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A scoping review to determine if adverse human health effects are associated with use of organophosphates for mosquito control

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Abstract

Organophosphate insecticides are widely used for adult mosquito control. Although proven effective in reducing mosquito populations and limiting arbovirus transmission, public concern exists regarding potential human health effects associated with organophosphate exposure. The aim of this scoping review was to describe any reported human health conditions associated with organophosphates during their use for adult mosquito control in the United States and Canada. Original peer-reviewed articles published in English language journals from 1 January 2000 to 22 May 2024, were obtained by searching from the databases MEDLINE, EMBASE, Agricultural & Environmental Science Collection, CAB Abstracts, and Scopus. The search identified 6,154 screened articles. Following an independent review, 10 studies were identified that described human health conditions associated with organophosphate exposure during adult mosquito control applications. Of the 10 included studies, only two articles were published within the last 11 years (2013 to 22 May 2024). Three types of study design were represented in the included studies: cohort ($n = 5$), case study ($n = 1$), and risk assessment ($n = 4$). The included studies could not determine causality between exposure to adulticides and development of illness or adverse impacts. Exposure to organophosphates did not contribute to an observed increase in metabolic toxicity, hospitalization rates, or self-reported symptoms and exposure. The available and limited evidence indicates that organophosphates can be used safely to control nuisance mosquitoes or mosquitoes that transmit arboviruses. Continued research regarding the human health effects

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Supplementary data

Supplementary data are available at *Journal of Medical Entomology* online.

associated with organophosphate applications for adult mosquito control could help evaluate the basis of the public's concerns and inform public health decision-making.

Keywords

adulticide; ultra-low volume; malathion; naled; integrated mosquito management

Introduction

The organophosphate class of insecticides (e.g., malathion, naled) have been used for decades and are registered by the Environmental Protection Agency (EPA) and commonly used for adult mosquito control in the United States (Centers for Disease Control and Prevention 2023b, Environmental Protection Agency 2023a). Organophosphates cause mosquito death by inactivating acetylcholinesterase, which in turn leads to accumulation of acetylcholine, neurological dysfunction, and subsequent death (Fukuto 1990, Centers for Disease Control and Prevention 2023b, Robb and Baker 2023). In humans, organophosphate toxicity is well-documented and associated with increased saliva and tear production, diarrhea, nausea, vomiting, sweating, muscle tremors, and confusion. However, symptoms associated with organophosphate human toxicity occur following substantially higher exposure levels compared with doses used for typical mosquito control (Institute of Medicine (US) Committee on Health Effects Associated with Exposures During the Gulf War 2000, Mendes et al. 2018, Chen et al. 2019, Aroniadou-Anderjaska et al. 2020).

During arboviral disease outbreaks, the most efficient and effective way to limit the number of mosquitoes that can spread viruses is through the application of adulticides, such as organophosphates (Bonds 2012, Centers for Disease Control and Prevention 2020, Environmental Protection Agency 2022). In the United States, EPA-registered adulticides are typically applied through ground or aerial ultra-low volume (ULV) spraying whereby ULV diffusers aerosolize droplets of insecticide to kill flying mosquitoes on contact (Environmental Protection Agency 2022). The ULV applications of insecticides allow for large geographical coverage using the minimum effective volumes to reduce the resultant risks that adulticides can pose for human, animal, and environmental health (Bonds 2012, Environmental Protection Agency 2022). Although the amount of organophosphates applied nationally for adult mosquito control is not known, the use of organophosphates is likely somewhat common given that mosquito control programs often preferentially use pyrethroids, and 49% of mosquito control programs reported conducting both larviciding and adulticiding, and 3% reported conducting only adulticiding (National Association of County and City Health Officials 2017).

In the United States, multiple arboviruses can cause illness through endemic and travel-associated infections including eastern equine encephalitis, La Crosse, St. Louis encephalitis, West Nile, dengue, and Zika viruses (Beckham and Tyler 2015, Fagre et al. 2023). Most notably, West Nile virus (WNV) is consistently the leading cause of domestically-acquired arboviral disease in the United States with over 56,500 human cases and 2,700 deaths reported since its introduction in 1999 (Centers for Disease Control and

Prevention 2023a). Modern-day advancements in global transportation systems, arthropod adaptation to urban environments, viral mutations, land perturbation, and climate change have contributed to the widespread and rapid emergence of arboviruses (Liang et al. 2015, Gould et al. 2017). In addition, the lack of vaccines or therapeutics for the majority of arboviral diseases including WNV disease (Gould et al. 2023), and the limited adherence to personal protective measures (Haenchen et al. 2016), makes effective mosquito control a critical tool to prevent arboviral diseases.

The rise in arboviral disease outbreaks has led to increased ground and aerial applications in regions that previously did not require mosquito control (19). Additionally, control measures in areas known for high mosquito populations have also intensified (Peterson et al. 2006). The practice and increased use of adulticide spraying have raised concerns among the public about the safety and risks of insecticide use (Rampold et al. 2020). The purpose of this review was to describe the currently available evidence of any reported adverse human health effects associated with organophosphates applied for adult mosquito control. By summarizing any potential health effects associated with organophosphate adulticide exposure, steps can be taken to mitigate potential risk or perceived risk, inform the use of evidence-based mosquito control, and prompt future research directions and guidelines.

Materials and Methods

PRISMA-ScR

Our scoping review was performed according to the PRISMA extension for scoping reviews (PRISMA-ScR) and accompanying checklist from Tricco et al. (2018). In Supplementary Appendix 1, we provide a guide to which pages address the specified “reporting items” from the PRISMA-ScR checklist. The protocol for this review was registered with Open Science Framework (<https://doi.org/10.17605/OSF.IO/H8JZQ>).

Search Strategy

Original peer-reviewed articles published in English language journals from 1 January 2000 to 22 May 2024, were obtained through a comprehensive literature search from the bibliographic databases MEDLINE, EMBASE, Agricultural & Environmental Science Collection, CAB Abstracts, and Scopus. The final search strategy for all databases can be found in Supplementary Appendix 2.

Data Collection and Storage

All identified articles from the searches were transferred to screening and data extraction software (Covidence Systematic Review Software, Veritas Health Innovation, Melbourne, Australia), and duplicates were removed. The search of all databases yielded 6,154 potentially relevant articles.

Identification of Relevant Studies

Eligible articles were screened for inclusion and exclusion criteria (Table 1). To be eligible for inclusion, the original peer-reviewed articles had to meet five criteria developed by authors CRC and RJN. First, studies needed to have been conducted in the United States

or Canada. Mosquito control in other countries differs substantially in methodology in large part because of differing endemic mosquito species and lack of stringent regulations and guidelines concerning appropriate insecticide applications and were thus excluded (Carrasco et al. 2019, Gorris et al. 2021). Second, this review aims to classify exposure to specific insecticides used for adult mosquito control. Studies involving insecticides other than organophosphates (e.g., pyrethroids) were excluded. Articles that examined exposure to multiple insecticides that also included organophosphates were included, but only data related to organophosphate exposure were included. Third, studies that examined insecticide exposure via routes other than ground or aerial spraying (e.g., bed nets, indoor spraying, indoor coils) were excluded given these methods are not typically used for adult mosquito control in the United States or Canada. Fourth, studies needed to report a human health effect associated with exposure to select insecticides. Studies conducted in vitro and animal studies were excluded. Fifth, only peer-reviewed articles written in English were included. Nonsystematic and systematic review articles were included. Articles identified through the article screening process not included in the original literature search that also met inclusion criteria were included. Presentations, white papers, grey literature, abstracts, and trade articles were excluded.

Selection of Relevant Studies

A team of six independent reviewers screened all relevant studies from the literature search for potential inclusion using Covidence software. In the first round of screening, a team of five independent reviewers (ZT, SKL, NF, JR, and RJN) assessed titles and abstracts of all included records using the predefined inclusion and exclusion criteria (Table 1). Each record was independently screened by random combinations of two reviewers and any discrepancies in eligibility were resolved by a third reviewer (CRC). The final round of screening included full-text review for inclusion and exclusion criteria using the same protocol described for title/abstract screening.

Data Extraction from Included Studies

Data were extracted for selected articles and included the following: characteristics (e.g., title, date of publication, citation information, DOI), class of insecticide (e.g., organophosphate or pyrethrins/synthetic pyrethroids), setting characteristics (e.g., distribution methods, location, temperature, and weather conditions), methodology (e.g., type of study performed, aim of study, duration of study), participant information (e.g., population description, recruitment method, age, sex, comorbidities, subgroups), outcomes (e.g., outcome description, diagnostic criteria of outcome, risk estimates, power, sample size), data analysis, and key conclusions.

Results

Identification of Potential Studies

The searches from MEDLINE, EMBASE, Agricultural & Environmental Science Collection, CAB Abstracts, and Scopus databases, yielded 6,154 articles that led to screening of 6,125 titles and abstracts after the removal of duplicates (Fig. 1). A total of 44 articles were identified for full-text screening. Twenty articles were identified as relevant.

Of these, 11 articles were excluded because they lacked mention of organophosphates. An additional reference was identified from the reference list of an article during full-text review. Ultimately, a total of 10 articles were included in this scoping review (Centers for Disease Control and Prevention 2003, 2005, O'Sullivan et al. 2005, Peterson et al. 2006, Duprey et al. 2008, Scharf et al. 2008, Valcke et al. 2008, Schleier et al. 2009, 2015, Likos et al. 2016).

Characteristics of the Included Studies

Of the 10 included studies, only two articles were published within the last 11 years (1 January 2013–22 May 2024) (Schleier et al. 2015, Likos et al. 2016), and eight were published from 2000 to 2012 (Centers for Disease Control and Prevention 2003, 2005, O'Sullivan et al. 2005, Peterson et al. 2006, Duprey et al. 2008, Scharf et al. 2008, Valcke et al. 2008, Schleier et al. 2009).

The majority of analyzed studies were conducted within the United States ($n = 9$) (Centers for Disease Control and Prevention 2003, 2005, O'Sullivan et al. 2005, Peterson et al. 2006, Duprey et al. 2008, Scharf et al. 2008, Schleier et al. 2009, 2015, Likos et al. 2016); one study was conducted in Canada (Valcke et al. 2008). Of the studies conducted in the United States, data were included from Arizona, California, Florida, Louisiana, Michigan, New York, North Carolina, Oregon, Texas, Virginia, and Washington. Two separate studies reported data collected from multiple states (Centers for Disease Control and Prevention 2003, Likos et al. 2016). All other included studies only reported data from a single geographical location. Weather data from New York and Massachusetts were used for two risk assessment studies.

Method of Insecticide Application and Insecticides Used

All included studies had defined methods of insecticide application: ground application, or aerial spraying by helicopter or airplane. The ULV spraying methods were specified in eight studies (O'Sullivan et al. 2005, Peterson et al. 2006, Valcke et al. 2008, Schleier et al. 2009, 2015); two studies did not specify ULV methods but conducted spraying events in accordance with insecticide labeling and regulations from the U.S. EPA and Health Canada Pest Management Regulatory Agency (PMRA) (Centers for Disease Control and Prevention 2003, Scharf et al. 2008, Environmental Protection Agency 2023a). One study used absorption of aqueous malathion as a proxy to measure potential insecticide exposure from recreational swimming during aerial spraying (Scharf et al. 2008). Malathion and naled were used commonly for adult mosquito control and were mentioned in all included articles. Only two studies examined health effects associated with a single insecticide (e.g., either only malathion or only naled) (27, 31). The other eight studies examined insecticide exposures to a combination of malathion, naled, and other insecticides that were not organophosphates (Centers for Disease Control and Prevention 2003, 2005, O'Sullivan et al. 2005, Peterson et al. 2006, Duprey et al. 2008, Scharf et al. 2008, Valcke et al. 2008, Schleier et al. 2009, 2015, Likos et al. 2016).

Types of Methods and Design

Three types of study design were represented in the included studies: cohort ($n = 5$), case study ($n = 1$), and risk assessment ($n = 4$). The five cohort studies included both retrospective and prospective cohort studies.

Cohort

In Table 2, we summarize five articles describing the cohort studies evaluating human health effects as an outcome of organophosphate insecticide exposure (Centers for Disease Control and Prevention 2003, 2005, O'Sullivan et al. 2005, Duprey et al. 2008, Likos et al. 2016). Two studies were retrospective investigations that examined the severity of insecticide-related illness and injury and hospitalizations associated with asthma exacerbation following insecticide exposure (Centers for Disease Control and Prevention 2003, O'Sullivan et al. 2005). One cohort monitored exposure calls and emergency department (ED) visits associated with insecticide exposure before and after a spray event in 2016 (Likos et al. 2016). This study also compared historical data with data collected during the 2016 spray event for ED visits for asthma, reactive airway disease, wheezing, or shortness of breath. Two prospective cohort studies assessed urine levels of a nonspecific organophosphate metabolite, dimethyl phosphate (DMP), before and after a spray event (31, 32). Participants of each of the cohort studies, except for Duprey et al. and Centers for Disease Control and Prevention (CDC), were recruited through hospitalization records, poison information call center records, or state-based surveillance of acute insecticide-related illness and injury cases that matched residential zip codes with spray events (Centers for Disease Control and Prevention 2005, Duprey et al. 2008). Duprey et al. recruited participants through random households chosen within each proposed spray zone based on sample clustering (Duprey et al. 2008). The CDC study published in 2005 recruited individuals randomly chosen within census blocks marked for spraying (Centers for Disease Control and Prevention 2005). All participants in each of the cohort studies were living in residential areas exposed to spray events and ranged in age and sex from adult females (aged 18–76 years), adult males (18–76 years), youth (10–12 years), children (5–6 years), toddlers (2–3 years), and infants (0.5–1.5 years). No data were reported for children aged 1.5–2 years.

Case Study

In Table 3 we summarize the single case study. Scharf et al. examined the dermal absorption rate of malathion and conducted a simulation experiment to determine the potential health impact on recreational swimmers exposed to waters following a malathion application (Scharf et al. 2008). In this study, 20 volunteers ($n = 2$ female, $n = 18$ male) aged 25–50 years had dermal exposure to aqueous malathion and absorption rates were compared to a hazard index (HI). This study was used to extrapolate information to determine theoretical insecticide values that recreational swimmers might be exposed to after an aerial spraying event. In this single study, exposure to aqueous malathion in concentrations that could be expected during recreational swimming following an aerial spray event did not result in substantial dermal absorption in simulated test subjects.

Risk Assessment

In Table 4 we summarize four risk assessment studies (Peterson et al. 2006, Valcke et al. 2008, Schleier et al. 2009, 2015). Toxicological risk is often expressed as risk quotients (RQ), which are determined through simulated environmental concentrations, exposure routes, and known toxicity endpoints; RQ values below 1.0 signify levels not warranting regulatory concern (Environmental Protection Agency 2023b). The exposure pathways range from acute to subchronic exposures, encompassing various scenarios such as inhalation, dermal exposure from spray deposition, hand-to-mouth exposure, and ingestion of garden produce, among others.

The four referenced studies assess risk to human health linked to insecticide use in mosquito control, focusing on different exposure routes and demographics (Peterson et al. 2006, Valcke et al. 2008, Schleier et al. 2009, 2015). They employed Bayesian inference for RQ determination relating to health effects from organophosphate exposure. Setting it apart, the study presented in Schleier et al. 2015 is a meta-analysis that includes data from the other three studies (Schleier et al. 2015). Schleier et al. 2015 revised an earlier RQ estimation for adult males exposed to malathion from 0.02 to 0.41, integrating new insights from additional studies (Peterson et al. 2006, Valcke et al. 2008, Schleier et al. 2009, 2015).

The remaining three studies covered more than one insecticide but included malathion and naled. The studies analyzed exposure from both ground or aerial in silico ULV spraying, using the AERMOD/ISCST3 or AGDISP models that assessed for the potential of drift under specified atmospheric and operating conditions (Bilanin AJ et al. 1989, Teske ME et al. 2019), and assessed the risk across a range of ages (Table 4) (Peterson et al. 2006, Valcke et al. 2008, Schleier et al. 2009). Assumptions made for the ULV simulations and risk estimates were broadly comparable and included: (i) all chemicals had a 24-h half-life in air; (ii) naled had an 18-h half-life; (iii) insecticides were applied at maximum application rates; and (iv) all insecticides were subject to the same weather conditions with no weather stress during the spray event.

Peterson et al. (19) indicated that aerial applications resulted in significantly lower deposition levels, denoting reduced human exposure and risk (Peterson et al. 2006). This contrasts with Valcke et al. (2008), who found increased risks with aerial spraying, likely due to increased application rates (Valcke et al. 2008). Notably, Peterson et al. did not publish their findings on aerial ULV (Peterson et al. 2006). The low risk assessed from aerial spraying found by Peterson is likely the reason why Schleier et al. (2009) only evaluated ground ULV risk.

Contrasting ground applications, Peterson and Valcke reported significantly different acute air concentrations at similar application rates ($9.76 \mu\text{g}/\text{m}^3$ vs. $159.6 \mu\text{g}/\text{m}^3$ for 61 g/ha and 63 g/ha, respectively) (Peterson et al. 2006, Valcke et al. 2008). This difference in air concentrations likely influenced RQs values, although final risk assessment requires consideration of more factors than application rates.

In Fig. 2 some reported RQ values for each population subgroup and exposure routes are outlined for the included studies. With the exception of acute and subchronic aerial exposure

for infants and toddlers reported in Valcke et al. (2008), all other reported RQ's were less than 1.0 (Peterson et al. 2006, Schleier et al. 2009, 2015). The RQ values >1.0 may indicate possible adverse health effects. Unfortunately, methodological differences (19, 24, 25, 26) make direct comparison among the studies challenging. Furthermore, age is used as a proxy for body weight and exposure behaviors, and the age categories (infant, toddler, etc.) are not the same.

Characteristics of Health-Related Effects Assessed by Included Studies

Poison Control Center and State-Based Insecticide Poisoning Surveillance

Programs—Of the included studies, one article examined insecticide exposure through monitoring calls to poison information centers (Likos et al. 2016). Likos et al. reported in the periods after ULV naled spraying events, a total of seven self-reported exposure calls were reported to the Florida Poison Information Center (Likos et al. 2016). Four of these calls included reports of symptoms such as vomiting, eye irritation, dizziness, vertigo, and edema. No data were reported that compared the number of poison control center calls before ULV spraying events or following other historical ULV sprayings. Given the lack of systematic data surrounding these self-reports, it is difficult to draw meaningful conclusions.

Another study identified 133 cases of acute insecticide-related illness potentially associated with mosquito control through state-based insecticide poisoning surveillance programs (Centers for Disease Control and Prevention 2003). Of the total mosquito-control insecticide-related illness cases identified, malathion and naled contributed to 48.1% and 17.3% of total cases, respectively. This study further classified the identified cases on a severity index in which malathion and naled cases were associated with illnesses of moderate to low severity. The cases reported in this study were associated with respiratory, neurological, gastrointestinal, ocular, dermal, cardiovascular, renal-genitourinary, and other miscellaneous illnesses.

ED Visits/Hospitalizations—ED visits and hospitalizations were reported in two included studies (O'Sullivan et al. 2005, Likos et al. 2016). The ED visits and hospitalizations for acute asthma exacerbation, reactive airway disease, wheezing, and shortness of breath were recorded for duration of spray events and compared with previous years' data. Likos et al. reported that ED visits were unchanged from the number of visits before spraying (Likos et al. 2016). Data comparison from the previous two years revealed the percentage of ED visits for the four conditions or symptoms (asthma exacerbation, reactive airway disease, wheezing, and shortness of breath) were similar on a week-by-week basis. O'Sullivan et al. specifically reported ED visits caused by acute asthma exacerbation for pediatric and adult visits (O'Sullivan et al. 2005). There were no significant differences in admission rates for asthma per day on the dates prior to and following a spray event compared with the average asthma admission rate for either adult or pediatric cases.

DMP/Absorption Values—DMP is a product of metabolized organophosphates and is readily excreted in urine within a few days of exposure (Barr et al. 2004). DMP indicates exposure to organophosphates; however, the correlation between measurable DMP values and potential adverse health effects remains unexplored (Barr et al. 2004). Duprey et al.

reported no increases in urinary DMP in urine samples collected after spray events compared with samples collected before spray events (Duprey et al. 2008). In this analysis, some participants reported several non-specific health-related symptoms that included nausea, vomiting, diarrhea, abdominal cramps, headaches, and trembling, but symptoms were more often reported before spraying than after. Notably, some participants engaged in activities that could contribute to increases in urinary DMP (i.e., applying flea and tick prevention treatments on pets or the lawn); however, these activities were more often reported before spraying occurred than after. Most urine samples collected were below the limit of detection (LOD) of 0.5 micrograms/L. Only the final collection period following the last spray event produced a median level of DMP of 1.85 micrograms/L, substantially below the 95th percentile of background level DMP of 13 micrograms/L (Barr et al. 2004).

Results from a CDC report published in 2005, also found no significant increases in urinary DMP in urine samples after ULV insecticide sprayings in North Carolina and Virginia in 2003 (Centers for Disease Control and Prevention 2005). In the North Carolina cohort, participants were exposed to ULV naled and permethrin. DMP was detected in 46% of prespray urine samples and 49% of postspray samples in North Carolina (LOD = 0.5 micrograms/L). In Virginia, participants were exposed to ULV naled and d-phenothrin and DMP was detected in 42% of prespray samples and 48% in postspray samples (LOD = 0.5 micrograms/L).

Absorption of aqueous malathion was also examined as a possible route of exposure and health effect associated with adult mosquito control. Scharf et al. measured skin dosage of malathion absorbed and derived permeability across skin (K_p -malathion) values among volunteers experimentally exposed to aqueous malathion (Scharf et al. 2008). The study reported the mean K_p -malathion values were 0.0005 L/cm²/h (range: 0.0–0.0051 L/cm²/h). Using K_p -values, HI values were extrapolated for theoretical 3-h swimming pool exposure to 30 ppb malathion + 30 ppb malaoxon. Malaoxon is the oxidized form of malathion when dissolved in bodies of water (Scharf et al. 2008). The HI model assumes participants absorbed all malathion in the exposure tank (12 µg/kg/day) and is compared to the Reference Exposure Level for malathion (200 µg/kg/day) for an HI of 0.6. The mean theoretically derived HI value for adult swimmers was 0.21 and for a child swimmer was 0.29. This laboratory-simulated experiment revealed that aqueous malathion resulting from aerial ULV spraying events would not be appreciably absorbed and did not meet levels of regulatory concern.

Discussion

This scoping review used standard systematic review methods to identify, select, and synthesize findings from 10 studies that reported health effects associated with organophosphates used for adult mosquito control in the United States and Canada (Centers for Disease Control and Prevention 2003, 2005, O’Sullivan et al. 2005, Peterson et al. 2006, Duprey et al. 2008, Scharf et al. 2008, Valcke et al. 2008, Schleier et al. 2009, 2015, Likos et al. 2016). We documented the current state of published literature that assessed health effects associated with organophosphates applied for adult mosquito control by describing the methodology of insecticide applications, quantification and severity of exposure, and

key findings. The results of this review identified evidence from 10 publications that when taken together indicated organophosphates used for mosquito adulticiding do not contribute substantially to increased metabolic toxicity in humans, increases in self-reported symptoms or conditions, hospitalization rates, or known risk to human health (Centers for Disease Control and Prevention 2003, 2005, O'Sullivan et al. 2005, Peterson et al. 2006, Duprey et al. 2008, Scharf et al. 2008, Valcke et al. 2008, Schleier et al. 2009, 2015, Likos et al. 2016). These conclusions are consistent with those from a contemporaneously published systematic review article that assessed the human health effects with the organophosphate naled and its major degrade dichlorvos (Mendoza et al. 2023). Although this review article included four of the same studies as in our scoping review (Centers for Disease Control and Prevention 2005, Peterson et al. 2006, Duprey et al. 2008, Schleier et al. 2009), it differed by also including studies involving occupational exposures, private pesticide applicator exposure, agricultural pesticide applicator exposure, and ingestion of pesticides through foods.

The resulting search and screening of peer-reviewed articles from the past 23 years only yielded 10 relevant studies, with most studies conducted before 2010 (Centers for Disease Control and Prevention 2003, 2005, O'Sullivan et al. 2005, Peterson et al. 2006, Duprey et al. 2008, Scharf et al. 2008, Valcke et al. 2008, Schleier et al. 2009, 2015, Likos et al. 2016). Many of the included studies were published around times of arboviral disease outbreaks. It is possible that more attention is given by the general public and researchers to adulticide applications and their potential health effects during times of outbreak control compared with adulticide applications for other intentions, like arboviral disease prevention or nuisance mosquito control. Because of the limited number and scope of the included studies, additional research with stronger study designs could help further elucidate any potential relationships between insecticide exposure and health effects. Planning robust studies well in advance of future adulticide applications that can be implemented on short notice will be important to provide additional and more definitive evidence about health effects in the general population following adulticide applications.

Two routes of metabolic toxicity were measured within the included studies (Centers for Disease Control and Prevention 2003, Duprey et al. 2008, Scharf et al. 2008). Urinary DMP and dermal absorption of malathion data were analyzed. No significant increases to DMP levels occurred following organophosphate spray events and dermal absorption of malathion in a laboratory setting were below relevant reference exposure levels of concern. Although these two indicators of organophosphate exposure can be helpful, these measurements cannot be broadly applied to the various human exposure routes following insecticide spray events. Continued research into methods that quantify insecticide exposure through noninvasive sampling in various populations would provide additional understanding of human exposures to organophosphates during wide-area use of adulticides.

Data describing persons who report symptoms to call centers and poison control centers is useful for assessing potential health effects following specific spray events. Cases of illness identified through insecticide exposure surveillance programs identified respiratory, neurological, and gastrointestinal illnesses potentially associated with insecticide exposure (Centers for Disease Control and Prevention 2003, Likos et al. 2016). The CDC report in 2003 classified cases suspected or linked to malathion or naled exposure to have moderate

to low severity (Centers for Disease Control and Prevention 2003). Although case studies can be helpful, exposure data can be affected by recall or reporting biases, for instance awareness of mosquito control applications could influence healthcare-seeking behaviors. This was illustrated by studies that did not observe significant differences in the number of calls after organophosphate spraying events compared with before the events (Likos et al. 2016). Development of robust surveillance systems that includes pre-event monitoring could be implemented to detect potential illnesses associated with spray events and could help improve understanding of the relationship between any health effects and adulticide exposures.

ED and hospitalization rates for asthma and reactive airway disease did not change significantly before, during, or after organophosphate spray events (O'Sullivan et al. 2005, Likos et al. 2016). While the included studies were limited to cases related to asthma and reactive airway disease, notably other respiratory, dermal, neurological, gastrointestinal, and other illness types have been reported to be associated with high levels of organophosphate exposure (Robb and Baker 2023). These reported toxicological responses to organophosphate exposure far exceed the levels used in EPA-approved ULV spraying events (Bonds 2012, Environmental Protection Agency 2022, Robb and Baker 2023). The ED cases identified by O'Sullivan et al. and Likos et al. would not have detected persons who suffered illness but did not seek care or those who visited outpatient clinics but were not transferred to the ED or hospitalized. In addition, exposures from household or occupational use of insecticides during times of high mosquito activity could contribute to human illnesses that make assessing illnesses caused by public health use of adulticides challenging. Duprey et al. reported in a household survey conducted before and after a spray event, 18.2% of respondents reported handling pesticides before spraying compared with 8.4% after spraying (Duprey et al. 2008). Further research is needed to determine if hospitalization data for illness and injury associated with insecticide exposure can be further characterized by home use or environmental exposures to organophosphates.

In our study, which included four risk assessments, three reported RQs below levels of concern (Peterson et al. 2006, Schleier et al. 2009, 2015). However, the study by Valcke et al. found RQs greater than 1.0 (Valcke et al. 2008); this was specifically for age categories in the 0 to 11 years range who were exposed to malathion following acute aerial spraying. RQs > 1.0 were also reported for subchronic exposures for age categories in the 0–4 years range. The EPA made similar observations, but only for acute aerial exposure for children aged 1–2 years; all exposures from ground applications are considered by the EPA to not pose a risk (Environmental Protection Agency 2016).

According to the EPA, for a child aged 1–2 years to experience an exposure that would result in an RQ > 1.0, each of the following conditions must be met: (a) live in an area directly treated; (b) maximum labeled rate is applied (3 fluid ounce product/Acre) while using the largest droplet size and at the lowest application height (100 ft); (c) weather is calm and nothing hinders the deposition on the ground (e.g., trees); (d) residues deposited do not dissipate (despite known rapid dissipation); (e) on the day of treatment the child engages in rigorous play outside in the treated area resulting in high skin exposure and high rate of contact; and (f) aerial deposition of malathion on the ground should be greater than 0.46

$\mu\text{g}/\text{cm}^2$. Notably, $0.46 \mu\text{g}/\text{cm}^2$ is approximately one-half of the concentration used in the Valcke et al. aerial scenario ($0.905 \mu\text{g}/\text{cm}^2$) (Valcke et al. 2008).

Notably, RQs for adults were modeled with age ranges that varied from 18 to 65 years. Within such a wide range in the age category, various levels of health and comorbidities could affect potential susceptibility to illness and injury caused by insecticide exposure. Further research on risks to populations such as children, elderly, and those with immunocompromising conditions, should be considered.

The potential morbidity, mortality, healthcare costs, and societal costs, caused by arboviral diseases should be considered when assessing the risk of potential health effects associated with adulticide spray events. For WNV, during 1999–2022, 28,684 cases of WNV neuroinvasive disease and 2,641 WNV-related deaths were reported in the United States (Centers for Disease Control and Prevention 2023a). The estimated hospitalization costs for each WNV neuroinvasive disease case is over \$142,000 (Snyder et al. 2021); this equates to an estimated cost of about \$3.2 billion in hospitalization costs since 1999. These estimates do not account for productivity lost by the patient or their caretakers, or long-term costs related to disability (Barber et al. 2010). For adults, when considering health outcomes of WNV exposure versus insecticide exposure as part of community spraying, the likelihood for severe outcomes from WNV exposure is substantially greater than for insecticide exposure (Peterson et al. 2006). Considering available data regarding the human health impacts, WNV poses a substantially higher risk to human health than organophosphate use as part of integrated mosquito management.

Limitations

This analysis is subject to several limitations. First, considering that organophosphates are commonly used for vector control, we only identified 10 studies relating to exposure to organophosphates with reported human health effects. Within those 10 studies, only two organophosphates were represented, malathion and naled. Other organophosphates (i.e., chlorpyrifos) have historically been used; however, given changes in organophosphate manufacturing and subsequent use, malathion and naled are the organophosphates used predominately for adult mosquito control. Secondly, the studies included in this review could not determine causality between exposure to adulticides and development of illness. Insecticide exposure often occurs alongside exposure to other chemicals or environmental factors that can influence health outcomes. Failing to account for these potential confounding factors can obscure the true relationship between insecticides and health effects. Finally, we only considered published articles without assessing the existing evidence in grey literature and other sources. The nonconsideration of grey literature and other sources restricts our findings to what was reported by scientific journals and identified in this literature search and could possibly prevent analysis of relevant cases that were rejected for publication or reported in other forums.

Conclusion

In summary, this scoping review indicates that according to available and limited evidence, no clear association exists between organophosphates used for adult mosquito control

applied according to EPA label instructions and human health risk. This review also highlights the need for developing guidance for assessing potential health effects following adult mosquito control in a community. Continued research regarding the human health effects of insecticide applications can help evaluate the basis of the public's concerns and provide meaningful insight to public health decision-making. Overall, the available evidence indicates that organophosphates can be used safely for adult mosquito control.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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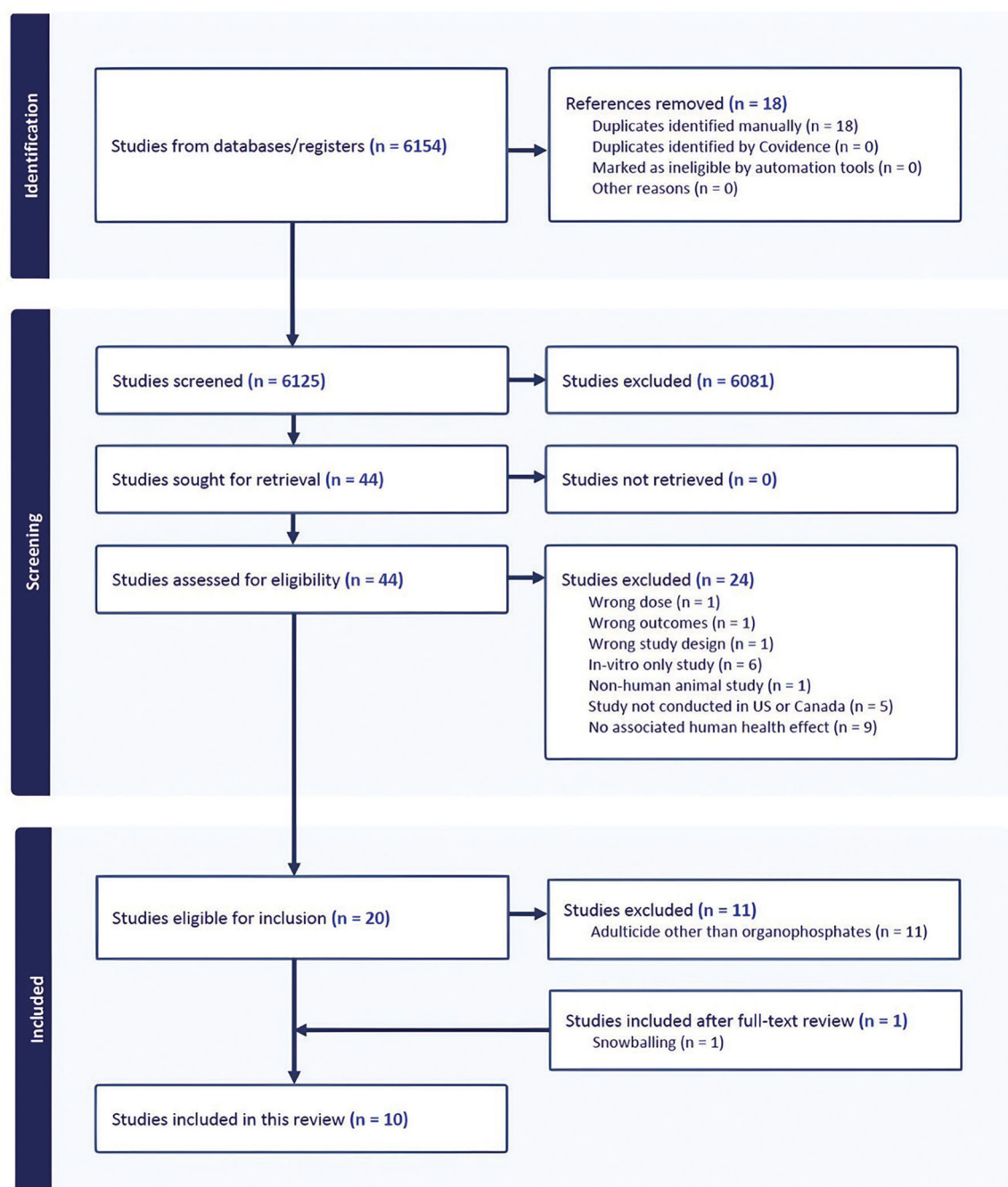


Fig. 1.
Flowchart of article selection with exclusion criteria.

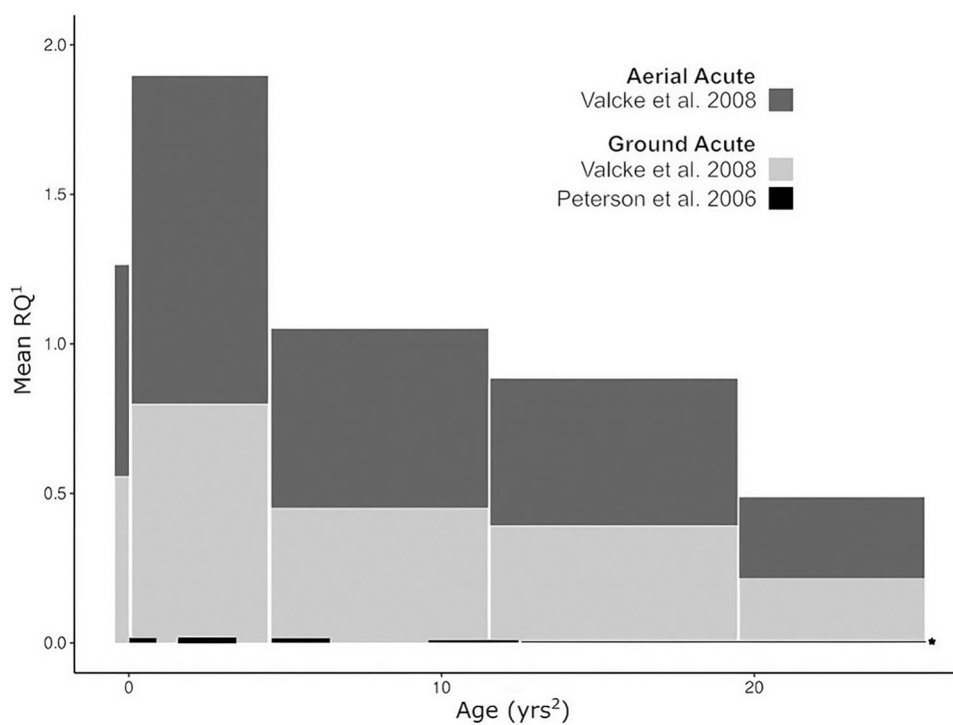


Fig. 2.
Summary of risk quotients reported.

Table 1.
Inclusion and exclusion criteria followed during title/abstract and full-text review screenings of eligible articles

Criteria subgroup	Inclusion	Exclusion
Location	Study conducted in United States or Canada	Studies conducted outside of United States or Canada
Insecticide used	Organophosphates: naled, malathion, chlorpyrifos	Studies involving insecticides that are not organophosphates (e.g., pyrethroids, organochlorines)
Insecticide application method	Ground or aerial spraying (e.g., ultra-low volume)	Bed nets, indoor spraying, indoor coils
Human health association	Studies that report human-health effect associated with organophosphates used for adult mosquito control	In vitro or animal studies
Article format	English language, published, nonsystematic & systematic review articles included	Presentations, white papers, grey literature, abstracts, and trade articles

Cohort studies evaluating human health effects associated with organophosphate exposure

Table 2.

Study	Study design	Insecticide(s) & application method(s)	Participants/population, sample size, location(s), duration	Outcome & unit of measurement	Findings
CDC 2003	Cohort study (retrospective)	Insecticide(s): Malathion, sumithrin [*] , resmethrin [*] ; Application method(s): Ground & aerial spraying	Participants/population: Residents in areas that conducted spraying with national case definition for insecticide poisoning (<i>n</i> = 133); Location(s): Arizona, California, Florida, Louisiana, Michigan, New York, Oregon, Texas and Washington; Duration: April 1999–September 2002	Outcome(s): Identified ocular, dermal, cardiovascular, renal–genitourinary, miscellaneous cases linked with exposure to insecticide use; Unit of measurement: Severity Index	Using the Severity Index for use in State-based Surveillance of Acute Insecticide-Related Illness and Injury, malathion and naled cases were associated with illnesses of moderate to low severity.
CDC 2005	Cohort study (prospective)	Insecticide(s): Naled, permethrin [*] , d-phenothrin [*] ; Application Method(s): ULV ^a aerial & ground spraying	Participants/population: Residents randomly selected from census blocks marked for spraying. North Carolina <i>n</i> = 75, Virginia <i>n</i> = 83. Location(s): North Carolina and Virginia Duration: September 30, 2003.	Outcomes(s): Urine sampling/testing for nonspecific organophosphate metabolite dimethylphosphate (DMP) compared to baseline; Unit of measurement: LOD DMP = 0.5 µg/L	Concentrations for all pre and post-spray pesticide metabolites were low. The findings did not indicate an overall increase in pesticide metabolite concentrations after mosquito control spraying events.
Duprey et al. 2008	Cohort study (prospective)	Insecticide(s): Naled; Application method(s): ULV ^a aerial spraying	Participants/population: Residents in the 5 proposed spray zones (<i>n</i> = 205), Location(s): St. Johns County, Florida; Duration: October 2–7, 2004	Outcomes(s): Urine sampling/testing for nonspecific organophosphate metabolite dimethylphosphate (DMP); Unit of measurement: LOD DMP = 0.5 µg/L (DMP < LOD = non detectable)	Aerial application of naled for large-scale mosquito control did not contribute to detectable urinary DMP levels in the study population.
Likos et al. 2016	Cohort study (prospective/retrospective)	Insecticide(s): Naled, sumithrin [*] , prallethrin [*] ; Btl [*] Application method(s): ULV ^a aerial & ground spraying	Participants/population: Residents in 4 zip-code areas with spraying and had an insecticide-related illness and reported to poison information centers (<i>n</i> = 7) or ED ^b visits; Location(s): Miami-Dade County, Florida; Duration: January 1, 2011–August 17, 2016	Outcomes(s): Exposure calls from Florida Poison Information Center or identified asthma, reactive airway disease, wheezing or shortness of breath ED ^b cases linked with exposure to insecticide use; Unit of measurement: insecticide-related illness and injury, yes/no	The total ED ^b patient visits in the 4 zip code areas with spraying were unchanged from number of visits before spraying. Patient visits for asthma, reactive airway disease, wheezing, or shortness of breath remained similar—compared week-week, and during the past 2 years before spraying.
O'Sullivan et al. 2005	Cohort study (retrospective)	Insecticide(s): Malathion, resmethrin [*] ; Application method(s): ULV ^a aerial & ground spraying	Participants/population: Asthmatic children and adults residing in spray areas who sought outpatient and inpatient ED ^b care (<i>n</i> = 1,318); Location(s): South Bronx, New York City, New York; Duration: August 1, 1999–September 30, 1999	Outcomes(s): Hospital visits and hospitalization of acute exacerbation of asthma symptoms; Unit of measurement: asthma attack, yes/no	No significant increases in hospital admissions or acute outpatient asthma care during nonspraying and spraying days in 1999 compared with ED data from 1997 and 1998

^{*} Insecticides that are not organophosphates and thus excluded from analysis.

^a Ultra-low volume.

^b Emergency department.

^c *Bacillus thuringiensis* subspecies *israelensis*.

Table 3.
Case study evaluating human health effects associated with organophosphate exposure

Study	Study design	Insecticide(s) & application method(s)	Participants/population, location(s), duration	Outcome & unit of measurement	Findings
Scharf et al. 2008	Case study	Insecticide(s): Malathion; Application method(s): Dermal application in laboratory setting	Participants/population: Volunteer subjects (<i>n</i> = 20)/hands and forearms exposed to aqueous malathion solution at 50 ppb; Location(s): n/a; Duration: 30–120 min	Outcomes(s): Dermal absorption of malathion; Unit of measurement: Hazard Index (HI) derived from Kp-malathion (HI max = 12 mcg/kg/day)	Exposure to aqueous malathion at concentrations expected following usual aerial applications not appreciably absorbed in test subjects.

Table 4. Simulated risk assessments evaluating human health toxicological risk associated with organophosphate exposure

Study	Risk assessment method	Insecticide(s), model application method(s), spray events	Population model, location/ weather model	Outcome(s)	Findings
Peterson et al. 2006	In silico ULV (air: AERMOD; deposition: ISCST3).	Insecticide(s): Malathion, naled, permethrin [*] , pyrethrin [*] , resmethrin [*] , phenothrin [*] , PBO ^a [*] ; Model application method(s): truck mounted ULV ^b /spraying; Spray events = 1 for acute exposure; 10 for subacute exposure	Population model: Adult males (> 18 yrs ^c), adult reproductive females (13–54 yrs ^c), infants (0.5–1.5 yrs ^c) & children (2–3, 5–6, 10–12 yrs ^c); Location/weather model: Albany, NY & Salem, MA	Outcomes(s): Acute & subchronic: inhalation exposure, dermal exposure from spray deposition, hand-to-mouth exposure from spray deposition on hands, ingestion of garden produce	Each subgroup from acute or subchronic outcomes had RQ ^d < 1.0. Health risks from residential exposure to mosquito adulticides were low and not likely to exceed levels of concern.
Schleier et al. 2009	In silico ULV (air: AERMOD; deposition: ISCST3)	Insecticide(s): Malathion, Naled, phenothrin [*] , resmethrin [*] , PBO ^a [*] , pyrethrins [*] ; Application method(s): truck mounted ULV ^b ; Spray events = 1 for acute exposure	Population Model: Adult males and adult females (18–65 yrs ^c), youth (10–12 yrs ^c), children (5–6 yrs ^c), toddlers (2–3 yrs ^c), infants (0.5–1.5 yrs ^c); Location/weather model: Albany, NY 1988	Outcomes(s): acute inhalation, dermal, and dietary and nondietary ingestion exposure	RQ ^d for malathion and naled below the RQ ^d level of concern
Schleier et al. 2015	Meta-analysis of eleven previous studies.	Insecticide(s): Malathion, permethrin [*] ; Application method(s): ULV ^b ; Spray Events = n/a	Population model Adult males; Location/weather model: n/a	Outcomes(s): Toxicological risk	The probability that exposure to malathion or permethrin after ULV ^b would exceed levels of concern was less than 0.0001
Valcke et al. 2008	In silico ULV (air deposition: AGDISP)	Insecticide(s): Malathion; Application method(s): aerial and ground ULV ^b ; Spray events = 7	Population model: Adult (> 19 yrs ^c), adolescents (> 11–19 yrs ^c), children (> 4–11 yrs ^c), toddlers (> 0.5–4 yrs ^c), infants (0–0.5 yrs ^c); Location/weather model: Quebec, Canada	Outcomes(s): Acute and subchronic exposure to malathion after aerial spraying	After aerial spraying RQ ^d means were > 1.0 for infants (acute = 1.27; subchronic = 1.12) and toddlers (acute = 1.87; subchronic = 1.62) and children (acute = 1.05)

* Insecticides that are not organophosphates and thus excluded from analysis in this review.

^a Piperonyl butoxide.

^b Ultra-low volume.

^c Years.

^d Risk quotient—RQ < 1.0 is below level of regulatory concern (Environmental Protection Agency 2023b).