2007 and in 70% of samples (n = 27; median: 0.02 ng/m^3) collected in 2008.

Coscollà et al. (2010) collected air samples between 2006-2008 from 2 urban and 3 rural sites in France, and tested them for a variety of pesticides. Ethoprop was detected in 2 (1%) of 262 samples analyzed, at levels of 0.21 and 0.48 ng/m^3. Both detections were in samples collected from the same rural site. Coscollà et al. noted that the detections at the rural site were most likely associated with ethoprop use on potato fields. Other organophosphorus pesticides detected in the air samples included chlorpyrifos, diazinon, and phosmet.

Hart et al. (2012) collected particulate matter (PM_{10}) from air samples in 2010 from various sites (1 urban, 3 rural, and 1 remote) in Spain, and tested them for a variety of pesticides. Ethoprop was detected in 13% of 217 total samples analyzed. The majority of ethoprop detections were in PM_{10} from the urban site samples (DF in urban site samples: 56%; mean: 153.1 pg/m^3; range: 15.2-1196.8 pg/m^3). The highest levels of ethoprop were measured by a sampler situated in a park with extensive gardens. The study authors noted that ethoprop is used in ornamental gardens. Other organophosphorus pesticides detected in the PM_{10} samples in this study included chlorpyrifos, diazinon, and malathion.

Water:

The maximum contaminant level (MCL) for glyphosate in drinking water is 700 µg/L (State Water Resources Control Board [SWRCB], 2014; US EPA, 2009a). The current Public Health Goal in California is 900 µg/L (OEHHA, 2007).

The Environmental Working Group (EWG) compiled tap water testing data from state water offices in their National Drinking Water Database, which covers 2004 to 2009 (EWG, 2009). The database listed two water utilities in California that found glyphosate in drinking water during that time period. The Imperial Irrigation District (in Imperial, CA) detected glyphosate once at a level of 16.5 µg/L in 2005. The City of Bakersfield reported one detection of 32 µg/L in 2006. There were 218 US water suppliers that reported testing for ethoprop, but none detected the chemical (EWG, 2009).

SWRCB maintains the on-line GeoTracker GAMA (Groundwater Ambient Monitoring and Assessment) Information System (SWRCB, 2015). Two detections of glyphosate in groundwater were reported in the last ten years. A level of 1.3 µg/L was found in an environmental monitoring well in Los Angeles County in 2009. In 2013, 20 µg/L glyphosate was measured in a water supply well at the Vandenberg Air Force Base in Santa Barbara County.

DPR (2016) summarized results from 2015 groundwater monitoring for pesticide residues, including bensulide and glyphosate. These compounds were not detected in any sample. Bensulide was tested in 64 wells across three counties (reporting limit 0.05 µg/L), and glyphosate was tested in 644 wells across 38 counties (reporting limit 0 to 25 µg/L). AMPA was not measured.

Glyphosate and AMPA have been commonly detected in surface water, ground water, and/or precipitation samples in other areas of the US (Battaglin et al., 2014; Chang et al., 2011; Coupe et al., 2012) and in Ontario, Canada (Struger et al., 2008; 2015). Majewski et al. (2014) reported detections of tribufos, in addition to glyphosate and AMPA, in rain samples collected in 2007 from the Mississippi Delta agricultural region. They also found the already designated organophosphorus pesticides chlorpyrifos, dichlorvos, dicrotophos, malathion, and methyl parathion in the rain samples. Mahler et al. (2017) detected glyphosate more frequently in urban stream samples collected in 2013 compared to streams impacted by agricultural land use in the Midwestern US. Measured concentrations were comparable in both types of streams.

Pesticide use near school sites:

The California Environmental Health Tracking Program (CEHTP, 2014) examined the use of agricultural pesticides near California public schools in 2010 as a way to understand the potential for pesticide exposure among children in school settings. Of the selected organophosphorus pesticides that are not currently on Biomonitoring California's designated list of chemicals, bensulide, ethephon, and glufosinate-ammonium were among the top ten pesticides applied within a quarter mile of schools in one or more of the counties assessed. Bensulide was additionally one of the top ten pesticides classified as a cholinesterase inhibitor used within a quarter mile of schools in the 15 counties assessed overall. For the already designated organophosphate pesticides, CEHTP (2014) found that chlorpyrifos and malathion were among the top ten pesticides applied within a quarter mile of schools, and acephate, chlorpyrifos, diazinon, dimethoate, malathion, naled, and oxydemeton-methyl were in the top ten pesticides classified as cholinesterase inhibitors used within a quarter mile of schools in the counties assessed overall.

DPR (2015c) made chlorpyrifos a restricted material in 2015. On March 16, 2017, DPR announced revised proposed rules on agricultural pesticide use near schools and child day-care centers in an effort to provide an extra measure of protection from pesticide exposures (DPR, 2017b). Additional data collection will improve the available information about pesticide use near schools.

Food residues:

Of the highlighted organophosphorus pesticides, bensulide, ethoprop, and tribufos are included in DPR's multi-residue screens of fresh produce samples (DPR, 2014). None of these organophosphorus pesticides were detected in DPR's most recent analysis of residues on produce (DPR, 2015d).

In their most recent annual analyses, the US Food and Drug Administration (FDA, 2014a; 2014b) and the US Department of Agriculture (USDA, 2015) detected residues of several of the highlighted organophosphorus pesticides in food samples. FDA (2014b) found trace levels of ethoprop in 2 samples of leaf and stem vegetables imported from Korea. FDA (2014b) also detected tribufos in one sample of cilantro imported from Mexico at 0.121 ppm. Of 4,204 food samples analyzed for bensulide by USDA (2015), the compound was detected in 3 lettuce samples, ranging from 0.004-0.007 ppm. Of 2,560 food samples analyzed for bensulide oxon, a breakdown product of bensulide, the compound was detected in 11 lettuce samples, ranging from 0.003-0.022 ppm. None of the 7,786 samples tested by USDA (2015) for ethoprop, nor any of the 2,574 samples tested for tribufos had detectable levels of these compounds.

As part of their annual pesticide data program report, USDA (2011) included the results of a specialty analysis conducted on soybean samples for glyphosate and AMPA. Of 300 soybean samples evaluated, glyphosate was detected in 271 samples (DF: 90.3%) ranging from 0.26-18.6 ppm, and AMPA was detected in 287 samples (DF: 95.7%) ranging from 0.26-20 ppm.

In 2015-2016, the Canadian Food Inspection Agency (CFIA) tested 3,188 domestic and imported food samples for glyphosate and AMPA (detection limits not reported), and found the highest detection frequencies for the sum of the two chemicals in bean, pea, and lentil products (47.4%), grain products (36.6%), and infant cereals (31.7%) and foods (30.7%) (CFIA, 2017). CFIA (2017) found that 98.7% of the samples tested did not exceed the glyphosate maximum residue limit (MRLs), which Canada sets for a variety of food products. The few samples in exceedance of the glyphosate MRLs were primarily grain products, with other exceedances in the categories of “juice and other beverages”, and “bean, pea, and lentil products”.

Known or suspected health effects

There is an extensive body of literature on organophosphate pesticides that show associations between human exposure to these compounds and a range of adverse health outcomes: neurotoxicity, including cognitive effects (Engel et al., 2016; Gunier et al., 2017; Kamel et al., 2007; Ophir et al., 2014; Rowe et al., 2016; Starks et al., 2012a; 2012b; Stokes et al., 1995; Voorhees et al., 2017); developmental toxicity (Harley et al., 2016; Rauch et al., 2012); diabetes (Saldana et al., 2007; Starling et al., 2014); other endocrine effects (Goldner et al., 2013); respiratory effects (Hoppin et al., 2008; 2009; Raanan et al., 2015; 2016; Valcin et al., 2007); and other effects (Mostafalou and Abdollahi, 2017; Ranjbar et al., 2015; Rusiecki et al., 2017; Wang et al., 2016).

Table 2 on the next page shows organophosphorus pesticides that are listed as causing cancer or reproductive toxicity under Proposition 65 (State of California, 2017), some of which have also been classified by the International Agency for Research on Cancer (IARC) (IARC, 2017a).

Table 2. Proposition 65 and IARC classifications for selected organophosphorus pesticides

<table>
<tr><th rowspan="2"></th><th rowspan="2">Organophosphorus pesticide</th><th colspan="2">Proposition 65[1]</th><th rowspan="2">IARC classification[2]</th></tr>
<tr><th>Carcinogen</th><th>Reproductive toxicant</th></tr>
<tr><td rowspan="3">Highlighted pesticide not on designated list</td><td>Ethoprop</td><td>Yes</td><td>--</td><td>Not classified</td></tr>
<tr><td>Glyphosate</td><td>Yes[3]</td><td>--</td><td>Group 2A</td></tr>
<tr><td>Tribufos</td><td>Yes</td><td>--</td><td>Not classified</td></tr>
<tr><td rowspan="6">Pesticide already on designated list</td><td>Diazinon</td><td>--</td><td>--</td><td>Group 2A</td></tr>
<tr><td>Dichlorvos (DDVP)</td><td>Yes</td><td>--</td><td>Group 2B</td></tr>
<tr><td>Malathion</td><td>Yes</td><td>--</td><td>Group 2A</td></tr>
<tr><td>Oxydemeton-methyl</td><td>--</td><td>Yes (Reproductive-female, male)</td><td>Not classified</td></tr>
<tr><td>Parathion</td><td>Yes</td><td>--</td><td>Group 2B</td></tr>
<tr><td>Tetrachlorvinphos</td><td>Yes</td><td>--</td><td>Group 2B</td></tr>
</table>

[1] Proposition 65 List of Chemicals. January 27, 2017 version. Available online: https://oehha.ca.gov/media/downloads/proposition-65//p65single01272017.pdf
[2] IARC List of classifications. Group 2A agents are considered “probably carcinogenic to humans” and Group 2B agents are considered “possibly carcinogenic to humans”. Available online: http://monographs.iarc.fr/ENG/Classification/latest_classif.php
[3] Glyphosate is listed under Proposition 65 as known to the state to cause cancer effective July 7, 2017. See notice at: https://oehha.ca.gov/proposition-65/crnr/glyphosate-listed-effective-july-7-2017-known-state-california-cause-cancer

Selected studies on known or suspected health effects of organophosphorus pesticides not already on the list of designated chemicals are briefly outlined below. We primarily cover non-cancer effects, and do not discuss the cancer studies that were the basis for the listings in Table 2. The epidemiological studies involved exposures to pesticide formulations. For animal and *in vitro* studies, we focused on those that tested the pesticide active ingredient. For full study details, refer to the published papers (citations provided in the reference list).

Selected human studies

Starks et al. (2012a) found that use of ethoprop and malathion by pesticide applicators in the Agricultural Health Study (AHS) was associated with reduced performance in neurobehavioral function tests. Use of chlorpyrifos, diazinon, dichlorvos, glyphosate, and malathion by AHS pesticide applicators was associated with rhinitis (Slager et al., 2010). Hoppin et al. (2017) found that use of glyphosate and malathion in the AHS was associated with both allergic and non-allergic wheeze. Uses of glufosinate-ammonium and other organophosphates evaluated were not associated with either wheeze outcome. Use of glyphosate was associated with incident rheumatoid arthritis in AHS farmers' spouses who themselves used the pesticide (Parks et al., 2016).

In a case-control study of pesticide applicators and their children in Minnesota, Garry et al. (2002) reported that parental glyphosate use was linked with increased odds of attention-deficit disorders in children.

In a case-control study in an agricultural area in Spain, García et al. (1998) found that paternal exposure to glufosinate-ammonium was linked with increased odds of child congenital malformations. This study also evaluated exposures to the highlighted organophosphorus pesticides fosetyl-aluminum and glyphosate, but did not observe a link between paternal exposure to these pesticides and congenital malformations. The already listed organophosphorus pesticides, azinphos-methyl, dimethoate, malathion, and methidathion, were also evaluated, and no link was observed.

In a study of pesticide sprayers in Greece, use of glufosinate-ammonium was associated with elevated levels of serum 8-hydroxydeoxyguanosine (8-OHdG), a marker of oxidative stress-induced DNA damage. Glyphosate use, and use of already designated organophosphorus pesticides (chlorpyrifos, dimethoate, phosmet), were also evaluated in this study, but were not found to have an effect on serum 8-OHdG (Koureas et al., 2014).

In a case-control study in central California, Narayan et al. (2013) reported that frequent use of household products containing organophosphorus pesticides increased the odds of Parkinson's disease by 71%. The study involved assessing exposure retrospectively, based on self-reporting of historical household pesticide use by participants and additional research by the study authors on active ingredients in the products. The organophosphorus pesticides identified as being in the household products used included bensulide, chlorpyrifos, demeton, diazinon, dichlorvos, disulfoton, glufosinate-ammonium, glyphosate, malathion, methidathion, oxydemeton-methyl, parathion, and tetrachlorvinphos.

<u>Selected toxicity information – by individual pesticide</u>

Bensulide: In US EPA's (2016b) human health risk assessment for bensulide, neurotoxicity (via inhibition of red blood cell and brain acetylcholinesterase) was identified as the most sensitive toxic effect. Recent *in vitro* findings for bensulide are described in the section below ("Additional laboratory and *in vitro* studies").

Ethephon: US EPA (2015a) reviewed toxicity data for ethephon in their human health risk assessment for registration review, and reported that it inhibited red blood cell and plasma cholinesterase and induced bacterial mutagenesis. Toxicity studies of ethephon that we located in the literature are briefly outlined here. El Raouf and Girgis (2011) found that pregnant mice and their fetuses exposed to ethephon via drinking water had increased chromosomal aberrations, decreased brain cholinesterase activity, and altered biochemistry. Wang et al. (2017) reported that ethephon affected the developing immune system in mice treated via gavage. Ethephon has also been found to inhibit human and mouse plasma cholinesterases (Haux et al., 2002; Liyasova et al., 2013). In a rat *ex-vivo* study, chlorpyrifos and ethephon were found to have both single and combined effects on altered small intestine muscle contraction due to acetylcholinesterase inhibition (Çetinkaya and Baydan, 2010).

Ethoprop: DPR (1995) summarized the chronic effects of ethoprop, which included brain cholinesterase inhibition in mice and rats treated via diet, and hepatoxicity in dogs administered oral capsules containing the pesticide. US EPA (2008a) conducted a scoping human health assessment for registration review, describing similar toxic effects as DPR. US EPA (2008a) also noted the classification of ethoprop as a likely human carcinogen. Recent *in vitro* findings for ethoprop are described in the section below ("Additional laboratory and *in vitro* studies").

Fosetyl-aluminum: In long-term studies reviewed by US EPA (2014a), dogs exposed to fosetyl-aluminum developed testicular degeneration, and exposed rats displayed urinary tract effects. The European Food Safety Authority (EFSA) (2013) also described these effects, noting that they were observed at "higher doses". US EPA had previously classified fosetyl-aluminum as a possible human carcinogen based on bladder tumors observed in rats treated via diet at the highest dose only (40,000 ppm, then reduced to 30,000 ppm) (Quest et al., 1991); however, US EPA (2016a) now lists it as "not likely to be carcinogenic to humans" based on a 1999 evaluation.

Glufosinate-ammonium: In an updated human health risk assessment conducted to evaluate new uses of glufosinate-ammonium, US EPA (2012) provided a short summary of the toxicity data considered, including developmental toxicity and inhibition of brain glutamine synthetase in exposed rats. Some published studies on glufosinate-ammonium are described briefly here. Mice treated via intraperitoneal (IP) injection with glufosinate-ammonium developed structural changes in the brain and mild memory impairments (Calas et al., 2008; Meme et al., 2009). Laugeray et al. (2014) reported that intranasal exposure to glufosinate-ammonium during pre- and post-natal periods led to autism spectrum disorder-like behaviors in mice. Herzine et al. (2016) exposed mouse dams to glufosinate-ammonium via intranasal administration and evaluated brain tissues from the perinatally exposed mouse pups. The study authors found that perinatal exposure to glufosinate-ammonium altered neurogenesis. Watanabe and Iwase (1996) observed evidence of embryotoxicity in cultured mouse embryos treated with glufosinate-ammonium.

Glyphosate: The toxicity and carcinogenicity of glyphosate have been reviewed in a number of reports and publications (see for example, US EPA, 2009b; Mesnage et al., 2015; IARC, 2017b). Here we summarize some recent animal and *in vitro* studies of glyphosate's potential non-cancer effects. Kumar et al. (2014) reported that mice exposed to glyphosate via nasal aspiration while anesthetized developed increased airway inflammation. This study found that glyphosate-rich air samples collected from farms during spraying season also increased airway inflammation in mice. Proteomic analyses of mouse livers following exposure to a single IP injection of glyphosate revealed altered lipid metabolism pathways (Ford et al., 2017). Chłopecka et al. (2014) reported that glyphosate altered intestinal motor activity in a rat *ex-vivo* study. Studies of zebrafish exposed to glyphosate showed evidence of effects on the developing heart and brain (Roy et al., 2016a; 2016b); other developmental effects (Zhang et al., 2017); reproductive effects (Lopes et al., 2014); and increased oxidative stress and decreased levels of brain and muscle acetylcholinesterase (though cholinesterase activity was not affected) (Lopes et al., 2017). In cell culture, glyphosate is a partial aromatase inhibitor (Benachour et al., 2007; Richard et al., 2005) and can alter DNA methylation (Kwiatkowska et al., 2017).

Tribufos: DPR (1998; 2004) summarized the chronic effects of tribufos exposure via the diet, which included brain cholinesterase inhibition in mice, rats, and dogs, and gastrointestinal and liver effects in mice and rats. US EPA (2009c) conducted a human health risk assessment of tribufos, describing similar toxic effects as DPR. US EPA (2009c) also noted the classification of tribufos as a likely carcinogen at high doses. Recent *in vitro* findings for tribufos are described in the section below.

<u>Additional laboratory and *in vitro* studies</u>

Studies have found that a number of organophosphorus pesticides, including chlorpyrifos, ethoprop, glyphosate, and tribufos, can disrupt lipid metabolism in treated mice (Ford et al., 2017 [also summarized above for glyphosate]; Medina-Cleghorn et al., 2014). These studies exposed the mice to the pesticides via a single IP injection.

Andersen et al. (2002) found that the highlighted organophosphorus pesticides ethephon and fosetyl-aluminum were not active in a screen of pesticide activity for estrogenicity, androgenicity, and aromatase activity in cell culture.

Based on the Endocrine Disruptor Screening Program (EDSP) Tier 1 results for ethoprop and glyphosate, US EPA (2015b; 2015c) did not recommend either compound for Tier 2 testing. No other highlighted organophosphorus pesticides were included in EDSP's Tier 1.

We consulted US EPA's high-throughput chemical Toxicity Forecaster (ToxCast™) Dashboard (Dix et al., 2007; Kavlock et al., 2012) for bioactivities of the highlighted organophosphorus pesticides. Of these, bensulide, ethephon, and ethoprop were tested in over 1,000 ToxCast assays. Bensulide was active in 169 ToxCast assays, including assays evaluating endocrine pathway effects, metabolic enzyme binding, and immune and inflammation targets. Ethephon was active in 11 assays, including assays evaluating DNA damage and altered cell cycle. Ethoprop was active in 28 assays, including assays evaluating upregulation of metabolic enzymes and immune and inflammation targets. We also consulted US EPA's Endocrine Disruptor Screening Program for the 21st Century (EDSP21) Dashboard, which contains data intended to assist with chemical prioritization for EDSP. Tribufos was evaluated in 26 assays testing for endocrine effects and was active in 2 assays measuring increased estrogen receptor activity.

Potential to biomonitor

Bioaccumulation and persistence:

OEHHA (2012) has specified a log octanol-water partition coefficient (log K_{ow}) of ≥ 4 as indicating potential for bioaccumulation. US EPA's (2016c) PBT Profiler tabulated experimental log K_{ow} values that are close to or above this benchmark for the following highlighted pesticides: bensulide (4.2), ethoprop (3.6), and tribufos (5.7). None of the highlighted pesticides had bioconcentration factors (BCFs) in fish above 1000, which is another indicator used to evaluate potential for bioaccumulation. US EPA (2015d) reported a BCF close to 1000 for tribufos (730 L/kg-whole fish), and stated that it may bioaccumulate in aquatic or terrestrial organisms. However, US EPA also noted that the metabolism and rapid elimination of tribufos are expected to mitigate the bioaccumulation concern.

Potential environmental persistence for the highlighted pesticides was examined by reviewing data on half-lives in environmental media, and selected findings are described below.

US EPA (2008b) indicated that bensulide dissipates primarily via aerobic soil metabolism, with a reported half-life of 1 year, and predicted that bensulide would be extremely persistent in terrestrial ecosystems. More recently, Antonious (2010) found that bensulide had a half-life of 27-44 days in field studies, depending on soil type.

US EPA (2015e) reported that the dissipation half-lives for ethoprop in soil field studies ranged from 3-60 days, which was more rapid than predicted based on the 100-day half-life measured for aerobic soil metabolism. US EPA concluded, based on studies across various media, that ethoprop is "moderately to strongly persistent in the environment." However, they also noted that there is significant uncertainty in the estimates of ethoprop's environmental half-lives, because of observed variability in persistence measured at different sites and potential impact of previous use history at the sites (US EPA, 2015e).

Laboratory and field studies have found that glufosinate-ammonium degrades in soil to 3-methylphosphinicopropionic acid (3-MPPA) (Smith, 1988; Smith and Belyk, 1989). US EPA (2014b) reported that glufosinate had field dissipation half-lives ranging from 8-17 days, which were comparable to aerobic soil metabolism rates. They also concluded that glufosinate residues may persist in aquatic environments, resulting in chronic exposure to aquatic organisms. Glufosinate is expected to remain primarily in the water column, rather than sediment, with concentrations decreasing over time via dilution and metabolic degradation (US EPA, 2014b).

WHO (1994) reported that the DT_{50} (the time required to dissipate to half the original concentration) for glyphosate in soil experiments was between 3 and 174 days, depending on soil and climate conditions; US EPA (2009d) reported similar information. More recently, Bento et al. (2016) found that glyphosate DT_{50} values in soil experiments varied between 1.5-53.5 days, noting that it persists up to 30 times longer in soil under cold and dry conditions. This study also reported soil DT_{50} values for AMPA (the degradate of glyphosate) ranging between 26.4-44.5 days. AMPA persisted in soil longer than glyphosate did, even under warm and moist conditions. Bento et al. (2017) characterized glyphosate and AMPA distribution in soil and found that the highest concentrations of both compounds were found in the smallest soil fractions (i.e., PM_{10} and less). In laboratory experiments, Mercurio et al. (2014) determined that the half-life of glyphosate in seawater ranged from 47-315 days, depending on light and temperature conditions.

DPR (2004) reported that tribufos had an estimated half-life of at least 60 days in soil, depending on soil type and anaerobic or aerobic conditions. US EPA (2015d) concluded that tribufos is persistent in aerobic and anaerobic soil, with a reported half-life of 745 days in a study of aerobic sandy loam soil. US EPA noted that tribufos appears to be “more persistent than is typical for most organophosphate chemicals.”

Metabolites and breakdown products:

Information on metabolites and/or environmental breakdown products located for the organophosphorus pesticides not already designated is summarized in Table 3 on the next page.

Table 3. Summary of metabolite and breakdown product information for highlighted organophosphorus pesticides

Organophosphorus pesticide	Metabolite/breakdown products	Reference
Bensulide	Rat metabolite and breakdown product: bensulide oxon	US EPA (2016b)
Ethephon	Major breakdown products: ethylene and phosphoric acid	Cunha et al. (2017); Maynard and Swan (1963)
Ethoprop	Major human and rat metabolite: O-ethyl-S-propyl phosphorothioate Other rat metabolites: O-ethyl phosphoric acid, S-propyl phosphorothioate, S,S-dipropyl phosphorodithioate, and ethyl phosphate	Lunchick et al. (2005); DPR (1995)
Fosetyl-al	Major plant metabolites: phosphonic acid and ethanol	EFSA (2013)
Glufosinate-ammonium	Major human metabolite and breakdown product: 3-MPPA	Aris and Leblanc (2011)
Glyphosate	Human metabolite, major plant metabolite, and breakdown product: AMPA Mouse metabolite: glyoxylate	Hoppe (2013); Borggaard and Gimsing (2008); Ford et al. (2017)
Tribufos	Proposed metabolites: S,S-dibutyl phosphorodithioate, S-butyl phosphorothioate, phosphate, n-butyl mercaptan, and others Breakdown product: 1-butane sulfonic acid	DPR (2004); US EPA (2015d)

Past biomonitoring studies:

Exposure to organophosphate pesticides has been demonstrated via measurement of non-specific dialkyl phosphate (DAP) metabolites in a wide range of biomonitoring studies (CDC, 2017; Barr et al., 2004; Bradman et al., 2005; 2015; Harley et al., 2016). Specific metabolites, including for chlorpyrifos and diazinon, have also been measured (CDC, 2017; Barr et al., 2005; Camann et al., 2013; Whyatt et al., 2003). Less biomonitoring data are available for the organophosphorus pesticides that are not currently on the list of designated chemicals. We briefly discuss below the biomonitoring studies located for the highlighted pesticides. Where appropriate, we converted units to µg/L for consistency.

Glyphosate and glufosinate-ammonium

A recent review summarizes a number of studies measuring glyphosate in human urine (Niemann et al., 2015). Various public health researchers have recently commented on the need for additional biomonitoring data on glyphosate, given its extensive use (Myers et al., 2016; Vandenberg et al., 2017). This section outlines selected studies that measured glyphosate and AMPA in a variety of matrices, including urine and serum, and one study that also included glufosinate-ammonium and its breakdown product 3-MPPA.

Adams et al. (2015) detected urinary glyphosate in 93% (n = 131) of samples collected from members of the US general population (average: 3.1 µg/L). The method detection limit was 0.2 µg/L. AMPA levels were not measured.

Curwin et al. (2007a) used an immunoassay approach to evaluate urinary glyphosate levels in members of 25 farm households (24 fathers, 24 mothers, and 66 children) and 25 non-farm households (23 fathers, 24 mothers, and 51 children) in samples collected in 2001 in Iowa. Up to 4 urine samples were collected per study participant. The limit of detection was 0.9 µg/L. Of the urine samples collected from farm households, detectable levels of glyphosate were found in 69 of 92 samples from fathers (DF: 75%; GM: 1.9 µg/L; range: 0.02-18 µg/L), 63 of 94 samples from mothers (DF: 67%; GM: 1.5 µg/L; range: 0.10-11 µg/L), and 191 of 235 samples from children (DF: 81%; GM: 2 µg/L; range: 0.022-18 µg/L). Of the urine samples collected from non-farm households, detectable levels of glyphosate were observed in 59 of 89 fathers (DF: 66%; GM: 1.4 µg/L; range: 0.13-5.4 µg/L), 60 of 93 mothers (DF: 65%; GM: 1.2 µg/L; range: 0.062-5 µg/L), and 160 of 182 children (DF: 88%; GM: 2.7 µg/L; range: 0.10-9.4 µg/L).

Acquavella et al. (2004) evaluated glyphosate levels in urine samples collected from South Carolina and Minnesota pesticide applicators (n = 48), their spouses (n = 48), and their children (n = 79). Urine samples were collected pre-application, on pesticide application day, and daily for 3 days post-application. The method detection limit for urinary glyphosate was 1 µg/L. Seven of 47 (15%) pesticide applicators had detectable pre-application urinary glyphosate levels. On pesticide application day, 29 applicators (60%) had detectable urinary glyphosate levels, ranging from 1-233 µg/L (GM: 3.2 µg/L). On post-application day 1, 23 (48%) of applicators had detectable urinary glyphosate levels, ranging from 1-126 µg/L (GM: 1.7 µg/L). On post-application day 2, 16 (33%) of applicators had detectable urinary glyphosate levels, ranging from 1-81 µg/L (GM: 1.1 µg/L). On post-application day 3, 13 (27%) of applicators had detectable urinary glyphosate levels, ranging from 1-68 µg/L (GM: 1.0 µg/L). The highest numbers of detectable levels for spouses and children were on application day, with 2 (4%) spouses having urinary glyphosate ranging from 1-2 µg/L, and 9 (12%) children having urinary glyphosate ranging from 1-29 µg/L. AMPA levels were not reported in this study.

Conrad et al. (2017) investigated time trends of glyphosate and AMPA in urine samples collected between 2001-2015 (n = 40 for each year samples were collected) and stored in the German Environmental Specimen Bank. The method LOQ was 0.1 µg/L. Sixteen (40%) of the samples collected in 2015 had quantifiable glyphosate (95th percentile: 0.45 µg/L; max: 0.57 µg/L), and 17 (42.5%) samples had quantifiable AMPA (95th percentile: 0.38 µg/L; max: 0.41 µg/L). In contrast, 4 (10%) and 6 (15%) of the samples collected in 2001 had quantifiable glyphosate (95th percentile: 0.26 µg/L; max: 0.40 µg/L) and AMPA (95th percentile: 0.25 µg/L; max: 0.29 µg/L) levels, respectively. The highest measured levels of glyphosate and AMPA were observed in 2013. For glyphosate, detected in 22 of 39 samples (56.4%), the 95th percentile concentration was 1.25 µg/L and the maximum was 2.8 µg/L. For AMPA, detected in 19 of 39 samples (48.7%) in 2013, the 95th percentile concentration was 1.54 µg/L and the maximum was 1.88 µg/L.

A subset of urine samples from 13 Danish mothers and 14 Danish child participants in the DEMOCOPHES (Demonstration of a study to Coordinate and Perform Human biomonitoring on a European Scale) project were evaluated for glyphosate using an immunoassay approach. Samples were collected in 2011-2012. The mean urinary glyphosate level in mothers was 1.28 µg/L (range: 0.49-3.22 µg/L) and the mean level in children was 1.96 µg/L (range: 0.85-3.31 µg/L). All samples evaluated for glyphosate had detectable levels and no difference in levels was observed between urban and rural residences (Knudsen et al., 2017).

Aris and Leblanc (2011) developed an analytical method to measure glyphosate, AMPA, glufosinate-ammonium, and 3-MPPA simultaneously in serum samples. They reported results for serum samples from pregnant women (n = 30), umbilical cords (n = 30), and non-pregnant women (n = 39) in Québec, Canada. The method detection limits for glyphosate, AMPA, glufosinate-ammonium, and 3-MPPA were 15, 10, 10, and 5 µg/L, respectively. Glyphosate, AMPA, and glufosinate-ammonium were not detected in serum samples collected from pregnant women or from umbilical cords. 3-MPPA was detected in 100% of the samples from pregnant women (mean: 120 µg/L; range: 21.9-417 µg/L) and from umbilical cords (mean: 57.2 µg/L; range: 8.8-193 µg/L). Of the non-pregnant women, 2 (5%) had detectable serum glyphosate (range: ND-93.6 µg/L), none had detectable serum AMPA, 7 (18%) had detectable glufosinate-ammonium (mean: 28.7 µg/L; range: ND-53.6 µg/L), and 26 (67%) had detectable 3-MPPA (mean: 84.1 µg/L; range: ND-337 µg/L).

Kongtip et al. (2017) measured glyphosate levels in serum samples collected from Thai women at childbirth (n = 82) and umbilical cord samples (n = 75). Of the serum samples collected from the women, 53.7% (n = 44) had glyphosate levels greater than the LOD of 0.4 µg/L. Of the umbilical cord serum samples analyzed, 49.3% (n = 37) had glyphosate levels greater than the LOD. The median levels of glyphosate measured were 17.5 µg/L (range: 0.2-189.1 µg/L) in the women and 0.2 µg/L (range: 0.2-94.9 µg/L) in the cord serum. AMPA was not measured in this study.

McGuire et al. (2016) tested for glyphosate and AMPA in breast milk (n = 41) and urine (n = 40) samples collected from 41 women living in Idaho and Washington. The LODs for glyphosate and AMPA in breast milk were both 1.0 µg/L, with LOQs of 10.0 µg/L for both analytes. The LODs and LOQs for glyphosate in urine were 0.02 and 0.10 µg/L, respectively; those for AMPA in urine were 0.03 and 0.10 µg/L, respectively. Glyphosate and AMPA were not detected in breast milk samples, but were detected in over 90% of the urine samples. Urinary levels of both were quantifiable in 72.5% (n = 29) of samples. The authors reported mean urinary glyphosate at 0.28 µg/L (SD: 0.38 µg/L; range: < LOD-1.93 µg/L) and mean urinary AMPA at 0.30 µg/L (SD: 0.33 µg/L; range: < LOD-1.33 µg/L).

Steinborn et al. (2016) tested for glyphosate in breast milk samples (n = 114) collected from German women in 2015. All glyphosate values in breast milk were below the reported LOD of 0.5 µg/L. AMPA was not measured in this study.

<u>Other highlighted organophosphorus pesticides</u>

Lunchick et al. (2005) measured ethoprop and its primary metabolite, O-ethyl-S-propyl phosphorothioate, in urine samples collected from pesticide applicators (n = 20) in Washington. Samples were collected on the day of ethoprop application and for each of the consecutive 3 days (total of 4 days of sample collection). None of the urine samples had ethoprop levels that exceeded the LOD of 1.6 µg/L, but the metabolite O-ethyl-S-propyl phosphorothioate was detected (reported as a total mass during the 4-day collection period; range of 4.2-982 µg).

In work conducted for a dissertation, Kuklenyik (2009) developed an analytical method to measure the parent chemicals for 39 organophosphorus pesticides in human serum. The pesticide panel included bensulide, ethoprop, and tribufos, and the LODs were 1.0, 85, and 27 ng/L, respectively. Kuklenyik applied the method to samples collected from farm workers using organophosphorus pesticides, but did not report those results.

Analytical considerations

The Environmental Health Laboratory (EHL) of the California Department of Public Health (one of Biomonitoring California's laboratories) has developed two analytical methods for organophosphate pesticides. EHL's universal pesticide method measures a number of specific urinary metabolites, including 3,5,6-trichloro-2-pyridinol (TCPy, a metabolite of chlorpyrifos and chlorpyrifos-methyl) and 2-isopropyl-6-methyl-4-pyrimidinol (IMPY, a metabolite of diazinon), using an isotope dilution high-performance liquid chromatography (HPLC)/tandem mass spectrometer (MS/MS) approach (Behniwal and She, 2017). The LOD for TCPy is 0.5 µg/L and for IMPY is 0.05 µg/L. EHL also measures four non-specific DAP metabolites in urine, using an isotope dilution gas chromatography (GC)/tandem mass spectrometer (MS/MS) method (Wang et al., 2013).

For Biomonitoring California to measure any of the highlighted organophosphorus pesticides, additional method development would be required.

Need to assess efficacy of public health action

Adding organophosphorus pesticides as a class to Biomonitoring California's list of designated chemicals would allow any member of the class to be included in a future study. The Program would have the flexibility to choose analytes appropriate to the particular scenario of interest. By measuring these pesticides in California residents, we can track the levels of exposure and how they change over time and by region. The results of biomonitoring studies can inform ongoing state efforts to reduce pesticide exposures of concern.

Attachment A: Organophosphate insecticides currently on the list of designated chemicals. Metabolites are shown indented underneath the parent compounds.

- Acephate
  - Methamidophos
- Azinphos methyl
  - Dimethyldithiophosphate
  - Dimethylphosphate
  - Dimethylthiophosphate
- Chlorethoxyphos
  - Diethylphosphate
  - Diethylthiophosphate
- Chlorpyrifos
  - Diethylphosphate
  - Diethylthiophosphate
  - 3,5,6-Trichloro-2-pyridinol (TCPy)
- Chlorpyrifos-methyl
  - Dimethylphosphate
  - Dimethylthiophosphate
  - 3,5,6-Trichloro-2-pyridinol (TCPy)
- Coumaphos
  - 3-Chloro-7-hydroxy-4-methyl-2H-chromen-2-one/ol
  - Diethylphosphate
  - Diethylthiophosphate
- Diazinon
  - Diethylphosphate
  - Diethylthiophosphate
  - 2-Isopropyl-4-methyl-6-hydoxypyrimidine
- Dichlorvos (DDVP)
  - Dimethylphosphate
- Dicrotophos
  - Dimethylphosphate
- Dimethoate
  - Dimethyldithiophosphate
  - Dimethylphosphate
  - Dimethylthiophosphate
  - Omethoate
- Disulfoton
  - Diethyldithiophosphate
  - Diethylphosphate
  - Diethylthiophosphate
- Ethion
  - Diethyldithiophosphate
  - Diethylphosphate
  - Diethylthiophosphate
- Fenitrothion
  - Dimethylphosphate
  - Dimethylthiophosphate
- Fenthion
  - Dimethylphosphate
  - Dimethylthiophosphate
- Isazophos-methyl
  - 5-Chloro-1,2-dihydro-1-isopropyl-[3H]-1,2,4-triazol-3-one
  - Dimethylphosphate
  - Dimethylthiophosphate
- Malathion
  - Dimethyldithiophosphate
  - Dimethylphosphate
  - Dimethylthiophosphate
  - Malathion dicarboxylic acid
- Methamidophos
- Methidathion
  - Dimethyldithiophosphate
  - Dimethylphosphate
  - Dimethylthiophosphate
- Methyl parathion
  - Dimethylphosphate
  - Dimethylthiophosphate
  - *p*-Nitrophenol
- Naled
  - Dimethylphosphate
- Oxydemeton-methyl
  - Dimethylphosphate
  - Dimethylthiophosphate
- Parathion (Ethyl parathion)
  - Diethylphosphate
  - Diethylthiophosphate
  - *p*-Nitrophenol
- Phorate
  - Diethyldithiophosphate
  - Diethylphosphate
  - Diethylthiophosphate
- Phosmet (Imidan)
  - Dimethyldithiophosphate
  - Dimethylphosphate
  - Dimethylthiophosphate
- Pirimiphos-methyl
  - 2-(Diethylamino)-6-methylpyrimidin-4-ol/one
  - Dimethylphosphate
  - Dimethylthiophosphate
- Sulfotepp
  - Diethylphosphate
  - Diethylthiophosphate
- Temephos
  - Dimethylphosphate
  - Dimethylthiophosphate
- Terbufos
  - Diethyldithiophosphate
  - Diethylphosphate
  - Diethylthiophosphate
- Tetrachlorvinphos
  - Dimethylphosphate

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