
Institute for Environment and Health

# A REVIEW OF THE EFFECTS OF LOW-LEVEL EXPOSURE TO ORGANOPHOSPHATE PESTICIDES ON FETAL AND CHILDHOOD HEALTH

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# Contents

# Executive Summary

Organophosphates (OPs) are used in the UK as general purpose insecticides, agricultural and horticultural pesticides and veterinary medicines. They are also used in human medicines, and in various public hygiene products for use both by professional operators and the general public (POST, 1998). Other organophosphorus esters are used as lubricants and plasticisers.

The Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) produced a report in 1999 that reviewed the available data on the health effects of low-level exposure to OPs, focusing on whether OPs as a class of pesticides produced neurotoxic effects following low-level exposure. The report concluded that there was little evidence for such an effect but recognised that there were some uncertainties, for example with regard to possible susceptible groups. A number of recommendations were made and were considered at an open meeting held early in 2000, where it was suggested that there was a need to specifically review the data available for infants and children. The aim of this report is to determine from the published literature whether there is any evidence that low-level exposure to OP pesticides induces reproductive effects and/or developmental effects in the fetus and the child.

Despite a comprehensive search of the literature, and consideration of the 'grey' literature, only six epidemiology studies were identified. Three of five studies found no association between low-level exposure to OP pesticides and adverse health effects such as miscarriage, pre-term delivery, small-for-gestational-age births, congenital malformations (such as nervous system, cardiovascular defects, oral clefts, hypospadias or epispadias), musculoskeletal defects and non-specific anomalies. One study reported a significant association between low-level exposure to the OP pesticide malathion and gastrointestinal anomalies for second trimester exposures. However the difference in aetiology of the two dominating defects (four trachaoesophageal fistulas and seven pyloric stenoses) and their association with second trimester exposure casts doubt on the true significance of these reported effects; the anomalies must be analysed separately to investigate this possible link further. A small study of nine agricultural workers found an association between OP pesticide metabolite levels in urine and increased frequency of sperm aneuploidies. This however was a preliminary study with a very small sample size and no firm conclusions can be drawn at this time.

The main focus of this review relates to human health effects identified in epidemiology studies. It was not our remit to consider the large amount of experimental animal data from reproductive toxicity studies submitted to the regulatory agencies on specific OP pesticides. However, some published animal data involving exposure of neonates or young animals were considered to give an indication of potential health effects that may not have been looked for or detected in humans. Some key points to emerge from these animal studies were:

- although younger animals are more sensitive than adults to acute high-dose toxicity from some, but not all, organophosphates, they can be less sensitive to general systemic effects following low and intermittent exposures due to their greater ability to replenish acetylcholine levels;
- both fetuses and infant animals may be more susceptible to developmental effects due to their relatively immature nervous systems which might respond differently to mature systems, and may show irreversible effects; and
- some specific agents, such as chlorpyrifos, appear to produce behavioural effects in adults after neonatal exposure to levels that have no such effect in adults. This effect may be mediated by novel mechanisms that are not directly related to acetylcholinesterase inhibition. This may be a class effect of OP pesticides, but there is insufficient information in the published literature to draw any definite conclusions.

Although this review is primarily concerned with the health effects of OP compounds, exposure from OP pesticides to the fetus and infants in the UK was also reviewed to put the toxicological findings in context. Data from the USA suggest that exposure to OP pesticides could potentially begin *in utero*, although further research is needed in order to understand better the relevance of these results to UK exposures. Fruit, vegetables and cereal products are probably the main source of exposure to OP pesticides for infants and children older than 6months. However, the available data indicate that exposure to individual OP pesticides from individual food items is usually well below the acceptable daily intake. Other contributory sources of exposure could potentially include the use of human and veterinary medicines, the application of OP pesticides in and around the home, exposure from agricultural applications of OP pesticides, and para-occupational exposure from parents who work with OP compounds. Further research is required to quantify long-term exposure of children to OPs in the UK and to assess the relative contribution of the individual sources.

The biomarker studies available were reviewed and suggest that children are exposed to OP compounds at low levels. The sources of such exposure are difficult to interpret from such studies, mainly because the sample sizes of the studies were relatively small. However, diet is assumed to be an important contribution to overall exposure, and probably accounts for the high proportion of children having detectable OP pesticide residues in their urine in Europe and the USA. There is some evidence to suggest that factors influencing exposure could include age, garden use of pesticides, proximity of a household to agricultural spraying, parental occupation, and whether the household is in an urban or non-urban area.

In conclusion, there is inadequate information from epidemiological studies to enable any firm conclusions to be drawn regarding effects of OPs on fetal or childhood health. From the limited number of epidemiology studies identified following an extensive literature search, there is no evidence of adverse health effects in the fetus or child, except for the findings of two limited studies that suggest exposure to OP pesticides might be associated with gastrointestinal anomalies and sperm aneuploidies, although these observations require further investigation before any definite conclusions can be drawn. Data from the animal studies suggest that a number of biological systems, not all cholinergically regulated, appear to be affected by OP pesticides, but the biological significance of this is unclear. There are two ongoing studies in the USA examining adverse effects in children (including neurodevelopmental and behavioural problems) arising from exposure to OP pesticides. The results of these investigations will help in assessments of the need, and/or determine priorities, for further health-related research, although a number of UK exposure-related aspects could be progressed independently of this. Some potential areas for further research are outlined.

# 1 General Introduction

## 1.1 Background

The Department for Environment, Food and Rural Affairs (DEFRA; formerly the Department of Environment, Transport and the Regions), the Health and Safety Executive (HSE) and the Department of Health (DH) are jointly funding a programme of research to address topics identified for further study following publication of a report on organophosphates (OPs) by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT, 1999). This COT report considered whether single, prolonged or repeated exposure to low doses of organophosphate compounds can cause long-term adverse health effects. Effects on human health suspected of being common to these compounds in general (i.e. class effects) were considered rather than compound-specific effects; in particular there was a focus on neurotoxicity. Following the publication of this report a workshop* was held in March 2000 to develop strategic research questions. Among the questions raised, the participants considered the possibility that children might be particularly vulnerable to health effects following exposure to OP pesticides. It was noted that a comprehensive review of the developmental toxicity of OP pesticides had not been carried out and attention was given to a possible link between pre- and postnatal exposure to OPs and subsequent cognitive impairment. A number of strategic research requirements were developed, including a requirement for a literature review to determine whether there is any evidence for potential effects in fetuses and infants following low-level exposure to OPs.

The aim of this literature review is to examine the available evidence for reproductive and developmental effects resulting from low-level exposure to OP pesticides in fetuses, infants and children. For the purpose of this review, low-level exposure is defined as exposure which is either short or long term that does not induce acute effects of OPs. Therefore this review does not include the well-documented acute neurotoxicity, intermediate syndrome and OP-induced polyneuropathy that follows acetylcholinesterase inhibition but, where evident, will include other class effects.

## 1.2 Organophosphate compounds

Organophosphate compounds include all compounds in which a phosphate group or phosphate derivative is part of an organic molecule (COT, 1999). Organophosphates are usually esters, amides, or thiol derivatives of phosphoric acid and most have the same general formula (see Figure 1).

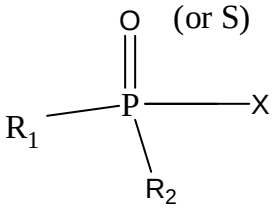


**Figure 1 General formula of an organophosphate compound**

The P=O-containing structure is sometimes referred to as the oxon and the P=S structure as the thion. The double-bonded atom may be oxygen or sulphur, and related compounds would, for example, be called phosphates or phosphorothioates (the nomenclature thiophosphate or thionophosphate is now less used; WHO, 1986; COT, 1999). The $R_1$ and $R_2$ groups are usually simple alkyl or aryl groups,

* Department of Health (2000) *Proceedings from Workshop on Research on Organophosphates, 28 March 2000*, available [May 2002] at www.doh.gov.uk/opwkshop.htm

both of which may be bonded directly to phosphorus (in phosphinates), or linked via –O–, or –S– (in phosphates), or $R_1$ may be bonded directly and $R_2$ bonded via one of the above groups (in phosphonates). The group X can be any one of a wide variety of substituted and branched aliphatic, aromatic or heterocyclic groups linked to phosphorus via a bond of some lability (usually –O– or –S–) and is referred to as the leaving group.

In the UK, OPs are used as general purpose insecticides and agricultural and horticultural pesticides, and in veterinary medicines. They are also used in human medicines, and in various public hygiene products for use by both professional operators and by the general public (POST, 1998). Other organophosphorus esters are used as lubricants and plasticisers. Organophosphorus warfare agents represent a further very specialised group. This review is concerned only with the organophosphorus pesticides, veterinary medicines and human medicines.

Currently there are 11 OP pesticides approved or licensed for use in the UK, and several others that were approved for use, but are now undergoing phased revocation*. These are used in agriculture to protect crops from harmful pests, and as non-agricultural pesticides for the control of pests in the home, garden and other non-agricultural environments. There are also three OP compounds approved as veterinary medicines for the control of parasites on animals, and one OP compound approved as a human medicine for the control of head louse and scabies infestation. Table 1.1 lists the OP compounds currently approved or licensed in the UK and their areas of use, as of 01 April 2002.

**Table 1.1 Organophosphate compounds currently approved or licensed for use in the UK, as of 01 April 2002[a]**

| Organophosphate | Use | | | |
|---|---|---|---|---|
| | Agricultural pesticide | Non-agricultural pesticide | Veterinary medicine | Human medicine |
| Azamethiphos | ✔ | ✔ | ✔ | |
| Chlorpyrifos | ✔ | ✔ | | |
| Chlorpyrifos-methyl | ✔ | | | |
| Diazinon | | | ✔ | |
| Dichlorvos | ✔ [b] | ✔ [b] | | |
| Dimethoate | ✔ | | | |
| Ethoprophos | ✔ | | | |
| Fenitrothion | | ✔ | ✔ | |
| Fosthiazate | ✔ | | | |
| Malathion | ✔ | | | ✔ |
| Phosmet | | | ✔ | |
| Pirimiphos-methyl | ✔ | ✔ | | |
| Tolclofos-methyl | ✔ | | | |

[a] The UK Government is currently undertaking a review of all anticholinesterase compounds, which may lead to the use of some of these OP compounds being restricted or revoked

[b] Approvals for dichlorvos-containing pesticide products have been suspended following advice to ministers from the Advisory Committee on Pesticides in March 2002

* The process by which a pesticide product is withdrawn from the market as a result of it being voluntarily withdrawn for commercial reasons or as a result of its approval being revoked. This usually occurs over a period of about two years (PSD & HSE, 2001).

The UK Government is undertaking a review of all anticholinesterase pesticide compounds to ensure they meet current safety standards[*]. The review has already led to several OP pesticides being withdrawn from the market and the use of several others being restricted. As the review is still on-going, it may lead to the restriction of use or revocation of approval of other OP compounds. Similarly, veterinary and human medicines containing OP compounds (which are considered under separate legislation from pesticides) are also being reviewed.

Following exposure to OP compounds, absorption occurs through the skin, mucus membranes, the gastrointestinal tract and by inhalation. OPs are lipophilic and once absorbed into the body have a large volume of distribution, the plasma component of which represents only a small proportion of the whole. Clearance from body compartments can show substantial variation and redistribution may occur (WHO, 1986; Jamal, 1997).

The accepted general 'class effects' of OP pesticides fall into three main groups (COT, 1999):

- acute effects of acetylcholinesterase inhibition (the acute syndrome);
- delayed effects following inhibition of acetylcholinesterase (the intermediate syndrome); and
- delayed polyneuropathy.

Acute toxicity is produced by irreversible phosphorylation and inhibition of cholinesterases, leading to accumulation of acetylcholine at synapses. This produces cholinergic effects, causing over-stimulation and subsequent disruption of transmission of impulses across the synapses in the central, peripheral and autonomic systems, including the muscarinic and nicotinic receptors. The intermediate syndrome follows cholinergic signs of OP poisoning (IEH, 1998a). It is characterised by the development of proximal muscle weakness (proximal limb, neck, and respiratory muscles), which can lead to respiratory failure. The mechanisms causing this syndrome are not understood but it is thought that the symptoms are caused by temporary loss of muscle connections, probably as a result of excess excitation (POST, 1998). OP-induced delayed neuropathy is a specific neurotoxic effect observed 2–3 weeks after exposure; it is serious, can be irreversible and is not related to the effect on acetylcholinesterase. It is characterised by a distal distribution and delayed onset of polyneuropathy (Jamal, 1997; IEH, 1998a).

These neurological effects of OPs have been discussed widely in the published literature (WHO, 1986; IEH, 1998a) and are the subject of other projects within the DH–DEFRA–HSE OP research programme. The classic neurotoxic effects will not be considered further in this review, which is concerned with reproductive and developmental effects only.

# 1.3 Childhood and fetal susceptibility

## 1.3.1 Toxicological considerations

Fetuses and children may be more or less sensitive than adults, depending on the pesticide to which they are exposed. There are differences in the ability of fetuses and children to absorb, distribute around their body, activate, detoxify and excrete xenobiotic compounds (their metabolic rates are greater than those of adults), all of which can affect the toxicity of pesticides in these age groups. These processes can change rapidly during development and can counteract one another, therefore there is no simple way of predicting metabolic kinetics or sensitivity to compounds in infants and children from data derived entirely from adult humans, or from toxicity testing in adult or adolescent experimental animals (National Research Council, 1993).

[*] MAFF (1999) *MAFF News Release. 24 Pesticide Chemicals Up for Review*, available [May 2002] at: www.defra.gov.uk/news/newsrel/1998/980513e.htm

Fetuses and children are also different from adults in that their organs are undergoing continual growth and differentiation, processes that may be adversely affected by exposure to chemicals, including OPs. Compounds that have a low molecular weight and/or are lipophilic readily cross the placenta into the fetal circulation. Particular periods during the development of the nervous system are sensitive to environmental insults because they are dependent on the emergence of critical developmental processes, for example proliferation, migration, differentiation, and myelination. The developing brain is vulnerable to many agents and there is wide recognition that children are an especially vulnerable subpopulation because of this. For example, childhood exposure to lead has been associated with significant deficits in cognitive function in school children (IEH, 1998b).

Evidence suggests that neural development extends from the embryonic period through adolescence. Therefore it is possible that humans have greater vulnerability to the effects of some chemicals well into their teenage years. Of additional concern is the possibility that developmental exposure to neurotoxins may accelerate age-related decline in function (Rice & Barone, Jr., 2000). Furthermore it has been suggested that sub-clinical effects may lead to lifetime morbidity (Reigart & Roberts, 2001). This morbidity may occur in the absence of the acute poisoning symptoms that often dominate the consideration of pesticide effects on children and, although subtle (i.e. non-subjectively apparent), these effects might have a profound societal impact when amortised across the entire population and across the life span of an individual.

### 1.3.2 Exposure considerations

The exposure of infants and children to pesticides may differ considerably from those of adults, both qualitatively and quantitatively (National Research Council, 1993). This is a result of the specific dietary and behavioural characteristics of infants and children, which can predispose them to receiving pesticide exposures higher than those of adults. In particular, infants and children take in more calories from food per unit of body weight than do adults, and also eat a narrower range of foods than adults (National Research Council, 1993). Hence, infants and children will consume relatively more of certain foods and drinking water than adults that, on a body weight basis, could result in higher exposures of children to pesticide residues. The behavioural characteristics of infants and children may also influence their exposure. Infants and children spend more of their time in proximity to floors, carpets, and other surfaces (Lu *et al.*, 2001), with a greater proportion of their body surface area in contact with surfaces than adults. This may result in higher dermal exposures to pesticide residues associated with these surfaces. Infants and children also have more frequent and a greater duration of hand-to-mouth activity than do adults (Lu *et al.*, 2001), and have a higher soil (and presumably house dust) ingestion rate than adults (ECETOC, 2001). This may result in the ingestion of pesticide residues adsorbed to objects that are mouthed, or from soil or house dust. Finally, the breathing zone of a child is much closer to the ground than that of adults (Bearer, 1995). As a result heavier chemicals may be present at higher concentrations in these lower breathing zones, thus resulting in higher exposures of children. Overall, these factors result in an increased likelihood that children will receive higher exposures to pesticides, on a mg/kg body weight basis, than adults.

# 2 Methodology

An initial literature search and discussions with experts in the field indicated that the amount of published research on possible health effects of childhood/fetal exposure to low levels of organophosphate (OP) pesticides was likely to be extremely limited. For this reason it was essential that the search retrieved all of the available literature on the subject.

Literature searches were performed across the Medline, Embase, Biosis, Toxline, Cancerlit, and CA Search databases using appropriate database descriptors or search phrases for 'organophosphate pesticides' and 'children' (Table 2.1) and with a year limit of 1990 onwards. Abstracts for review and original articles were downloaded separately. Titles only, for articles published between 1980 and 1989 were also downloaded. In total over 700 abstracts and 700 titles were downloaded, however some duplicates exist between the searches. An automated 'alert' search was also set up to run on a monthly basis in order to identify newly published studies. This alert identified 149 abstracts. For further details see Annex 1.

**Table 2.1 Literature search descriptors**

| Database | Pesticides descriptors | Population descriptors |
|---|---|---|
| Medline, Toxline and CancerLit | ORGANOPHOSPHORUS-COMPOUNDS<br>ORGANOTHIOPHOSPHORUS-COMPOUNDS<br>INSECTICIDES-ORGANOPHOSPHATE | CHILD, FETUS, EMBRYO, PARENTS, PREGNANCY |
| Embase | ORGANOPHOSPHATE-PESTICIDE | CHILD, FETUS, EMBRYO, ADOLESCENT, NEWBORN |
| Biosis, CA Search | 'ORGANOPHOSPHORUS or ORGANOPHOSPHATE' in the same sentence as 'PESTICIDE or INSECTICIDE' | CHILD, CHILDREN, EMBRYO, FETUS, ADOLESCENCE, ADOLESCENT, NEWBORN, PREGNANCIES OR PREGNANCY, PARENT(S) |

A number of attempts were made to obtain 'grey literature' from industrial sources but these were unsuccessful. In addition, an international conference in Berlin, *Exposure of children to pesticides*, was attended in September 2001 in order to obtain any as yet unpublished data and information regarding ongoing research (see Section 6.2 for more details).

For the purposes of the review, fetal and childhood exposure data from the UK were used when available. However when UK data were unobtainable, data from other countries were considered and relevance to the UK assessed. For the review of health effects, data were taken from studies conducted anywhere in the world, as long as they were deemed to be of adequate quality.

The criteria for selecting studies of adverse health effects from the literature were that exposure was low level, potentially leading to health effects in the fetus and the child, as opposed to short-term exposures resulting in acute effects such as poisoning.

The emphasis of this review is on human health effects, but some animal data (retrieved from the literature using the descriptors in Table 2.1) were considered. The retrieved animal data are not the result of an extensive literature search but rather a brief review of some published studies in young or neonatal animals to give an indication of potential chronic health effects that may not have been looked for or detected in humans.

# 3 Health Effects of Low-level Exposure to Organophosphates in the Fetus and During Childhood

## 3.1 Introduction

A number of comprehensive reviews of the health effects of low-level exposure to organophosphate (OP) pesticides have been conducted for adults. One of the most widely recognised in the UK is the review of the health effects of OPs by the Department of Health's Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT, 1999). The COT concluded that the evidence for effects following prolonged low-level exposure was less convincing than that for neurological and neuropsychological findings following recognised poisoning incidents. In addition it was concluded that the balance of evidence does not support low-level exposure causing peripheral neuropathy or clinically significant neuropsychological effects; however, there were insufficient data relating to psychiatric illness to allow a conclusion to be made. The report did identify gaps in knowledge and further research was recommended to address these issues.

A number of epidemiological studies have been summarised in reviews by IEH (1998a) and Ray (1998). The majority, perhaps unsurprisingly, involved adults exposed occupationally. The main problem with the studies reviewed was that exposure was poorly characterised and confounders were not accounted for adequately. The authors concluded that some well-defined, and thus most reliable, studies failed to reveal any changes, and others revealed only subtle changes. However, where effects were observed, they were reversible, therefore casting doubt on reports of permanent long-term effects. The reports concluded that concerns about adverse health effects of low-level exposure to anti-acetylcholinesterases in general appear unwarranted, but there were insufficient data to rule out the possibility of subtle, agent-specific effects. In a comprehensive review by Eskenazi *et al.* (1999) it was stated that there are no data in children to support or refute the hypothesised health effects of chronic low-level pesticide exposure.

A thorough and comprehensive literature search was conducted to provide epidemiological evidence for a class health effect (reproductive or developmental) of low-level exposure to OPs in children and the fetus. However, it became apparent from the literature search that there are insufficient epidemiological data involving children to determine comprehensively whether a class effect exists, partly because the few studies that are available were conducted using only a few of the available OP compounds. Therefore data were also retrieved for health effects resulting from low-level exposure to individual OP pesticides.

Since other authors have reviewed neurological effects in adults it is not intended to repeat discussions that have already been published. As relatively few epidemiological studies were retrieved from the literature, this review progressed to examining experimental animal studies in order to determine whether there is any indication of a cause for concern for human health, and hence to allow a better judgement to be made with respect to the need for further research. There is an abundance of experimental animal data in the literature showing the effects of OP pesticides on the fetus, neonates and adult animals. However, most of these data relate to acute neurotoxic effects and therefore have not been considered in this review. Some animal studies were selected for review because they were published studies that investigated the effects of low-level exposure to OP pesticides in young animals.

The following sections review epidemiological data and some experimental animal data, in order to address the adverse health effects on the fetus and child of low-level exposure to OP pesticides. The last section of this chapter indicates some potential mechanisms of action of OP pesticides.

# 3.2 Human evidence

There is clear evidence for increased susceptibility of children to levels of exposure that are sufficiently high to evoke frank poisoning. Thus in an outbreak of poisoning due to flour contaminated with parathion, the highest death rate was in children under 5 years old (Diggory *et al.*, 1977). This finding is consistent with the lower levels of the organophosphate-hydrolysing A-esterases found in the blood of children under 1 year of age as compared with adult levels (Ecobichon & Stephenens, 1973).

## 3.2.1 Epidemiological studies

Although the following study by McConnell *et al.* (1999) was designed to observe acute health effects, it is pertinent to this review because of the long-term exposure and absence of acute health effects in the presence of statistically decreased cholinergic levels in the exposed children. This study examined sub-clinical health effects of environmental pesticide contamination in Nicaragua. A cross-sectional study was conducted using 82 children aged 5 to 12 years of age (mean, 7.3) living in one of the following three sites:

- a community adjacent to a large crop-dusting airport, through which run-off drains from the airport during the rainy season (June to December);
- two blocks of a community facing the airport, but protected from run-off by a road; or
- two blocks from a community on the other side of the city from the airport, presumed to be unexposed to pesticides.

Each house was visited and the parents were asked to bring all children of the appropriate age to a house in the corresponding community, where finger-stick blood samples were obtained and processed for levels of plasma acetylcholinesterase. Each child or the accompanying older sibling or adult was asked about the following seven symptoms compatible with cholinesterase inhibition during the week prior to the examination: headache, blurred vision, diarrhoea, nausea, vomiting, stomach ache, or excessive sweating. Water in the wells used for drinking water in each of the communities was tested for most of the pesticides that were reported to have been mixed and loaded at the airport.

As can be seen from Table 3.1, the children from the community where play could occur in the run-off had mean levels of cholinesterase significantly below those of the children in the unexposed community and the community with the intervening road. The difference between the communities with respect to the proportion of children with two or more symptoms suggestive of mild overexposure to cholinesterase inhibitors was not statistically significant. In the children from the community contaminated by pesticide run-off, there was no difference between the mean cholinesterase level among children with more than two symptoms and those with two or fewer symptoms.

**Table 3.1 Demographic characteristics and cholinesterase activity in children at three sites in Nicaragua**

| Characteristic | Community | | | | | |
|---|---|---|---|---|---|---|
| | Exposed to run-off N = 17 | | Exposed across road N = 22 | | Unexposed N = 43 | |
| Mean age (SD) | 7.3 | (2.2) | 7.8 | (2.4) | 8.2 | (2.2) |
| Sex | | | | | | |
| No. boys (%) | 11 | (65) | 10 | (45) | 24 | (56) |
| No. girls (%) | 6 | (35) | 12 | (55) | 19 | (44) |
| Mean cholinesterase[a,b] (SD) | 2.4 | (0.49) | 2.8 | (0.47) | 2.9 | (0.38) |
| Median cholinesterase[a,b] (range) | 2.4 | (1.6–3.8) | 2.8 | (1.8–3.8) | 2.8 | (2.1–3.7) |
| Relative risk of low cholinesterase activity (95% CI) | 15.2 | (3.4–68) | 4.6 | (0.53–39) | 0 | |
| Symptom prevalence[c] (%) | 4 | (24) | 6 | (27) | 14 | (33) |

Adapted from McConnell *et al* (1999)

CI, confidence interval; SD, standard deviation

[a] In International units/ml blood/min

[b] Three outlying cholinesterase measurements were not included in the analysis because they came from three siblings who had levels more than six standard deviations greater than the mean

[c] Two or more symptoms suggestive of mild overexposure to cholinesterase inhibitors (headache, nausea, or blurred vision)

Concentrations of cholinesterase-inhibiting OP insecticides in water samples are summarised in Table 3.2. McConnell *et al.* (1999) state that the concentrations of OP pesticide were not high in any of the samples. However, when compared with the mandatory drinking water limits within the EU (0.1 µg/l for individual pesticides and 0.5 µg/l for total pesticides), many of these levels are higher than would be permissible in the UK. The lowered levels of cholinesterase among children in the community exposed to run-off could be due to the children playing bare-footed in puddles grossly contaminated by run-off from the airport, or to drinking contaminated water. Other possible contributing factors might be inhalation of pesticide-impregnated dust from the airport, or pesticide residues in food.

**Table 3.2 Organophosphate pesticide contamination of well water at three sites in Nicaragua**

| Organophosphate pesticide | Concentration (µg/l) in drinking water sample | | |
|---|---|---|---|
| | Community exposed to run-off (well water) | Other two communities not exposed to run-off (city water) | Inside airport |
| Chlorpyrifos | 0.3 | n.d. | n.d. |
| Diazinon | 0.06 | n.d. | 0.08 |
| Fenthion | 4.5 | n.d. | n.d. |
| Fenthion sulfoxide | 1.4 | n.d. | n.d. |
| Mephosfolan | 1.2 | n.d. | 0.2 |
| Methyl parathion | 1.0 | n.d. | 0.7 |

Adapted from McConnell *et al* (1999)

n.d. not detectable (detection limit not given)

The authors concluded that observed symptoms, following exposure to OP pesticides, depend on the percentage inhibition from the individual's baseline levels and on the abruptness of the decline, rather than the absolute level of cholinesterase activity. The authors went on to suggest that chronically lowered cholinesterase might be associated with chronic health effects but that there are very few data that can support this, particularly for children.

In a review of the general toxicity of all pesticides Hayes and Laws (1991) stated that various reproductive outcomes have been investigated in human studies, but that these could only be associated with exposure to herbicides such as chlorinated hydrocarbons, and that no clearly positive result could be demonstrated. There were no studies on OP pesticides reported in the review by Hayes and Laws (1991). In addition, a review by Kitos and Suntornwat (1992) on the teratogenic effects of OP compounds in experimental animals (see Section 3.3.2) and humans, emphasised the absence of human data to show a causal relationship between exposure to OP pesticides and birth defects.

In a case–control study by Thomas *et al.* (1992), reproductive outcomes were investigated in relation to malathion spraying to control a fruit fly infestation in the San Francisco Bay area, between 1981 and 1982. The primary aim of the study was to test for an association between malathion exposure and spontaneous abortion; however, associations with stillbirth, congenital malformations and intrauterine growth retardation were also addressed. A cohort of 7450 pregnancies was studied, which excluded multiple pregnancies, pregnancies ending in an induced abortion and pregnant women less than 18 years of age. Cases (1126) of various adverse outcomes were identified, and exposures during pregnancy were compared with a random sample of all non-cases (1128) in the cohort. Cases were grouped under spontaneous abortion, stillbirth, intrauterine growth retardation, or reportable congenital anomalies. A number of adverse outcomes were not included in the analysis: 14 neonatal deaths without intrauterine growth retardation or anomalies, 48 ectopic pregnancies, and 171 non-reportable anomalies. In addition, there were 374 pregnancies for which the outcome was unknown. Of the 5987 normal births 1128 were randomly selected as controls. All cases and controls were mailed a questionnaire to obtain information on dates and outcomes of previous pregnancies, the addresses of all residences and employers during the pregnancies, and other potentially confounding factors. There was an attempt to contact all non-respondents by telephone. Response rates were comparable for live births, spontaneous abortions, and reportable anomalies, but were slightly lower for stillbirths and intrauterine growth retardation. For adverse outcomes that are diagnosed at birth the normal live births were used as controls. For adverse outcomes that occur throughout gestation a random sample of viable fetuses (at the time that the outcome occurred) were used as controls. The time-dependent nature of the exposure and outcomes was addressed using time-dependent covariates based upon weekly exposure indices. This was particularly important for spontaneous abortions and stillbirths because early termination of pregnancy precludes the further accumulation of exposure. Residential histories were converted to geographical coordinates in order to link them to spraying data. After adjustment for confounders (maternal age, alcohol consumption, previous miscarriages, cigarette smoking, indoor insecticide use, gestational age depending on the effect), the study found an association, although not statistically significant, between cumulative exposure to malathion and stillbirth (relative risk = 1.95; 95% CI, 0.88–4.35). However, the association only existed with cumulative exposure one month before death, and not with cumulative exposure to the time of death. This casts doubt on the biological plausibility of the association. The only reportable congenital anomalies with a statistically significant association with malathion exposure were gastrointestinal anomalies (pyloric stenosis, i.e. obstruction of pyloric orifice of the stomach) following exposure in the second trimester of pregnancy with an unadjusted relative risk of 3.29 (95% CI, 1.09–9.87) and an adjusted relative risk of 4.14 (95% CI, 1.01–16.6). Risk was adjusted for alcohol consumption, bottled water consumption, maternal age, and gestational age. The authors commented that "the defects that dominated this group (four tracheoesopohageal fistulas and seven pyloric stenoses) are unrelated in aetiology, the former having a first trimester origin that is plausibly related to exposure, the latter a second trimester origin." The difference in the aetiology of the defects and their association with second trimester exposure were not discussed further by the authors. The main weakness of this study was the use of residence histories as a surrogate for exposure of an individual, which would be likely to dilute the association between exposure and effects.

The 1986 Canadian Census of Agriculture served as a sampling frame for the selection of farms for the Ontario Farm Family Health Study (1991–1992). Using this data Savitz *et al.* (1997) investigated the association between male exposure to pesticides and pregnancy outcome. Ontario was chosen for the study because of the number and diversity of farm operations in the province. To be eligible, each couple had to be living year round on the study farm, the wife had to be 44 years of age or younger

and at least one member of the couple had to be working on the farm. Information on the farm operator, husband, wife, demography and lifestyle, pesticides currently and historically used on the farm and around the home, medical history and a complete reproductive history were collected using three questionnaires. Non-respondents were contacted for a telephone interview. All pregnancies were classified according to outcome. Pregnancies were excluded if the time interval of the pregnancy could not be determined (incompatible or missing dates of conception and delivery) if the pregnancy did not occur while the woman was living on the farm, or if it was unlikely that the study husband was the father. There was an analysis for risk of miscarriage, pre-term delivery and small-for-gestational-age births, and the sex ratios of offspring were determined. Stillbirths and other more rare outcomes were not addressed due to an insufficient number of couples in the sample. Using a checklist, men were asked about their farm activities over the five years preceding the interview. Five activities were assumed to involve direct exposure to pesticides, the mixing and applying of: crop herbicides, crop insecticides and fungicides, livestock chemicals, yard herbicides, and building pesticides. Farm activities consistent with potential for sperm-mediated effects that were undertaken by male workers in the period from three months before conception through to the month of conception were evaluated in relation to occurrence of miscarriage, pre-term delivery and small-for-gestational-age births. Subsets of men, defined by the combination of chemical activity reported by the husband and the use of specific chemicals reported to have occurred on the farm, were analysed in an attempt to link specific farm activities with specific chemical activities. However, this only gave a crude indication of exposure. From the 1898 couples interviewed, 3984 eligible pregnancies were included in the analysis. Although there were limitations in the exposure assessment, no associations were found between OP pesticide exposure and the reproductive endpoints (Table 3.3). Nor was the sex ratio of offspring associated with farm chemical activities, including those activities involving OP pesticides. The exposure assessment was the most important limitation of this study. For instance there was some overlap in exposures that could not be adjusted for, the amount of time spent mixing and applying pesticides could not be quantified, and the group designated 'unexposed' still lived on the farm and may have been exposed to levels of pesticides above background exposure. In addition, the authors could not be sure that observed effects (observed for other chemicals) were not due to maternal exposure.

**Table 3.3 Male farm worker activities and risk of pre-term delivery, miscarriage and small-for-gestational-age births related to organophosphate pesticide exposure[a] in the Ontario Farm Family Health Study**

| Activity[b] | Cases | Risk (per 100) | Unadjusted RR | Adjusted OR[c] | 95% CI |
|---|---|---|---|---|---|
| **Pre-term delivery** | | | | | |
| Controls | 31 | 3.2 | | | |
| Any chemical | 80 | 3.9 | 1.2 | 1.2 | 0.7–1.9 |
| Crop insecticides | 6 | 4.4 | 1.4 | 1.7 | 0.5–5.2 |
| Livestock chemicals | 5 | 10.0 | 3.1 | 2.7 | 0.7–11.0 |
| **Miscarriage** | | | | | |
| Controls | 102 | 9.5 | | | |
| Any chemical | 244 | 10.4 | 1.1 | 1.1 | 0.8-1.3 |
| Livestock chemicals | 7 | 11.1 | 1.2 | 0.9 | 0.3-2.4 |
| Building pesticides | 7 | 13.0 | 1.4 | 1.3 | 0.5-3.1 |
| **Small-for-gestational-age births** | | | | | |
| Controls | 69 | 7.3 | | | |
| Any chemical | 164 | 8.1 | 1.1 | 1.0 | 0.6-1.3 |
| Crop insecticides | 7 | 5.2 | 0.7 | 0.8 | 0.3-2.0 |

Adapted from Savitz *et al.* (1997)

CI, confidence interval; OR, odds ratio; RR, risk ratio

[a] This table contains results that relate to OP pesticides from a study that investigated the effects of several classes of pesticide.

[b] All the activities, except exposure to any chemical, relate to exposure to OP pesticides

[c] Adjusted for mother's age, mother's education, father's education, per capita income, mother's off-farm job, mother's ethnicity, mother's smoking during pregnancy, mother's caffeine use during pregnancy, primary language, and month of conception.

In a follow-up to the Savitz *et al.* (1997) study, Arbuckle *et al.* (2001) used the data from the Ontario farm families to explore further the critical windows of exposure, the target sites and interaction among the pesticides, and other risk factors for spontaneous abortion. Eligibility and exclusion criteria are the same as in the Savitz *et al.* study. The exposure assessment was intended to capture potential occupational and residential pesticide exposures; hence a history of monthly agricultural and residential pesticide use was constructed. OP pesticides were studied as a group but within the analysis there was no breakdown of this group into individual active ingredients. The husbands carried out most pesticide applications, and only 20% of wives reported that they had handled pesticides. Reproductive and pesticide exposure histories were merged to produce pesticide unit variables. Exposure to pesticides was analysed for two windows: preconception, the four-month period from three months before conception to the first calendar month of conception; and post-conception, the first trimester, for associations with early (<12 weeks) and late (12–19 weeks) spontaneous abortions. A total of 2110 women provided information on 3936 pregnancies, including a total of 395 spontaneous abortions. As can be seen in Table 3.4 no statistically significant association between OP pesticide exposure and spontaneous abortion was found in this group of individuals.

**Table 3.4 Spontaneous abortion risk and exposure to organophosphate (OP) pesticides in farm families in Ontario**

| Timing of exposure to OP pesticide | All gestational ages | Early abortion (<12 weeks) | | Late abortion (12–19 weeks) | |
|---|---|---|---|---|---|
| | Crude OR (95% CI) | No. of exposed cases* | Crude OR (95% CI) | No. of exposed cases* | Crude OR (95% CI) |
| Pre conception | 1.0 (0.7–1.4) | 24 | 1.0 (0.6–1.6) | 18 | 1.0 (0.6–1.7) |
| Post conception | 0.6 (0.4–1.0) | 10 | 0.5 (0.3–1.0) | 12 | 0.9 (0.5–1.5) |

Adapted from Arbuckle *et al.* (2001)

* The total number of cases of spontaneous abortion is 395, with 226 and 169 early and late abortions, respectively.

García *et al.* (1998) conducted a case–referent study on the relationship between occupational exposure to pesticides among agricultural workers and selected congenital defects in Valencia, Spain. The case and reference material was selected from 261 pairs matched at birth in eight hospitals over a period of two years (1993–1994). The referent population consisted of couples who resided in the catchment areas of the hospitals. The cases were identified through the discharge records of the hospitals, and consisted of live births up to the age of 1 year. The reference and cases were matched by hospital and date of birth at a ratio of 1 : 1. The parents of the case patients and the referents were interviewed to collect information about exposure to pesticides and potential confounding factors. Paternal exposure to pesticides and a possible association with the occurrence of congenital malformations (nervous system, cardiovascular defects, oral clefts, hypospadias or epispadias, musculoskeletal defects and non-specific anomalies) was investigated. Although of limited statistical power, no association was found between exposure to OP pesticides, the most frequently used active ingredients reported, and malformations (Table 3.5).

**Table 3.5 Risk of congenital malformations following paternal exposure to organophosphate pesticides in a study of children born in Valencia, Spain**

| | Cases[a] | Referents | Crude OR | 95% CI of the crude OR | Adjusted OR[b] | 95% CI of the adjusted OR |
|---|---|---|---|---|---|---|
| **Chemical class** | | | | | | |
| Organophosphate pesticides | 31 | 26 | 1.14 | 0.64–2.05 | 0.77 | 0.38-1.58 |
| Active ingredient c | | | | | | |
| Azinphos methyl | 6 | 8 | 0.71 | 0.23–2.25 | 0.46 | 0.11-2.03 |
| Dimethoate | 11 | 7 | 1.67 | 0.61–4.59 | 0.95 | 0.29-3.16 |
| Fosetil Al | 8 | 6 | 1.17 | 0.39–3.47 | 0.57 | 0.14-2.33 |
| Glyphosate | 20 | 15 | 1.23 | 0.59–2.56 | 0.94 | 0.37-2.34 |
| Malathion | 6 | 8 | 0.75 | 0.26–16 | 0.30 | 0.06-1.43 |
| Methidathion | 6 | 12 | 0.45 | 0.16–1.31 | 0.27 | 0.06-1.17 |

Adapted from García *et al,* 1998

CI, confidence interval; OR, odds ratio

[a] Number of interviewees reporting having handled the pesticide during the acute risk period

[b] Multivariate models were built for every class and active ingredient of pesticides by comparing individuals reporting exposure to the active ingredient during the acute risk period with those reporting no exposure to that particular active ingredient, and by adjusting for pat ernal (industrial worker, age >40) and maternal (spontaneous abortion, twins, drug consumption, heavy smoking, education and occupation) confounders

[c] The top ten most frequently quoted active ingredients were analysed for an association with congenital malformations. The remaining four were not OP pesticides

Recio *et al.* (2001) investigated the frequency of sperm aneuploidy for chromosomes X, Y and 18 and its relationship with urinary OP pesticide metabolites in agricultural workers. Nine healthy men were chosen from an agricultural community in Mexico, a community surrounded by agricultural fields whose main products were vegetables. They had no history of chemotherapy, radiotherapy or chronic illness. Four of the men were pesticide sprayers and the rest were agricultural workers who worked on the field, but were not directly involved with spraying pesticides. The participants had been resident on the farm for more than 15 years. The pesticides most frequently applied were methyl parathion, metamidophos, endosulfan and dimethoate. Two semen samples were collected from each participant: the first during crop preparation when small quantities of pesticides were sprayed (before the spraying season); the second at the beginning of the heavy spraying season when large quantities of pesticide were sprayed (during the spraying season). In addition, a spot urine sample was collected from each participant before semen sample collection and five OP pesticide metabolites (diethylphosphate (DEP), diethylthiophosphate (DETP), dimethylphosphate (DMP), dimethylthiophosphate (DMTP), and dimethyldithiophosphate (DMDTP)) were measured. Total dialkylphosphates (DAP) were calculated as the sum of the five metabolites. There were no differences in sperm parameters, such as concentration and motility, between the seasons. The most important finding, in this preliminary work, was the direct association between some OP pesticide metabolite levels in urine and increased frequency of sperm aneuploidies even after controlling for age and lifestyle. Aneuploidies were found in 0.67% of total sperm nuclei. The most frequent aneuploidy was the lack of a sex chromosome or sex null (0.19%), followed by XY18 (0.15%) and XY18-18 (0.06%). Poisson regression analysis using a generalised estimating equation showed significant associations between DEP ($\beta = 0.00022$; $p = 0.0001$) and sex null (Table 3.6). Smaller but still significant associations were also observed with DMTP and total DAP. The frequency of total aneuploidies was associated with DMDTP ($\beta = 0.00009$; $p = 0.0001$). This is a small preliminary study of only nine samples and further studies are required with larger populations to assess the significance of these findings.

**Table 3.6 Relationships between sperm aneuploidy frequencies and urinary organophosphate metabolites (OPm) in a study of agricultural workers in Mexico**

| | Sex null (n = 18) | | | XY18 (n = 18) | | |
|---|---|---|---|---|---|---|
| **OPm** | **ß [a]** | **RR** | **95% CI** | **ß[a]** | **RR** | **95% CI** |
| DMP | –0.006 | 0.99 | 0.97–1.02 | 0.017 | 1.02 | 1.00–1.04 |
| DEP | 0.22** | 1.36 | 1.18–1.55 | –0.11* | 0.86 | 0.73–1.00 |
| DMTP | 0.003* | 1.02 | 1.01–1.04 | –0.004 | 0.97 | 0.93–1.00 |
| DMDTP | 0.10 | 1.05 | 0.99–1.11 | –0.20* | 0.90 | 0.82–1.00 |
| DETP | –0.052 | 0.99 | 0.83–1.18 | 0.15 | 1.02 | 0.85–1.22 |
| Total DAP | 0.003* | 1.04 | 1.01–1.08 | –0.003 | 0.96 | 0.91–1.01 |

| | XY18-18 (n = 18) | | | Total aneuploidies (n = 18) | | |
|---|---|---|---|---|---|---|
| **OPm** | **ß[a]** | **RR** | **95% CI** | **ß[a]** | **RR** | **95% CI** |
| DMP | 0.001 | 1.00 | 0.07–1.03 | 0.004 | 1.00 | 1.00–1.01 |
| DEP | –0.14 | 0.82 | 0.66–1.02 | 0.012 | 1.02 | 0.95–1.09 |
| DMTP | 0.006 | 1.04 | 0.99–1.08 | 0.002 | 1.02 | 1.01–1.03 |
| DMDTP | –0.24* | 0.88 | 0.78–1.00 | 0.09 | 1.05 | 1.02–1.08 |
| DETP | 0.78 | 1.11 | 0.82–1.5 | –0.68 | 0.91 | 0.83–1.00 |
| Total DAP | –0.005 | 0.94 | 0.87–1.01 | 0.003 | 1.04 | 1.02–0.05 |

Adapted from Recio *et al.* 2001

CI, confidence interval; RR, relative risk.

Results were calculated from a generalized estimating equation with Poisson link. RRs were adjusted for age, alcohol intake and total sperm concentration. The interquartile ranges (75–25) used to calculate RRs were DMP: 969.2; DEP: 1381.1; DMTP: 6239.4; DMDTP: 513.1; DETP: 134.3; total DAP: 11821.4 (ppb)

[a] ß was multiplied by 1000, *$p$ <0.05, **$p$ <0.001

## 3.2.2 Case reports

Case reports are reports of effects in isolated individual subjects often with no reliable exposure estimates. No conclusions can be drawn regarding any causal relationship between effects described and exposure to OP pesticides. The case reports below are included in this review for completeness.

Sherman (1995) described case reports of four children. These case reports are given little weight in this review because they lack a reliable exposure estimate and it is not possible to exclude the possibility that these observations are chance findings. The exposure of three of the mothers to chlorpyrifos-containing products had occurred in the home, the fourth had been exposed at work. All were exposed in their first trimester of pregnancy. Two of the children studied were born to the same mother (whose first pregnancy had resulted in a healthy child); this family had used a chlorpyrifos-containing consumer product on their carpet for the control of fleas, and, in addition, a commercial pest control operator had applied a chlorpyrifos product. The study reports that the four children (two male and two female, ages not specified) underwent extensive medical evaluations by physicians, neonatalists, neurologists, and other specialists at major medical centres in the USA. These professionals also reviewed the children's medical records. In addition, the study author interviewed the parents and examined three of the four children. The other child was assessed using videotape and autopsy records. All four children had structural brain defects, growth retardation, and ventricular, eye, and palate defects. Three children had hydrocephaly, microcephaly, mental retardation, blindness, hypotonia, wide-spread nipples, and deformities of the teeth, external ears and external genitalia. A fourth had abnormalities of the inner ear: cochlear and semi-circular canals. Initially, an inherited cause for the defects was suggested, but the author stated that it was unlikely that a progenitor, either male or female, with similar defects could have reproduced. One of the mothers had

been exposed to chlorpyrifos, while at work, for approximately three days during her first trimester. For this same mother it was also suggested that exposure to a product containing petroleum distillate might have contributed to the birth defects by potentiation of the effects of chlorpyrifos and interference with paraoxonase function, but this was based purely on speculation. These effects cannot be directly related to the chlorpyrifos exposure as the study was limited in that it did not characterise exposure to pesticides, or indeed any other chemical, or physical insult during the pregnancy. In addition, the study reports do not adequately describe how confounding factors were considered.

### 3.2.3 Summary of human evidence

An extensive review of the published literature was conducted and only six epidemiological studies were identified that investigated adverse effects on fetal and childhood health following low-level exposures to OP pesticides. In addition, four case reports of teratogenicity were identified, but no conclusion can be drawn from these regarding effects of OP pesticides. One study (McConnell *et al.*, 1999) found no association between low-level exposure and acute health effects. Three of the six studies found no association between exposure to OP pesticides and adverse health effects such as miscarriage, pre-term delivery, small-for-gestational-age births and sex ratios (Savitz *et al.*, 1997; Arbuckle *et al.*, 2001), and congenital malformations such as nervous system, cardiovascular defects, oral clefts, hypospadias or epispadias, musculoskeletal defects and non-specific anomalies (García *et al.*, 1998).

Thomas *et al.* (1992) found no statistically significant association between exposure to malathion and spontaneous abortion, stillbirth, or intrauterine growth retardation, but did find a statistically significant increase in gastrointestinal anomalies, but no association with any other congenital malformations. Recio *et al.* (2001) found a direct association between OP pesticide metabolite levels in urine and increased frequency of sperm aneuploidies in a small preliminary study of nine agricultural workers, but further research is necessary to confirm this finding.

## 3.3 Other evidence

Although birth occurs at a far later stage of development in humans than in other species (particularly rodents), the overall process of brain development is similar, despite differences in the relative size of specific brain regions (Rice & Barone Jr., 2000). Hence, provided due caution is used in extrapolation, animal studies can be of value to indicate the nature and mechanisms of developmental effects that can be produced by OPs, particularly since they can be studied in animals under defined conditions of exposure that would not be possible in humans.

### 3.3.1 Evidence from experimental animal studies

As indicated in Section 3.1 there is an abundance of experimental animal data showing the effects of OP pesticides on the fetus, neonates and adult animals, but most of these data relate to acute neurotoxic effects and therefore have not been considered in this review. The following animal studies were selected for review because they investigated the adverse effects of low-level exposure to OP pesticides in young animals. As stated earlier the main focus of the literature search for this review was human health effects and it was not intended to review the extensive amount of data from reproductive toxicity studies on specific OP pesticides available to the regulatory agencies; however, some animal data have been included to give an indication of potential health effects that may not have been looked for or detected in humans.

The lower capacity for hydrolysing organophosphates shown by human neonates (Ecobichon & Stephenens, 1973) is also shared by neonatal rodents (National Research Council, 1993; Moser *et al.*, 1998; Lassiter *et al.*, 1998; Zheng *et al.*, 2000). It is likely that this limited detoxification capacity is an important factor in determining susceptibility to those exposure levels high enough to saturate capacity, and for those agents in which A-esterases are the major factor in detoxification. Thus, in terms of acute toxicity, 16-day-old rats were markedly more sensitive than adults to malathion;

newborn pigs and rats to chlorpyrifos; and 7-day-old rats to parathion and methyl parathion (Pope, 2001). However for other agents not primarily detoxified by age-dependant systems (notably methamidophos) there was little difference in acute toxicity with age (Padilla *et al.*, 2000). Equally this greater sensitivity of neonates to high-level exposure does not always extrapolate to lower exposure levels, where even a limited detoxification capacity may suffice. Thus neonatal rats were somewhat less sensitive than adults to brain acetylcholinesterase inhibition after intermittent dosing with chlorpyrifos at dose levels not evoking acute toxicity (Pope & Liu, 1997). However, neonatal rats were more sensitive than adults to repeated low doses of methyl parathion, a sensitivity that may be related to direct interactions with muscarinic receptors (Liu *et al.*, 1999).

It does not appear that the primary target of acute toxicity, acetylcholinesterase, is inherently more sensitive to inhibition by active OPs in neonates than in adults (Mortensen *et al.*, 1998). Rather it is replaced more rapidly after inhibition in neonatal rats than in adults (Pope *et al.*, 1991), which confers increased resistance to exposures when these are sufficiently separated in time (days to weeks) to allow for significant reactivation or resynthesis of acetylcholine. The reactive down-regulation of receptors that is seen as a protective response to sustained modest brain acetylcholinesterase inhibition is similar or somewhat greater in neonatal rats than in adults (Liu *et al.*, 1999).

As regards non-acetylcholinesterase mediated actions of OPs, changes in intracellular signalling as a result of interactions with muscarinic receptors are produced more readily in neonatal rat preparations than in those from adults (Olivier *et al.*, 2001). The sensitivity to paraoxon was 1.7-fold greater in neonatal tissues, and that to chlorpyrifos was 9-fold greater. This may reflect the incomplete maturation of muscarinic receptor signalling in the relatively immature brain of the neonatal rat. An important point to consider is: were this mechanism to be active in humans it would be agent specific, and not proportional to acetylcholinesterase inhibiting potential.

The arguments for and against differential vulnerability of developing animals and humans to one specific agent, chlorpyrifos, are set out in a USEPA document[*]. This agent may not, however, be typical of organophosphates as a class.

The persistent behavioural consequences of neonatal chlorpyrifos exposure in rats were examined in Levin *et al.* (2001). Chlorpyrifos was administered, by subcutaneous injection (dissolved in dimethylsulphoxide to provide rapid and complete absorption), to neonatal rats (10 rats per sex, per treatment group) on postnatal days 1–4 (1 mg/kg) or 11–14 (5 mg/kg; older animals tolerate a higher dose). These doses had been shown previously not to evoke any overt signs of toxicity. The authors suggest that chlorpyrifos may interfere with the development of gender differences in behaviour patterns, and that this is an area for further research. The authors also stress that the behavioural effects of postnatal chlorpyrifos exposure are not as dramatic as the changes in neurochemical markers, largely because of the redundancy of neural systems underlying critical behavioural functions, and the resultant ability to adapt alternative neural substrates to maintain function.

Dam *et al.* (2000) administered chlorpyrifos to neonatal rats using the same protocol as Levin *et al.* (2001). Behavioural performance during the period of exposure was tested using reflex righting at postnatal day 3–4 (22 hours after the preceding day's treatment), and negative geotaxis on postnatal day 5–8. Locomotor skills were evaluated on postnatal days 21 and 30 (the post-weaning period and several weeks after termination of exposure, respectively). Cholinesterase activity in each brain region was also determined. Despite the lack of systemic toxicity, chlorpyrifos exposure had profound effects on the development of coordination skills and locomotor activity. Both immediate and long-term deficits in coordination and open field activities occurred. The effects were gender selective; initially only females showed impairment of reflex righting and negative geotaxis and, with the onset of more complex behaviours, only males showed deficits in locomotor activity and rearing. Not all of the effects observed could be explained on the basis of cholinesterase inhibition (males would be

[*] USEPA (2002) *Organophosphate Pesticide Tolerance Reassessment and Registration*, available [May 2002] at: http://www.epa.gov/oppsrrd1/op/chlorpyrifos/rev_tox.pdf

expected to show greater initial effects, as they have a higher rate of hepatic activation to chlorpyrifos oxon, an active metabolite of chlorpyrifos and a potent cholinesterase inhibitor, but the reverse was observed). These deficits were not observed when older animals (postnatal day 11–14; outside the window for adverse effects on brain cell development) were exposed to higher doses (5 mg/kg) of chlorpyrifos. The relevance of these data to humans is unclear.

In adult animals some specific OPs (such as dichlorvos) can have effects on cognition at dose levels that do not produce acute toxicity. This effect does not, however, correlate well with the ability of these agents to inhibit acetylcholinesterase (Richards *et al.*, 2000), and some agents, such as parathion, do not alter learning behaviour (Ivens *et al.*, 1998). Jett *et al.* (2001) highlighted the lack of studies of the effect of OP pesticides on cognitive function after repeated, low-dose exposures, and conducted a study to assess whether such an effect exists. Long-Evans rats were injected subcutaneously with 0, 0.3 or 7 mg/kg chlorpyrifos every four days before (postnatal day 7, 11, 15) or after weaning (postnatal day 22, 26). Animals were weaned on postnatal day 21, and were tested with the Morris swim task from postnatal day 24 through to 28. The only effect observed in the rats exposed before weaning was impaired spatial learning after five days of training, in the highest dose group. Rats administered 0.3 or 7 mg/kg chlorpyrifos after weaning were also impaired in this task, without significant changes to brain cholinesterase activity. Therefore chlorpyrifos does appear to cause deficits in cognitive function in juveniles, even at low doses, and these deficits do not appear to be mediated through inhibition of brain cholinesterase. The authors concluded that it is likely that the effects of chlorpyrifos on cognitive function are mediated indirectly by a disruption of developmental processes that manifest later in life, as well as by a direct impact on molecular pathways that underlie learning and memory. However, the mechanism and significance to humans of this dysfunction is unknown.

Defects in the development of fertilized hen eggs, injected with various OP pesticides, have been observed. Many of these are associated with the inhibition of the enzyme kynurine formamidase and a depression of nicotinamide adenine dinucleotide (NAD) levels at a critical period of development. However this pathway is not critical in mammals, and is not accepted as a model for teratogenicity. For the vast majority of OP pesticides, no adverse effects of continuous feeding of OP pesticides on pre- or postpartum mortality have been reported, nor have embryonic defects been proved, except at doses that significantly retarded growth in the mother (WHO, 1986). Recent reports by Lassiter *et al.* (2002) have shown that daily gestational treatment of rats with chlorpyrifos at doses producing 30% brain acetylcholinesterase inhibition led to abnormal brain development centred upon the proliferating ventricular zone and cortical plate. These effects were associated with a decrease in brain-derived neurotrophic factor and increased neuronal apoptosis in the surrounding brain areas (White *et al.*, 2002). It is not clear whether this effect is chlorpyrifos specific or a generic action. However, neuronal proliferation in this area does continue (at a much diminished level) into adulthood in both rats and man, and it is theoretically possible that the mechanism may apply also to the post-natal brain.

### *Summary of experimental animal data*

Some key points emerge from these animal studies that have implications for human health.

- Although younger animals are more sensitive than adults to acute high-dose toxicity from some but not all OPs, they can be less sensitive to general systemic effects following low and intermittent exposures, due to their greater ability to replenish acetylcholine levels.
- Both the fetus and young animals may be more susceptible to developmental effects due to their relatively immature nervous systems, which can respond differently to mature systems and may show irreversible effects.
- Some specific agents, such as chlorpyrifos, appear to produce behavioural effects in adults after neonatal exposure to levels that have no such effect after adult exposure. This effect may be mediated by novel mechanisms that are not directly related to acetylcholinesterase inhibition.

These mechanisms may be a class effect of OP pesticides but there is insufficient information in the published literature to draw any definite conclusions.

### 3.3.2 Possible mechanisms of action

While conducting this review it became apparent that there are published data available that could be used to help elucidate potential mechanisms of toxicity of OP pesticides at low doses. A comprehensive literature review of these data has not been conducted, but some of the key issues from the few studies reviewed have been summarised below.

- Exposure to low doses of chlorpyrifos induced a decreased expression of serotonin (5-HT) in the forebrain and the brainstem of male neonatal rats, and decreased expression in the brainstem but increased expression of 5-HT in the forebrain of female neonatal rats. The gender-selective effects on 5-HT systems could contribute to similar gender dimorphism in behavioural performance (Raines *et al.*, 2001).

- Chlorpyrifos exerts a more potent antimitotic action on developing neural cells (glia and neurons) than does its oxon, despite the fact that the latter is a more potent cholinesterase inhibitor, suggesting that chlorpyrifos exerts its antimitotic action independently of cholinesterase inhibition (Qiao *et al.*, 2001).

- Serum proteins can bind chlorpyrifos, thus protecting neural cells. However, fetal and neonatal serum is deficient in these proteins relative to adults, therefore for the same plasma concentration a greater proportion will be active in the immature organism (Qiao *et al.*, 2001).

- Chlorpyrifos has been shown to inhibit DNA synthesis, impair G-protein function within the adenylyl cyclase signalling cascade, impair cell differentiation, disrupt nuclear transcription factor DNA binding activity and produce reactive oxygen species in glial cells, indicating that cholinesterase activity might not be an appropriate indicator of safety for all effects (Garcia *et al.*, 2001).

- Low concentrations of malathion altered the levels of enzymes in the glutathione cycle in human fetal cells, which caused a corresponding increase in lipid peroxidation, which could possibly interfere with fetal brain development (Gupta *et al.*, 1992). Another study demonstrated production of reactive oxygen species in PC12 cells exposed to various concentrations of chlorpyrifos, with similar implications (Crumpton *et al.*, 2000).

- Parathion interfered with the myelination process and/or with already deposited myelin. Adverse effects only occurred with high inhibition of acetylcholinesterase activity (Zurich *et al.*, 2000).

- A direct association has been found between OP pesticide metabolite levels in the urine of nine men and increased frequency of sex-null aneuploidy in sperm (Recio *et al.*, 2001).

# 4 Fetal and Infant Exposure to Organophosphates in the UK

## 4.1 Introduction

Although this review is primarily concerned with the health effects of organophosphate (OP) compounds, exposure has also been reviewed in order to put toxicological findings in context. This section aims to give a broad overview of fetal and infant exposure to OP pesticides as a class in the UK and is based largely on data published within the past five years.

The approach taken in this review of exposure is to look at the average level of exposure of the fetus, infant and child to OP compounds as a class in the UK. As no dose–response effects were identified in the review of health effects (see Section 3), the average level of exposure is considered to be the most reasonable measure of exposure from which to assess potential chronic toxic effect (National Research Council, 1993). However, currently there are no standard methods for estimating exposure to a class of chemicals with a common mechanism of toxicity, such as OPs, nor are there any established guideline values with which to compare such intakes. A method for estimating exposure to groups of chemical is currently being used for the first time by the US Environmental Protection Agency to assess exposure to OPs under the Food Quality Protection Act[a]. However, the amount of data necessary to assess exposures using this method is considerable; hence undertaking such an assessment is beyond the scope of this review. The methodologies required to assess exposures to groups of pesticide mixtures in the UK are currently being considered, particularly in relation to food, by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) Working Group on Risk Assessment of Mixtures of Pesticides (WiGRAMP)[b], which is due to report later this year.

## 4.2 Sources of exposure

Exposure to the fetus, infants and children to OPs in the UK may potentially arise from a number of sources, including:

- residues of OP compounds in maternal blood;
- residues of OP compounds taken into the home on clothing and equipment by people working with OPs;
- residues of OP compounds in food and water;
- human or veterinary medicines containing OP compounds;
- the use of OP pesticides in and around the home and garden; and
- non-domestic sources of OP pesticides, for example spray drift or use of OPs in non-domestic buildings.

These potential sources of exposure are discussed in more detail in the following sections.

[a] US EPA (2002) *Organophosphate Pesticide Tolerance Reassessment and Registration,* available [May 2002] at: www.epa.gov/pesticides/cumulative/pra-op/

[b] Food Standards Agency (2002) *Working Group on Risk Assessment of Mixtures of Pesticides (WiGRAMP),* available [May 2002] at: www.food.gov.uk/science/ouradvisors/toxicity/COTwg/wigramp/

# 4.3 Parental exposure

Parents may be a source of exposure to the fetus and infants and children through residues of OPs in maternal blood or through para-occupational exposure, that is OP pesticide residues taken home on clothing and equipment by parents working with OPs.

## 4.3.1 Fetal exposure

Many OP compounds are lipophilic and would therefore be expected to cross the placenta, once absorbed into the mother's blood (Richardson, 1995), resulting in possible fetal exposure. Only one published human study was identified that has attempted to measure fetal exposure to OP pesticides. The study determined the background levels, detection limits and stability of six OP metabolites (diethylphosphate (DEP), diethylthiophosphate (DETP), diethyldithiophosphate (DEDTP), dimethylphosphate (DMP), dimethylthiophosphate (DMTP), and dimethyldithiophosphate (DMDTP)) in the post-partum meconium of 20 newborns from the New York Presbyterian Hospital, USA, without knowledge of parental pesticide use (Whyatt & Barr, 2001). The study identified DEP in 19 of the 20 samples (range 0.8–3.2 µg/g), DETP in all 20 samples (range 2.0–5.6 µg/g), and DMP and DEDTP in one sample each (16 and 1.8 µg/g, respectively); DMTP and DMDTP were not detected in any samples. The results indicate that fetal exposure to OPs is possible. However, this was a preliminary study and the levels of maternal exposure were not determined, thus precluding an assessment of their relevance to UK exposure levels. Further research is needed to determine the time frame of exposure represented by the metabolite levels in meconium and the relationship between the biomarker levels and actual exposure (Whyatt & Barr, 2001).

## 4.3.2 Para-occupational exposure

No data are available on the extent of para-occupational exposure (exposure arising indirectly from occupational sources, e.g. in farming families) in the UK (COT, 1999). There have, however, been several studies in the USA, and these are included here to provide information on factors that may influence exposure. However, given the climatic, ecological and cultural differences between the USA and the UK, it is difficult to judge how important these factors are in determining children's exposure in the UK.

One US study of children living with a parent occupationally exposed to pesticides (as either an applicator or a farmworker), and living in proximity to a treated orchard, measured the levels of four OP pesticides (azinphos-methyl, chlorpyrifos, ethyl-parathion and phosmet) in house dust and in the excretion of dialkylphosphate metabolites in children between 9 months and 6 years of age (Loewenherz *et al.*, 1997; Lu *et al.*, 2000). The study took place in June and July of 1995 and involved 49 applicator families, 13 farmworker families and 14 reference families (families in which no member's work involved contact with agricultural pesticides and whose residence was more than 402 m (0.25 miles) from any pesticide-treated orchard). The study found that concentrations of the selected OP pesticides in house dust were significantly higher in the homes of agricultural families (made up of applicator and farmworker families) than in those of reference families (Kruskal-Wallis one-way ANOVA, $p < 0.001$, for azinphos-methyl and dimethyl OP pesticides; $p = 0.02$ for phosmet), and that concentrations of the OP pesticides were also significantly higher in the house dust of homes within 61 m (200 feet) of an orchard (Whitney *U*-Wilcoxon Rank Sum W test, $p < 0.01$ for azinphos-methyl; $p = 0.01$ for dimethyl OP pesticides; Lu *et al.*, 2000). Similarly, median DMTP and dimethyl OP metabolite concentrations in urine were four to five times higher in children of agricultural families than in children of reference families (Whitney *U*-Wilcoxon Rank Sum W test, $p = 0.07$), and were significantly higher in the urine of children living within 61 m (200 feet) of an orchard (Whitney-*U*-Wilcoxon Rank Sum *W* test, $p = 0.01$). An association was found between house dust concentrations and urinary metabolite concentrations; however, the level of significance was low (Spearman Rank Correlation, $p = 0.09$; Lu *et al.*, 2000). Unfortunately, the presence of both para-occupational characteristics and proximity to orchards for the families studied did not allow

conclusions to be drawn regarding the relative importance of these individual sources for children's exposure (Loewenherz *et al.*, 1997).

In a further analysis of the data from the study of Loewenherz *et al.*, doses of OP pesticides received were estimated assuming that the dialkylphosphate metabolites were entirely attributable to azinphos-methyl or phosmet, the two most frequently used OP pesticides in the region (Fenske *et al.*, 2000). Creatinine-adjusted mean dose estimates for the spray season were 2.8 µg/kg/day for children of agricultural families and 0.3 µg/kg/day for children of reference families. Comparison with the World Health Organization Acceptable Daily Intake (ADI) revealed that 19% of children (12 of 62) from agricultural families and 22% of children (3 of 14) from reference families exceeded the ADI for azinphos-methyl (5 µg/kg/day), and for phosmet the percentages of children exceeding the ADI (20 µg/kg/day) were 3.3% and 0%, for agricultural and reference groups respectively (Fenske *et al.*, 2000). The calculated doses were thought to be an underestimate of true exposure, because it was assumed that 100% of the OP compounds were excreted as dialklyphosphate metabolites in the urine. Human volunteer studies have demonstrated that only about 70% of azinphos-methyl is actually excreted in the urine. However, this should be set against the fact that the measurement of exposure took place during the spraying season when exposures were likely to be at peak levels for the study population.

In another study, McCauley *et al.* (2001) looked at the levels of azinphos-methyl, amongst other pesticides, in the homes of 25 migrant agricultural workers in Oregon, USA. The study found an association between median azinphos-methyl house dust concentrations and distance from the field ($p = 0.04$). However, this association became insignificant ($p = 0.32$) when three samples with non-detectable levels were incorporated into the analysis, by assigning one-half the limit of quantitation. The study also found an association between the number of persons in each household who worked in agriculture and the level of azinphos-methyl in house dust. The median concentration of azinphos-methyl increased by 170% for each additional person in the household working in agriculture ($p = 0.002$). When samples with non-detectable levels were incorporated into the analysis, the increase for each additional person working in agriculture rose to 230%. However, this analysis had only one or two families in each of the 'four persons working in agriculture' and 'five persons working in agriculture' categories, and no families in the 'three persons working in agriculture' category. As a result, the mean azinphos-methyl concentrations in house dust in the highest two categories were based on only a few samples, and hence could have been disproportionately influenced by high or low values at the extremes of the range. Therefore these data points may have acted as influential observations in the analysis and so the resulting association should be interpreted with caution.

Overall, these data suggest that para-occupational sources and proximity to agricultural spraying of OP pesticides may result in higher exposures of children to OP pesticides than is the case for children without these sources of exposure. However, further research is required to verify these results, to investigate the interaction between the two sources and to understand their relevance to children in the UK.

## 4.4 Dietary exposure

Various approaches to assessing exposures to pesticides in the diets of infants and children were reviewed by the US National Research Council (NRC) in 1993. As part of their review they proposed a method for assessing exposure to a class of pesticides based on assigning toxicity equivalence factors (TEFs) to each of the pesticides of concern, and then estimating total exposure by multiplying the actual level of each pesticide residue by its TEF, and summing the results. The NRC tested their method using five OPs, and this demonstrated some exposure above US recommended levels. However, the assessment of exposure was directed to assess acute health risks (i.e. focusing on peak exposures), and hence is of limited relevance when looking at long-term exposure. The assessment of exposure to classes of pesticides is currently being reviewed by WiGRAMP in the UK, and the

recommendations from this review will help inform the future exposure assessment practice of UK regulatory agencies.

### 4.4.1 The diets of infants and children in the UK

There have been several studies of the diets of infants and children in the UK, focusing on children aged 6–12 months (Mills & Tyler, 1992) and 1.5–4.5 years (Gregory *et al.*, 1995). The studies provide an insight into the diets of infants and children and, combined with pesticide residue monitoring data, can help identify important sources of dietary OP exposure.

The study on British infants aged 6–12 months looked at the diets of 488 infants recruited in November 1986 (Mills & Tyler, 1992). Part of the study looked retrospectively at feeding practices from birth and found that, during the first week or two of life, 55% of infants were fed solely breast milk and that the duration of breastfeeding was very variable but, by 32 weeks, over 90% of mothers had stopped breastfeeding. Infants in the survey, on average, received solids by 13 weeks (range: 3–32 weeks), and 82% of infants were fed some commercial infant food. By 6 months almost all infants (92%) were fed some 'family foods'[*], with 90% of those aged 6–12 months eating the same or similar food to the rest of the family. The infants consumed a very wide range of foods, with an increase in variety with increasing age; over 80% of the infants aged 6–12 months consumed basic foods such as bread (89%), fruit (80%), potatoes (91%) and vegetables (89%).

The study by Gregory *et al.* (1995) identified a nationally representative sample of 2101 children aged 1.5–4.5 years, for 1675 of whom records of weighed dietary intake between July 1992 and June 1993 were collected. The study found that the infants ate a very wide range of foods with, generally, the quantity of food consumed, and the proportion of children eating a particular food, increasing with age. There were some other differences according to age: more of the younger children ate bananas, commercial infant foods, fish that was either coated or fried, yoghurt and whole milk. More of the older children ate bread, buns, cakes and pastries, ice cream, sugar confectionary, meat products, chips and savoury snacks. There were no significant differences in the average amounts of fruit eaten by the youngest and oldest age groups. About half the sample had eaten apples, pears or bananas, but citrus fruits, such as oranges and satsumas were only eaten by about one-quarter of children. Table 4.1 summarizes the foods consumed by infants of different age groups according to quantity consumed.

[*] 'Family foods' refers to all foods other than commercially prepared infant foods

**Table 4.1 Mean quantities of food consumed (g/infant/week) according to age (excluding tap water and miscellaneous foods)[a]**

| 6–9 months | Mean | 9–12 months | Mean | 1.5–2.5 years | Mean | 2.5–3.5 years | Mean | 3.5–4.5 years | Mean |
|---|---|---|---|---|---|---|---|---|---|
| Infant formula | 1833 | Milk[b] | 2791 | Squash and soft drinks | 2322 | Squash and soft drinks | 2691 | Squash and soft drinks | 2892 |
| Milk[b] | 1551 | Infant formula | 585 | Milk[b] | 2283 | Milk[b] | 1955 | Milk[b] | 1730 |
| Infant foods in jars and cans | 769 | Tea and coffee | 542 | Fruit | 337 | Fruit | 353 | Potatoes | 387 |
| Breast milk | 517 | Infant foods in jars and cans | 481 | Tea and coffee | 317 | Potatoes | 331 | Fruit | 348 |
| Infant fruit juices and drinks | 483 | Squash and soft drinks | 408 | Potatoes | 303 | Meat, meat products and dishes | 293 | Bread | 333 |
| Tea and coffee | 191 | Infant fruit juices and drinks | 353 | Meat, meat products and dishes | 257 | Tea and coffee | 292 | Meat, meat products and dishes | 328 |
| Instant infant food | 136 | Potatoes | 215 | Fruit juices | 259 | Bread | 288 | Tea and coffee | 291 |
| Fruit | 135 | Yoghurt | 210 | Vegetables excluding potatoes | 256 | Fruit juices | 282 | Fruit juices | 229 |
| Squash and soft drinks | 119 | Vegetables excluding potatoes | 193 | Bread | 231 | Vegetables excluding potatoes | 273 | Cakes, buns, puddings | 227 |
| Potatoes | 111 | Cakes, buns, puddings | 177 | Cakes, buns, puddings | 162 | Cakes, buns, puddings | 206 | Pasta and rice | 172 |
| Meat, meat products and dishes | 106 | Meat, meat products and dishes | 177 | Yoghurt | 159 | Pasta and rice | 160 | Breakfast cereals | 144 |
| Yoghurt | 102 | Fruit | 160 | Pasta and rice | 155 | Breakfast cereals | 145 | Biscuits | 117 |
| Cakes, buns, puddings | 101 | Bread | 133 | Breakfast cereals | 125 | Yoghurt | 143 | Yoghurt | 116 |
| Vegetables excluding potatoes | 98 | Fruit juices | 132 | Infant formula | 93 | Biscuits | 112 | Cheese and cheese dishes | 92 |
| Breakfast cereals | 72 | Breakfast cereals | 124 | Biscuits | 87 | Cheese and cheese dishes | 93 | Sugar confectionary | 87 |
| Total [c] | 6818 | | 7498 | | 8272 | | 8524 | | 8609 |

Adapted from Mills & Tyler (1992) and Gregory *et al*. (1995)

[a] Only the foods consumed in the relatively greatest mean quantities are displayed, in descending order of mean quantity consumed

[b] Whole milk, semi-skimmed milk, skimmed milk

[c] Including miscellaneous foods

## 4.4.2 Monitoring of food, water and total diets for organophosphates in the UK

### *Monitoring schemes*

In the UK there are a number of schemes that monitor the presence of OP compounds in food, water and the total diet. These include the Pesticide Residues Committee (PRC; formerly the Working Party on Pesticide Residues (WPPR)), which monitors pesticide residues in food, drink and total diets, the Veterinary Medicines Directorate (VMD), which monitors animal products for OPs used as veterinary medicines, and the Drinking Water Inspectorate (DWI), which oversees the monitoring of pesticide residues in water carried out by water companies.

The PRC oversees the monitoring of the UK food and drink supply for pesticide residues. The purpose of the monitoring is to:

- back up the statutory approvals process for pesticides;
- check that residues do not exceed statutory UK maximum residue levels; and
- check that human dietary intakes of residues are within acceptable levels (PRC, 2001).

The range of foodstuffs available in the UK is very broad, as is the range of pesticides used in agriculture and food production (PRC, 2001). As a result, the PRC operates a rolling programme of monitoring for both foodstuffs and pesticides. Each year, the PRC samples different foods, generally based on surveys of consumption rates (i.e. those foods eaten more frequently are sampled more frequently). The range of pesticides sought in the foodstuffs may also change from year to year, depending on the residues that may be expected from a knowledge of the pesticides in use, and the need for information on residue patterns to address current concerns[*].

The pesticide residue data published by the PRC are the most comprehensive available on pesticide, and hence OP, residues in food in the UK, and allow identification and estimation of sources and levels of dietary exposure to OP pesticides in the UK. However, a number of factors need to be considered when using the data for the purposes of assessing long-term exposure in the general population. In particular, the sampling undertaken by the PRC is targeted towards foods that are more likely to contain residues, and hence the results may be skewed towards high levels rather than being representative of pesticide levels in a commodity item as a whole[*]. In addition, because the sampling is targeted and not statistically based, it is not possible to quantify how representative the samples are of that food item in the UK, or whether the levels of pesticide residues detected are representative of those typically found in that foodstuff [*]. Finally, the analytes sought vary from year to year, thus it is not always possible to perform inter-year comparisons of exposure to classes of pesticides. Nevertheless, the use of targeted monitoring is an effective method of sampling when working within budgetary constraints, commensurate with achieving a high level of consumer protection for individual pesticide residues in individual foodstuffs.

The VMD monitors the residues of veterinary medicines in food items derived from animals, including the periodic monitoring of selected food items for some OP residues. Monitoring occurs on a fixed proportion of the animals and animal products (red meat, poultry, salmon and trout, eggs, wild and farmed game, honey and milk) that the UK forecasts will be slaughtered or produced during the year (VMD, 2001). This means that, within prescribed confidence levels, the results of the VMD residues surveillance programme are nationally representative (VMD, 2001).

[*] MAFF (2000) *Annual Report of the Working Party on Pesticide Residues: 1999 (from 2000 known as the Pesticide Residues Committee). Supplement to The Pesticides Monitor 2000*. MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

Drinking water is monitored for pesticides under the Water Supply (Water Quality) Regulations 2000 (SI 2000, No. 3184) to ensure that the statutory limits of 0.1 µg/l[a] for individual pesticides and 0.5 µg/l for total pesticides are not exceeded. Water samples are taken from consumers' taps; the number of water samples taken is dependent on the volume of water supplied by a water company. Pesticides monitored are chosen on based on the likelihood of a particular pesticide being present in the water source (DoE & Welsh Office, 1989).

## *Data from monitoring schemes*

The following sections summarise the available DWI data on OP pesticide residues in drinking water, the PRC and WPPR data on OP pesticide residues in food in the UK since 1996, and the VMD data on residues of OP veterinary medicines in animal products since 1998.

### Drinking and bottled water

During 2000, 606 979 analyses of drinking water samples were made for individual pesticides, of which only 45 samples exceeded the 0.1 µg/l limit for individual pesticides[b]. None of these exceedances involved OP pesticides and the low number of exceedances forms part of a trend of decreasing levels of pesticides in drinking water over the past ten years. Although it is not reported how many or which OP pesticides the analyses included, these results suggest that over 99.99% of drinking water supplied by water companies is either pesticide free or contains minimal traces of pesticides.

Monitoring of private water supplies for pesticides is the responsibility of local authorities, although there is no requirement to maintain public records. However, one study was identified that monitored the presence of sheep dip pesticides in private water supplies in Wales during the dipping season (National Assembly for Wales, 1999). Only 4 of 369 samples from 8 sites contained levels of OPs above the standard of 0.1 µg/l and none of the exceedances was considered to pose a hazard to health.

Monitoring of bottled water is not covered by the Water Supply (Water Quality) Regulations 2000 (SI 2000 No. 3184), but comes under the remit of the PRC. The PRC has carried out one monitoring survey, during 2000, of 50 samples of a range of types of bottled water for a range of pesticides, including three OPs[c]. No residues of any pesticide were found above the reporting limit of 0.1 µg/l.

These results suggest that both drinking and bottled water would make a minor and probably insignificant contribution towards total exposure to OP pesticides.

### Breast milk and infant milk formula

Only one UK survey of OP compounds in human breast milk has been carried out by the WPPR[d]. The WPPR sought ten fat-soluble OP compounds in 50 samples of breast milk collected from hospital maternity units between 1997 and 1998. No OP pesticide residues were detected in any of the samples. The WPPR has also conducted a survey of pesticide residues in infant formula milk. Nine

[a] This limit was set to minimise the occurrence of pesticides in drinking water and is not a health-based limit (DoE & Welsh Office, 1989)

[b] DWI (2001) *Drinking Water 2000 (Annual Report – Technical Web Version only).* London, UK, Drinking Water Inspectorate, available [May 2002] at http://www.dwi.gov.uk/pubs/annweb00/index.htm

[c] Pesticide Residues Committee (2001) *Pesticide Residues Monitoring Report. Fourth Quarter Results: October – December 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

[d] MAFF (1998) *Annual Report on the Working Party on Pesticide Residues: 1997. Supplement to The Pesticides Register 1998*. MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr/htm

OP pesticides were sought in 20 samples of infant formula milk obtained in 1997; none of the samples had any detectable OP pesticide residues[a].

### Infant foods

The PRC (previously the WPPR) usually analyses infant foods annually. Over the period 1991–2001 several surveys of different infant foods were undertaken (see Table 4.2). In these surveys, OP pesticide residues were found only in fruit-based and cereal-based infant foods. These data were used to estimate OP pesticide intakes from commercially produced infant foods, assuming that a 6–12 month-old infant consumes three 200 g jars of infant food a day containing the highest level of residues detected[b]. All estimated intakes of individual OP pesticides were below their respective ADIs.

The levels of pesticides in infant formula and baby food are regulated by Directive 99/39/EC, which amends Directive 96/5/EC on processed baby foods for infants and young children. The Directive sets a 'blanket' maximum residue level (MRL) of 0.01 mg/kg for individual pesticides in baby foods and infant formula, and prohibits the use of certain pesticides, including ten OPs, where the 0.01 mg/kg MRL, under worst-case intake conditions, could still lead to exceedances of the ADI. As a result, the Directive helps to limit, and possibly reduce the exposure of babies and infants to OP pesticides. The Directive has been incorporated into English law through SI 1509/2000 and SI 1510/2000, and comes into force in England on 01 July 2002; similar regulations will apply in Scotland, Wales and Northern Ireland [b].

In addition to the monitoring of foods undertaken by the PRC, the VMD has monitored the levels of selected OPs in commercially available infant foods. In 1998, the VMD surveyed 52 samples each of beef, chicken, egg, lamb and pork-based baby foods for ten OP compounds. None of the samples had any detectable OP residues (VMD, 2000).

### General non-infant specific foods

A summary of the monitoring of foods undertaken by the PRC for OP compounds in non-infant specific foods is presented in Annex 2. A list of those items in which OP pesticide residues have been found in more than 5% of the samples, or which have been found to contain multiple residues of OPs, is presented in Table 4.3. Although it should be borne in mind that the sampling is targeted and not statistically based, the monitoring data suggest that OP pesticide residues, as would be expected, are more likely to be found in cereal products, fruits and vegetables. Some individual OP pesticide residues in fruit and vegetables have been sufficient to result in occasional exceedances of the ADI (e.g. methamidophos in sweet peppers [b]); however, the majority of risk assessments undertaken by the PRC show that OP pesticide residues in food would not result in exceedances of the ADI for individual OPs in individual commodity items through dietary intake. Whether or not the combined intake of different OP pesticide residues from different food items could result in exposures above an acceptable level has not been evaluated, although methodologies for undertaking such an assessment are currently being reviewed by WiGRAMP (see Section 4.1).

[a] MAFF (1998) *Annual Report on the Working Party on Pesticide Residues: 1997. Supplement to The Pesticides Register 1998*. MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr/htm

[b] MAFF (2000) *Annual Report of the Working Party on Pesticide Residues: 1999 (from 2000 known as the Pesticide Residues Committee). Supplement to The Pesticides Monitor 2000*. MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

**Table 4.2 Summary of monitoring for organophosphate (OP) pesticide residues in infant food**

| Infant foods surveyed and year of survey | Number of OP pesticides sought | OP pesticide residues detected* (reporting limit; mg/kg) | Concentration range (mg/kg) | Positive samples (%) | Total number of samples |
|---|---|---|---|---|---|
| **Fruit based** | | | | | |
| 2000 | 39 | No OP pesticide residues detected | – | 0 | 140 |
| 1998 | 33 | Phosalone (0.01) | 0.01–0.02 | 4.5 | 88 |
| | | Pirimiphos-methyl (0.01) | 0.05 | 1.1 | |
| 1997 | 33 | Phosalone (0.01) | 0.01–0.05 | 25.0 | 48 |
| 1994 | 35 | Phosalone (0.01) | 0.03–0.05 | 3.3 | 60 |
| **Vegetable based** | | | | | |
| 1998 | 31 | No OP pesticide residues detected | – | 0 | 55 |
| 1993 | 12 | No OP pesticide residues detected | – | 0 | 53 |
| **Cereal based** | | | | | |
| 1999 | 17 | No OP pesticide residues detected | – | 0 | 72 |
| 1995 | 11 | Pirimiphos-methyl (0.05) | 0.05–0.1 | 6.7 | 120 |
| 1994 | 10 | No OP pesticide residues detected | – | 0 | 58 |
| 1991 | 10 | Malathion (0.05) | 0.05–0.08 | 6.1 | 49 |
| | | Pirimiphos-methyl (0.05) | 0.07–0.18 | 10.2 | |
| **Meat/egg/fish based** | | | | | |
| 2001 | 20 | No OP pesticide residues detected | – | 0 | 68 |
| 1998 | 7 | No OP pesticide residues detected | – | 0 | 48 |
| 1995 | 0 | – | – | – | 70 |
| **Dehydrated** | | | | | |
| 1995 | 19 | No OP pesticide residues detected | – | 0 | 60 |

Data from MAFF, 1996, 1995, 1994, 1992a and the following web-published reports.

MAFF (2000) *Pesticides Residues Monitoring. Report of the Pesticide Residues Committee. First Quarter Results. January-March 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

MAFF (2000) *Annual Report of the Working Party on Pesticide Residues: 1999 (from 2000 known as the Pesticide Residues Committee. Supplement to The Pesticides Monitor 2000.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1999) *Annual Report of the Working Party on Pesticide Residues: 1998. Supplement to The Pesticides Monitor 1999.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1998) *Annual Report of the Working Party on Pesticide Residues: 1997. Supplement to The Pesticides Register 1998*. MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

Pesticide Residues Committee (2001) *Pesticide Residues Monitoring Report. Fourth Quarter Results. October-December 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticide Residues Committee (2001) *Pesticide Residues Monitoring Report. First Quarter Results. January-March 2001*, available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

OP, organophosphate

* At or above the reporting limit

**Table 4.3 Summary of commodity items in which organophosphate (OP) pesticide residues have been found in greater than 5% of the samples or which have been found to contain multiple residues of OPs[a]**

| Commodities in which OP pesticide residues have been found in more than 5% of the samples | Commodities in which OP pesticide residues have been found in more than 5% of the samples and/or which have been found to contain multiple OP pesticide residues |
|---|---|
| **Cereal products** | |
| Breakfast cereals, biscuits | Bread |
| **Fruit** | |
| Apricots, bananas, gooseberry, kiwi fruit, melons, passion fruit, star fruit, strawberries | Apples, dried fruit, grapes, lemons, mandarins and clementines, oranges, peaches and nectarines, pears, plums |
| **Vegetables** | |
| Aubergine, baby vegetables, broccoli, carrots, peas (edible, podded) | Celery, green beans, lettuce, peppers (sweet) |
| **Animal products** | |
| Pies/pastries/sausage rolls[b] | |

[a] See Annex 2 for details
[b] OP pesticide residues in pies/pastries/sausage rolls were attributed to OP pesticide residues in the pastry rather than the meat

The data also suggest that animal products contain few if any OP pesticide residues. This is supported by the monitoring of animal products undertaken by the VMD, which, with the exception of some OP pesticide residues found in ovine kidney fat in 1998 and 1999, did not find any OP pesticide residues in animal products between 1998 and 2000 (see Table A2.7, Annex 2).

These data are similar to those from a recent US study that carried out 24-hour duplicated diet sampling of 13 children aged between 2 and 5 years old, twice in a year, in order to assess dietary OP pesticide exposures (Fenske *et al.*, 2002). The study found that fresh fruits and vegetables had the most frequent pesticide determinations, and that OP pesticides were not present at detectable levels in any of the dairy samples. The study estimated that the cumulative daily dose in chlorpyrifos equivalents was 2.5 µg/kg/day. This is below the ADI of 10 µg/kg/day for chlorpyrifos.

### Total diet

Approximately once every five years the WPPR carries out a Total Diet Survey to determine average intakes of pesticide residues in dietary constituents, and to allow a more realistic estimate of consumer exposure to pesticide residues in food to be carried out[*]. Food samples for the survey are purchased from a variety of retail outlets in randomly selected towns throughout the UK over a 12-month period, and prepared as for eating, with the relative proportions of foods within each group reflecting their relative importance in the UK diet. The pesticides analysed are selected to include those which have been regularly found in previous monitoring or could be expected to occur. Therefore not all food groups are analysed for all pesticides (MAFF, 1997). The national estimates of dietary intakes of pesticides are calculated for adults on the basis of the mean pesticide residue in particular food groups (taking results below the reporting limit as zero) and the mean dietary intake of the particular food group. On the basis of this, the Total Diet Surveys for 1984–1985 and 1989–1990 showed no exceedances of the ADI for individual OP pesticides in adults (MAFF, 1989; 1992b).

In the 1995–1996 Total Diet Survey a different approach to assessing exposure was taken: it used the 97.5th percentile consumption of individual commodities and the highest residues reported from the

[*] MAFF (1997) *Annual Report of the Working Party on Pesticide Residues: 1998. Supplement to The Pesticide Register 1997*. MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

monitoring data (MAFF, 1997). This method does not estimate mean, long-term exposure, but rather estimates peak exposures, which are unlikely to occur frequently, and are of less relevance to this review. Nonetheless, this was the first survey to assess the exposure of infants and children, and the results for the OP pesticides monitored are presented in Table 4.4.

**Table 4.4 Summary of the dietary intakes of organophospahte (OP) pesticides determined from the Total Diet Survey, 1996**

| Pesticide | ADI (mg/kg/bw/day)[a] | Dietary intake as a percentage of ADI | | |
|---|---|---|---|---|
| | | Adults | School children | Infants |
| Chlorpyrifos-methyl | 0.01 | 0.6 | 0.8 | 1 |
| Dimethoate | 0.0008 | 13 | 15 | 45 |
| Etrimfos | 0.003 | 2 | 3 | 3 |
| Parathion | 0.004 | 1 | 1 | 4 |
| Phosalone | 0.02 | 3 | 3 | 9 |
| Phosphamidon | 0.0005 | 12 | 16 | 20 |
| Pirimiphos-methyl | 0.03 | 0.7 | 1 | 1 |
| Propetamphos | 0.0001[b] | 140 | 180 | 200 |
| Triazophos | 0.001 | 1 | 1 | 4 |

Adapted from MAFF (1997) *Annual Report of the Working Party on Pesticide Residues: 1996. Supplement to The Pesticides Register 1997*. MAFF Publications. Available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

ADI, acceptable daily intake
[a] These are current ADIs and not necessarily those used in the original survey
[b] This is a temporary ADI (COT, 1999)

The results indicate that the ADI for propetamphos could have been exceeded in infants, by up to two fold. However, as mentioned above, the exposure assessment method used here is more appropriate for assessing peak exposures; average long-term exposures to individual pesticides are likely to be lower. The WPPR concluded that occasional exceedance of the ADIs for these individual pesticides were unlikely to result in any adverse health effects[a].

Combined exposures of dimethoate have recently been assessed in detail as part of the Government's review of anticholinesterase compounds[b]. In particular, it was found that although exposure from individual crop uses remained below the ADI, if exposure from all approved uses and imports were taken into account, the ADI could be exceeded in toddlers (1.5–4.5 years) by both dimethoate and omethoate (a breakdown product and metabolite of dimethoate), and for infants (6–12 months) by dimethoate. However, it is not clear whether these exceedances relate to peak or long-term exposures. Although assessment of these data indicated no immediate health risk, a strategy for reducing consumer exposure has been developed by the approval holder and approved by the ACP[c]. The issue of combined exposure will be addressed further in the final stages of the anticholinesterase review when the exposure of consumers to all OPs that remain approved is assessed.

[a] MAFF (1997) *Annual Report of the Working Party on Pesticide Residues: 1996. Supplement to The Pesticides Register 1997*. MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm
[b] PSD (2001) *Note of the Dimethoate Stakeholders' Forum. 19 March 2001*, available [May 2002] at: www.pesticides.gov.uk/anticholinesterase/dimethoate_stakeholders.html
[c] PSD (2001) *Minutes of the 290th Meeting of the Advisory Committee on Pesticides (ACP) on 4th March 2002*, available [May 2002] at: www.pesticides.gov.uk/committees/acp/ACP-290_mins1.htm

# 4.5 Exposure from human and veterinary medicines

## 4.5.1 Human medicines

Head lice[a] and scabies[b] treatments containing malathion are the only human medicines approved by the UK Medicines Control Agency (MCA) that contain an OP compound (COT, 1999). Malathion treatments are available on prescription and over the counter, and in 1998 approximately 2.4 million malathion-containing treatments were sold in the UK (Dennis & Lee, 1999). The treatments are not recommended for use on infants under six months without medical supervision. However, as there are no indications to the contrary, malathion-containing treatments can be used during pregnancy (BNF, 2001). Other treatments that may be used against head lice and scabies include permethrin and phenothrin based treatments.

Both scabies and head lice have been reported as increasing in prevalence in the UK (data until 1995), and are significantly more prevalent in children and women ($p < 0.000001$; Downs *et al.*, 1999). The 1994 general practitioner (GP) consultation rates (which do not take into account those who treat themselves without consulting a GP) for head lice were 118.7 per 100 000 in 0–4 year-olds and 194 per 100 000 in 5–15 year-olds; for scabies the rates were 52.9 per 100 000 in 0–4 year-olds and 60.5 per 100 000 in 5–15 year-olds.

No published studies were identified that have looked at children's exposure to malathion from head lice or scabies treatments, nor were any published data identified that have looked at the frequency or manner of use of such products. One published UK study has, however, looked at exposure of adult volunteers to malathion head lice treatments (Dennis & Lee, 1999). This study was conducted by the approval holder in response to a request by the MCA to provide data on absorption of malathion from the use of such products. The study examined a number of commercially available treatments and treatment regimes and found that a typical dose of preparation for head lice delivers 100–200 mg malathion to the scalp, of which one- to two-thirds is washed off following the allocated treatment time. Urinary levels of three dialkylphosphates (DMP, DMTP and DMDTP) were monitored and results showed that 0.2–3.2% of the applied malathion was eliminated in the urine, with dialkylphosphate levels decreasing to baseline values by 96 hours after treatment, thus indicating no accumulation of metabolites associated with repeat treatments. A summary of the results of the study is presented in Table 4.5. The study noted that head lice products are often used to treat children and that further research was required to assess the effects of such products in children.

[a] The treatment of head lice involves the application of a 0.5% lotion of malathion to dry hair, the scalp and affected areas. The hair is then combed and allowed to dry naturally. The lotion is removed by washing 12 hours later. Application should not be repeated at intervals of less than 1 week or for more than 3 weeks. Alternatively a 1.0% shampoo is applied to hair for 5 minutes, rinsed, repeated and rinsed again and then the treatment is repeated at intervals of 3 days (BNF, 2001).

[b] Treatment for scabies involves the application of a 0.5% preparation over the whole body. The treatment is removed by washing after 24 hours. Manufacturers recommend that application excludes the head and neck, although, in the case of young children application may need to extended to the scalp, neck, face and ears. Application should not be repeated at intervals of less than 1 week or for more than 3 weeks (BNF, 2001).

**Table 4.5 Mean recovery (range) of malathion in hair washings and urine of adult volunteers**

| Formulation (duration of treatment) | Malathion applied (mg) | Malathion recovered in hair washings (mg) | Malathion recovered in urine (mg) | Recovery (%) | | |
|---|---|---|---|---|---|---|
| | | | | Hair washings | Urine | Total |
| **Single dose** | | | | | | |
| *Skin intact* | | | | | | |
| Aqueous base (12 h) | 126 (60–220) | 63 (20–120) | 2.9 (1.7–4.3) | 49.9 | 2.3 | 52.2 |
| Alcohol base (2 h) | 89 (50–140) | 41 (20–70) | 2.1 (1.0–3.6) | 45.8 | 2.4 | 48.2 |
| *Damaged skin* | | | | | | |
| Aqueous base (12 h) | 114 (70–160) | 67 (30–110) | 3.7 (1.8–7.7) | 59.0 | 3.2 | 62.3 |
| Alcohol base (10 h) | 97 (0.04–160) | 31 (8–50) | 1.6 (0.6–2.6) | 31.6 | 1.6 | 33.2 |
| **Repeat dose** | | | | | | |
| *Alcohol base (10 h)* | | | | | | |
| Dose 1 | 101 (30–200) | 25 (10–70) | 2.4 (0.9–7.4) | 24.9 | 2.4 | 27.3 |
| Dose 2 | 88 (30–220) | 33 (10–120) | 1.9 (0.5–5.7) | 37.8 | 2.2 | 40.0 |
| Dose 3 | 96 (50–200) | 14 (10–20) | 2.0 (0.5–4.6) | 14.8 | 2.1 | 16.9 |
| *Shampoo (2 × 5 min)* | | | | | | |
| Dose 1 | 237 (180–280) | 112 (80–140) | 1.2 (0.8–1.7) | 47.0 | 0.5 | 47.5 |
| Dose 2 | 240 (210–320) | 121 (90–140) | 0.6 (0.3–1.2) | 49.8 | 0.2 | 50.0 |
| Dose 3 | 236 (190–300) | 201 (150–260) | 0.8 (0.2–2.0) | 85.3 | 0.4 | 85.7 |

Adapted from Dennis and Lee (1999)

Although no studies were identified that have looked at the exposure of children or adults to malathion treatments for scabies, one published UK study was found that used microdialysis to monitor the absorption of a commercially available malathion treatment (used to treat both head louse and scabies infestation) though the volar (flexor) surface of the forearm in healthy adults (Boutsiouki *et al.*, 2001). The study was unable to detect malathion in dialysate after a 5-hour application of a commercial product, although malathion was detected in dialysate following application of a laboratory preparation containing malathion. It was suggested that this was as a result of reduced bioavailability of malathion in the commercial formulation.

The above studies suggest that head lice and scabies treatments are more likely to be used to treat infants, children and women. When malathion-containing treatments are used according to label instructions to treat head lice the exposure in adults will be at low levels (i.e. below the 0.3 mg/kg/bw ADI for malathion) and short lived. However, there is a lack of data on exposure following treatment for scabies and a lack of data on the exposure of infants and children from the use of such products for either head louse or scabies infestation. A further data gap exists in the lack of information on the patterns and frequency of use of such products, and hence the patterns and frequency of the resultant exposure episodes.

The Committee on Safety of Medicines (CSM) has recently reviewed the data relevant to the safety of malathion and concluded that there is no evidence to suggest that serious systemic adverse reactions are associated with topical malathion[*]. The CSM also concluded that there was no need for any regulatory action, but did express concern at anecdotal reports that many parents use these products

[*] Medicines Control Agency (2000) Safety of malathion for the treatment of louse and scabies infestation. *Current Problems in Pharmacovigilance, 26*, 2, available [May 2002] at: www.mca.gov.uk/ourwork/monitorsafequalmed/currentproblems/cpmay2000.pdf

repeatedly on their children[a]. However, the Committee noted that the product information for all malathion-containing preparations warns against repeated use.

### 4.5.2 Veterinary medicines

Several OP compounds, approved for use in veterinary medicines in the UK, may be used domestically. In particular, diazinon is the active ingredient (AI) in five flea collar products for cats and dogs that are available on general sale (NOAH, 2001). There are no published UK studies on the exposure of children to OPs in flea collars, although the Veterinary Products Committee, an independent scientific committee that advises the VMD has noted that[b] "…pet animals may wear flea collars for long periods [120–300 days (NOAH, 2001)] as a preventative measure and that this could lead to long-term exposure of pet owners to low levels of OP compounds." This is subject to ongoing review by the VMD.

One study published in the USA has examined exposure to chlorpyrifos following dipping of dogs to control fleas (Boone *et al.*, 2001). This study found initial geometric mean transferable residues of chlorpyrifos of 971.2 µg/dog (95% CI, 491.9–1917.3 µg/dog) on a cotton glove from stroking a 258 $cm^2$ (40 $in^2$) area of the back of a dog for 5 minutes, 4 hours after treatment. By 21 days after treatment the geometric mean transferable residues had decreased by 97% to an average of 26.6 µg/dog (95% CI, 13.5–53.6 µg/dog). The authors calculated that this would result in an average daily exposure to a child of between 0.2 and 0.6 µg/kg bw/day of chlorpyrifos over the 21-day period (based on the geometric mean transferable residues and assuming that the child played with a dog for 5 minutes per day over an 515 $cm^2$ (80 $in^2$) area, and that the absorption rate of chlorpyrifos is 3%; Boone *et al.*, 2001). This equates to an exposure of between 2 and 6% of the ADI for chlorpyrifos (10 µg/kg bw/day) per day over the 21-day period. Although such products are not licensed in the UK (and the product is also no longer supported by the manufacturer in the US; Boone *et al.*, 2001), the study does highlight that pets treated for fleas with OP-containing products may potentially be a source of low-level exposure to children.

## 4.6 Other environmental exposures

In addition to dietary exposures, infants and children may be exposed to OPs from environmental sources, such as the domestic environment (e.g. the use of pesticides in the home), or the non-domestic environment (e.g. spray drift). The following sections summarise some of the available data on these sources of exposure.

### 4.6.1 Domestic exposure

The application of OP pesticides in and around the home, either by amateur or professional applicators, is a potential source of exposure (IEH, 1999). As of 01 April 2002 there were 66[c] approved pesticide products containing an OP available for amateur use in the UK, and several others that are available but are undergoing phased revocation. There are no data available on the extent of exposure arising from household use of OP pesticides in the UK (COT, 1999), nor were any data identified on the frequency, pattern or duration of use of pesticides in the domestic environment. This precludes making a reasonable estimate of the contribution of such events to the long-term exposure of infants and children in the UK. There have, however, been a number of US studies looking at levels of pesticides in the domestic environment, particularly after application of a pesticide product. Several

[a] Medicines Control Agency (2001) *Summary of the Committee on Safety of Medicines Meeting Held on 27 May 1999*, available [May 2002] at: www.mca.gov.uk/aboutagency/regframework/csm/csm27599.pdf

[b] Veterinary Products Committee (1999) *Report of the Veterinary Products Committee to the Licensing Authority on Products with an OP as Active Ingredient (Other than Sheep Dips)*, available [May 2002] at: www.vpc.gov.uk/reports/vpcnonop.pdf

[c] Of these 66 products, 44 contain dichlorvos. Approvals for dichlorvos containing pesticide products have been suspended following advice to Ministers from the Advisory Committee on Pesticides in March 2002

studies have demonstrated that indoor applications of OP pesticides result in residues on target and non-target surfaces and in indoor air that may persist for a number of days following the application and that they have the potential to result in exposure to infants and children (Gurunathan *et al.*, 1998; Lu & Fenske, 1998). However, more recent improvements in sampling methodologies suggest that some of these studies may have over-estimated the dermal exposure to residues of OP pesticides indoors (Lu & Fenske, 1999). Additionally, such studies only describe intermittent exposure episodes; little research has been conducted to quantify the contribution of such exposure episodes to total or long-term exposure.

### 4.6.2 Non-domestic exposure

Other possible sources of exposure to OPs in the UK could include spray drift from the application of OP pesticides to crops, or the use of OP pesticides in non-domestic environments (e.g. hospitals, schools, nurseries, etc.). However, no UK data were identified that would allow evaluation of the relative importance of these as possible sources of exposure.

## 4.7 Biomarker studies

There have been no UK biomarker studies of children's exposure to OP pesticides, although there have been several European and US studies that provide an indication of exposure levels and the factors that affect the exposure of infants and children to OPs. Many studies have looked at dialkylphosphate metabolites, which are specific to OPs as a class (Adgate *et al.*, 2001) and so can be used to help determine a child's total exposure to OP compounds.

### 4.7.1 European studies

A study in Germany examined the levels of DMP, DEP, DMTP, DETP, DMDTP and DEDTP in urine spot samples of 309 children up to 6 years of age (Heudorf & Angerer, 2001). The aim of the study was to determine whether chlorpyrifos detected in house dust samples in former US forces housing (median level in house dust: 0.19 mg/kg; thought to be from chlorpyrifos applications four years earlier) had resulted in increased internal exposures of the inhabitants. The study found that for all metabolites, except DEDTP, children below the age of 6 years had significantly higher metabolite concentrations per gram of creatinine than the other age groups monitored (6–<14, 14–<20 and =20 years). The ratio of child (<6 years old) to adult (≥20 years old) exposure (based on the mean metabolite concentrations) ranged from 2.86 for DETP to 0.22. However, the study did not find any significant correlations between chlorpyrifos in house dust and the levels of diethyl metabolites (the metabolites of chlorpyrifos) in the whole group or in the children below 6 years of age. The level of exposure of adult participants in the study did not differ from that of the general population in Germany (Heudorf & Angerer, 2001); no data were presented with which to compare the level of exposure of the child participants.

A similar study, undertaken in the Tuscany region of Italy, examined the exposure of 195 children of 6–7 years of age with the aim of comparing adult and child exposures and determining whether certain lifestyle factors influenced OP levels, as measured by urinary excretion of six dialkylphosphate biomarkers (DMP, DMTP, DMDTP, DEP, DETP and DEDTP; Aprea *et al.*, 2000). The study found significantly higher levels of all metabolites in children compared with a population of 124 adults in the general population of southwest Tuscany (Student's *t*-test, $p < 0.05$). The ratio of child to adult exposure (based on the mean metabolite concentrations, with adult data taken from Aprea *et al.*, 1996) ranged from 0.69 for DEDTP to 1.86 for DMP, with all the metabolites, except DEDTP and DETP, having a child to adult ratio above 1.0. The study also found that reported pest-control treatments in the preceding month were significantly related to increased urinary levels of DMTP, DETP, the sum of all methyl metabolites and the sum of all metabolites (Bonferroni/Dunn *post hoc* test, $p < 0.05$). The presence of a garden was also significantly related to the urinary excretion of DMDTP (Bonferroni/Dunn *post hoc* test, $p < 0.05$). The child's sex, the presence of cut flowers or

plants in the house, pet ownership, and the consumption of one organic school meal a day were not significantly related to urinary excretion of the dialkylphosphate metabolites (Aprea *et al.*, 2000).

A summary of the results of the studies of Heudorf and Angerer (2001) and Aprea *et al.* (2000) is presented in Table 4.6.

## 4.7.2 US studies

There have been several US studies of children's exposure to OPs. The study of Loewenherz *et al.* (1997) is summarised in Section 4.3.2. However, besides demonstrating an effect of parental occupation and proximity to an orchard on exposure, the study also found a weak trend of increasing metabolite concentrations with decreasing age among children of pesticide applicators (Mann-Whitney *U*-test, $p = 0.06$), and that the younger children within these families had significantly higher concentrations than their older siblings (Wilcoxon Signed Rank test, $p = 0.04$).

Lu *et al.* (2001) measured six dialkylphosphate metabolites (DMP, DMTP, DMDTP, DEP, DETP and DEDTP) in urine samples of 96 children aged 2–5 years living in two Seattle metropolitan communities. The median concentrations of the dimethyl and diethyl dialkylphosphate metabolites were 0.11 and 0.04 µmol/l, respectively, for all children. Metabolite concentrations were significantly higher in children living in households where garden pesticide use within the previous six months was reported (Mann-Whitney *U*-test, $p = 0.05$ and $p = 0.02$ for dimethyl and diethyl dialkylphosphates, respectively). No significant differences in dialkylphosphate concentrations were found that were related to season, community, sex, age, family income, housing type, or reported pet treatment or indoor pesticide use within the previous six months.

Adgate *et al.* (2001) examined the exposure of a probability-based sample of 102 children aged 3–13 years from urban (Minneapolis and St. Paul, USA) and non-urban (Rice and Goodhue counties, USA) households during the summer of 1997. The sampling preferentially selected households where children were likely to have higher exposures, based on a residential inventory documenting storage and use of products containing the target pesticides (Quackenboss *et al.*, 2000); however, statistical weightings were developed to adjust for oversampling the nominally higher-pesticide-use households. The study measured the levels of metabolites for malathion (malathion dicarboxylic acid (MDA)) and chlorpyrifos (3,5,6-trichloro-2-pyridinol (TCP)), amongst other metabolites, in first morning void urine samples. 3,5,6-Trichloro-2-pyridinol was detected in 93% of samples and MDA in 36.6% of samples, with weighted population mean concentrations of 9.6 µg/l (SE, 0.9; 95% CI, 7.8–11 µg/l) for TCP and 1.7 µg/l (SE, 0.3; 95% CI, 1.1–2.3 µg/l) for MDA. On a log scale, mean TCP levels were significantly higher in urban than non-urban children ($p = 0.036$). However, metabolite levels did not vary systematically by sex, age (<6 years versus >6 years), race, household income, or putative household pesticide use.

Overall these data show that infants and children can be exposed to levels of OP pesticides that are higher, on a mg/kg bw basis, than those of adults in the general population. However, possibly as a result of the relatively small populations studied, no factors appear to be consistently related to increased levels of exposure to OP pesticides, except for proximity to agricultural spraying of OP pesticides and para-occupational sources of OP pesticides exposure, although the importance of such factors in the UK is uncertain (see Section 4.3.2). Factors that may also have some influence on exposure include age, presence of a garden, and home or garden use of pesticides.

**Table 4.6 Summary of dialkylphosphate concentrations (µg/g creatinine) in the urine of two European populations of children**

| Organophosphate metabolite | Country of study | Age of children | % Positive samples | Mean ± SD | 25th Percentile | Median | 75th Percentile | Range |
|---|---|---|---|---|---|---|---|---|
| Dimethylphosphate | Germany | <6 years | 77.0 | 63.4 ± 117.6 | 8.8 | 27.4 | 65.7 | <LOD–1096.4 |
| | Italy | 6–7 years | 96.0 | 22.5 ± 24.8 | 8.2 | 13.8 | 28.0 | 0.9–185.5 |
| Dimethylthiophosphate | Germany | <6 years | 86.4 | 77.4 ± 167.2 | 9.2 | 28.9 | 69.7 | <LOD–1800.9 |
| | Italy | 6–7 years | 94.0 | 24.2 ± 27.6 | 8.2 | 14.1 | 27.0 | 0.6–216.9 |
| Dimethyldithiophosphate | Germany | <6 years | 33.3 | 4.9 ± 26.9 | <LOD | <LOD | 2.0 | <LOD–424.7 |
| | Italy | 6–7 years | 34.0 | 4.8 ± 11.0 | 0.9 | 1.5 | 4.7 | 0.5–119.4 |
| Diethylphosphate | Germany | <6 years | 76.7 | 8.4 ± 12.1 | 1.3 | 4.8 | 9.3 | <LOD–79.1 |
| | Italy | 6–7 years | 75.0 | 7.4 ± 7.1 | 2.7 | 5.5 | 9.8 | 0.8–55.5 |
| Diethylthiophosphate | Germany | <6 years | 45.3 | 4.0 ± 12.7 | <LOD | <LOD | <LOD | <LOD–115.5 |
| | Italy | 6–7 years | 48.0 | 4.9 ± 6.4 | 1.1 | 2.5 | 5.8 | 0.5–48.4 |
| Diethyldithiophosphate | Germany | <6 years | 3.2 | 0.0 ± 0.1 | <LOD | <LOD | <LOD | <LOD–1.5 |
| | Italy | 6–7 years | 12.0 | 2.2 ± 3.1 | 0.9 | 1.1 | 2.1 | 0.4–26.1 |

Adapted from Aprea *et al.* (2000) and Heudorf and Angerer (2001)

LOD, Limit of detection, 1 µg/l

## 4.8 Summary of exposure data

The limited available data and the lack of suitable methodology do not allow reliable estimates to be derived of the total exposure of infants and children to OPs as a class of compounds in the UK. As a result, there has not yet been any assessment of children's long-term exposure to OP pesticides as a class in the UK from any source. However, WiGRAMP has been considering methodologies for conducting such assessments of exposure, and it is likely that this will be taken forward by the regulatory agencies following publication of the WiGRAMP report.

The available data suggest that exposure to OP pesticides could potentially begin *in utero*, although further research is needed in order to understand better the significance of these results. As the diet of most infants under 6 months consists mainly of milk (either breast, infant formulae or cows), water and commercial infant foods, the exposure to OP pesticides from the diet is likely to be very low as a result of the very low levels of OP pesticides in these dietary constituents. Once infants begin to consume 'family foods', dietary exposure is likely to become a more important exposure pathway, particularly as cereals, fruit and vegetables form important parts of the diet of infants and are the food types in which OP pesticide residues are most frequently found. Thus fruit, vegetables and cereal products will probably be the main source of exposure to OP pesticides for infants and children older than 6 months. However, the available data indicate that exposure to individual OP pesticides from individual food items is usually well below the ADI. Other contributory sources of exposure could potentially include the use of human and veterinary medicines, the application of OP pesticides in and around the home, exposure from agricultural applications of OP pesticides and para-occupational exposure from parents who work with OP compounds. Further research is required to quantify the relative contribution of these sources to long-term exposure of children to OPs in the UK.

Overall the available biomarker studies suggest that children are exposed to OP compounds at low levels. The sources of such exposure are difficult to interpret from the biomarker studies, mainly because the sample sizes may not be sufficiently large to detect differences in exposure associated with different factors. However, diet is assumed to be an important contribution to overall exposure, and probably accounts for the high proportion of children having detectable OP metabolites in their urine in Europe and the USA. There also seems to be some evidence to suggest that factors influencing exposure may include age, garden use of pesticides, proximity of a household to agricultural spraying, parental occupation and whether the household is in an urban or non-urban area.

# 5 Overall Evaluation of the Epidemiological Data on the Effects of Low-level Exposure to Organophosphate Pesticides on Fetal and Childhood Health

## 5.1 Introduction

Low-level exposure (in view of the different potencies of OPs), is defined as that which does not evoke overt toxicity. The potential of OPs to cause low-level toxicity is a controversial area of toxicology and one that is extremely difficult to study. It is hampered by a number of factors such as difficulty in measuring actual exposure levels, exposure to a range of different OPs and other chemicals, length of time between exposure and appearance of symptoms, and the diverse nature of the symptoms (POST, 1998).

The aim of this section is to provide an overall evaluation of the available epidemiological data to assess fetal and childhood health effects following low-level exposure to OP pesticides.

## 5.2 Evaluation of health effects

Following a comprehensive review of the literature very few epidemiology studies were identified that investigated the adverse health effects in neonates and children from exposure to low levels of OP pesticides. Six studies and four case reports were retrieved from the literature. Very little or no weight can be attributed to the case reports as they are one-off reported incidences of effects and they lack reliable exposure estimates. They were included in Section 3 for completeness.

The study by McConnell *et al.* (1999) investigated children (5–12 years) continuously exposed to OP pesticides from airport run-off in Nicaragua for acute health effects such as headache, blurred vision, diarrhoea, nausea, vomiting, stomach ache, or excessive sweating, symptoms compatible with cholinesterase inhibition. Although the focus of this review is on chronic health effects as a result of long-term exposure to OPs, the McConnell study is worth noting as the children exposed to the run-off had mean levels of cholinesterase significantly below those of the unexposed children but did not show acute systemic effects. It is possible that the exposed children may have developed a tolerance or resistance to the OP pesticides however there was no assessment of chronic effects. These children were continuously exposed to apparently low levels of OP pesticides and a follow-up study to investigate possible developmental effects would be useful.

Of the five remaining studies, three studies looking at miscarriage, pre-term delivery, small-for-gestational-age births and sex ratios (Savitz *et al.*, 1997), spontaneous abortion (Arbuckle *et al.*, 2001), and congenital malformations such as nervous system, cardiovascular defects, oral clefts, hypospadias or epispadias, musculoskeletal defects and non-specific anomalies (García *et al.*, 1998) showed no adverse effects resulting from low-level exposure to OP pesticides.

Thomas *et al.* (1992) examined the association between malathion exposure (via spraying fruit fly) and spontaneous abortion, stillbirth, congenital malformations and intrauterine growth retardation in 7450 pregnancies. No significant association was reported for spontaneous abortion, stillbirth or intrauterine retardation but a significant association was reported for gastrointestinal anomalies with a relative risk of 4.14 (95% CI, 1.01–16.6) for second trimester exposures. In this study the adjusted relative risk (4.14; 95% CI, 1.01–16.6) reported is higher than the unadjusted relative risk (3.29; 95%

CI, 1.09–9.87) which is unusual as the adjusted relative risk is normally lower when confounders are taken into account. There were 13 cases of gastrointestinal anomalies and the authors report two defects (tracheoesopohageal fistulas and pyloric stenoses) that are unrelated in aetiology yet associate both defects with exposure to malathion in the second trimester, even though they indicate that one of the defects (the tracheoesopohageal fistulas) has a first trimester origin. The uncertainty with regard to the defects and the timing of the exposure plus the large confidence intervals casts doubt on the true significance of these reported effects and the anomalies must be analysed separately to investigate this possible link further.

An association between OP pesticide metabolite levels in the urine of nine agricultural workers and increased frequency of sperm aneuploides was reported by Recio *et al.* (2001). However this is a preliminary study with a very small sample size and no firm conclusions can be drawn.

From the few studies identified from the literature at this time, there is no convincing human evidence that OP pesticides cause developmental or reproductive effects. However gastrointestinal anomalies and sperm aneuploidies might potentially be associated with low-level exposure to OP pesticides but no definite conclusions can be drawn from the limited data available.

## 5.3 Evaluation of exposure data

The available data indicate that exposure to OP pesticides could potentially begin *in utero* (Richardson, 1995). Only one human study was identified that measured fetal exposure to OP pesticides and four of the six OP pesticides investigated were detected in the post-partum meconium of 20 newborns. The limitations of this study include small sample size (20) and no reporting of parental exposure. A number of US studies (Loewenherz *et al.*, 1997; Fenske *et al.*, 2000; Lu *et al.*, 2000; McCauley *et al.*, 2001) suggest that children exposed to para-occupational sources and living in proximity to agricultural spraying of OP pesticides may have higher exposures than children without these factors. However, given the climatic, ecological and cultural differences between the US and the UK, it is difficult to judge how important these factors may be in determining fetal and childhood exposure in the UK.

Diet is a source of childhood exposure to OP pesticides in the UK. OP pesticides were not detected in breast milk[a] in one survey conducted on 50 samples, nor have they been detected in infant formula in one survey conducted on 20 samples. Surveys of commercially based infant foods have shown occasional OP pesticide residues in fruit based and cereal based infant foods. However, risk assessments have shown that the resultant exposure would be below the respective ADIs for the individual OP pesticides. New regulations that will come into force in the UK in July 2002 set a low MRL of 0.01 mg/kg for all pesticide residues in infant foods and will help limit and possibly reduce infant exposure to OPs.

Drinking water and bottled water make only very minor, and insignificant, contributions to total OP pesticide exposure from diet. For children, and infants older than six months, fruit, vegetables and cereal products will likely be the main source of exposure to OP pesticides. Some individual OP pesticide residues in fruit and vegetables have been sufficient to result in occasional exceedances of the ADI (e.g. methamidophos in sweet peppers[b]). Whether or not the combined intake of different OP pesticide residues from different food items could result in exposures above an acceptable level has not been evaluated, although how to undertake such an assessment is currently being reviewed by WiGRAMP.

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[a] MAFF (1999) *Annual Report of the Working Party on Pesticide Residues 1998. Supplement to The Pesticides Monitor 1999*. MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

[b] MAFF (2000) *Annual Report of the Working Party on Pesticide Residues 1999 (from 2000 known as the Pesticide Residues Committee. Supplement to The Pesticides Monitor 2000*. MAFF Publications. Available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

Treatments for head lice and scabies contain malathion. No studies were identified that looked at children's exposure to malathion from head lice or scabies treatment. However if the treatments are used according to the label instructions the levels of exposure will be within acceptable levels for adults. Exposure to malathion may be increased if the treatments are used more often than recommended. There are no published UK studies on the exposure of children to OP pesticides in flea collars, although the Veterinary Products Committee of the VMD have noted that "pet animals may wear flea collars for long periods [120–300 days (NOAH, 2001)] as a preventative measure and that this could lead to long-term exposure of pet owners to low levels of OP compounds". This is currently being reviewed by the VMD and VPC.

Exposure to OP pesticides may arise from other environmental sources, such as the domestic environment (e.g. use of pesticides in the home) or the non-domestic environment (e.g. spray drift). There are no data available on the extent of exposure arising from household use of OP pesticides in the UK nor were any data identified on the frequency, pattern or duration of use of pesticides in the domestic environment. There are also no exposure data on spray-drift from the application of OP pesticides to crops, or the use of OP pesticides in non-domestic environments in the UK (e.g. hospitals, schools, nurseries).

Biomarker studies from the US and continental Europe suggest that children are exposed to OP compounds at low levels. There is some evidence to suggest that important factors influencing exposure include garden use of pesticides (Lu *et al.*, 2001), proximity of the household to agricultural spraying (Loewenherz *et al.*, 1997), parental occupation (Loewenherz *et al.*, 1997), and whether the household is in an urban or non-urban area (Adgate *et al.*, 2001). There is also some evidence to suggest that younger children may receive higher exposures to OP pesticides than older children and adults per mg/kg body weight (Aprea *et al.*, 2000; Heudorf & Angerer, 2001).

Other than diet there is very little information regarding sources of fetal and childhood exposure to OP pesticides. As a result it is not possible to estimate the exposure of fetus or child to OPs as a class of compounds in the UK. The dietary data does indicate however that exceedances of individual OPs in individual food items would occur very infrequently.

# 5.4 Overall evaluation

There is inadequate information from the epidemiology studies to enable any conclusions to be drawn regarding effects of exposure of OP pesticides on fetal and childhood health. From the six epidemiology studies reviewed following an extensive literature search, there is no reported evidence of adverse health effects (reproductive or developmental) in the fetus or child except for two limited studies that suggest that exposure to OP pesticides might be associated with gastrointestinal anomalies and sperm aneuploidies, but these observations require further investigation before any definite conclusions can be drawn.

Data from the animal studies suggest that a number of biological systems, not all cholinergically regulated, appear to be affected by the OP pesticides but the biological significance of this in relation to humans is unclear.

Regarding the exposure data, most of the available information relates to diet or drinking water. This indicates that exceedances of the ADI for individual OP pesticides in water or individual food items occur only very infrequently. Very little exposure data are however available in other uses, and it is not possible to estimate total exposure of infants and children to OP pesticides, as a class.

# 6 Ongoing Reviews and Research

## 6.1 Government review of anticholinesterase compounds

Following an announcement by the UK Food Safety Minister in May 1998, the PSD and HSE are conducting a review of all anticholinesterase compounds approved under the Control of Pesticides Regulations 1986. Anticholinesterase compounds used in veterinary medicines (which are considered under separate legislation) are also being reviewed by VMD. The reviews are being conducted to reassess the risk that these products present to consumers, workers and the environment. This will ensure that products are supported by a data package that has been evaluated to modern standards. As part of the review process PSD will conduct an assessment of cumulative pesticide exposures to consumers and workers based on information generated following the conclusion of the individual reviews.

## 6.2 Exposure of Children to Pesticides Workshop, 27–29 September 2001, BgVV, Berlin

This workshop, held in September 2001, was organised by the German Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV). The attendees to the workshop (approximately 50) were mainly from Germany, with others from USA, Sweden, France, Switzerland and the UK. The main objective of the workshop was to propose an approach to estimate childhood exposure to pesticides, but also consider childhood health effects of exposure to pesticides. Although there was a significant amount of ongoing research into pesticides and child health, there was none in the area of low-level OP pesticides. One of the outcomes of the workshop was that more research is required in this area. The workshop report is due to be published summer 2002.

## 6.3 Center for Health Assessment of the Mothers and Children of Salinas Study, University of California, USA

The Center for Health Assessment of the Mothers and Children of Salinas (CHAMACOS)[*] study is taking place in an agricultural community in Montery County, California. The purpose of the study is to assess the extent of children's low-level long-term exposure to pesticides (including OPs) and to allergens, and to determine whether such exposure can lead to adverse health consequences. The aims of the study are:

- to estimate sources, pathways and levels of *in utero* and post-natal pesticide exposure of children living in an agricultural community by measuring biological and environmental samples;
- to determine whether exposure to pesticides is associated with poorer neurodevelopmental functioning and behavioural problems, delayed growth, and increased respiratory symptoms and disease;
- to determine whether exposure to environmental allergens and respiratory irritants is associated with increased respiratory symptoms and disease; and

[*] University of California (2001) *About Us*. Available [May 2002] at: http://ehs.sph.berkeley.edu/chamacos/

- to evaluate the impact of 'Healthy Home' interventions on the reduction of pesticide exposure to farmworker children.

Enrolment into the study ended in October 2000, by which time 550 women had been recruited. It is intended to follow the children up to the age of 2 years.

## 6.4 Mothers and Newborns Study, Columbia University, USA

The Mothers and Newborns Study [a] comprises a cohort of over 500 low-income mothers residing in Northern Manhattan and the South Bronx, recruited during pregnancy, whose newborns will be followed prospectively to 2 years of age (and possibly beyond). The aim of the study is to look at the influence of environmental factors on asthma, impairments to growth and development, and cancer. The environmental factors assessed will include pre- and post-natal exposure to airborne particulate matter, polycyclic aromatic hydrocarbons, pesticides (including OPs), environmental tobacco smoke, polychlorinated biphenyls, and home allergens. The influence of inadequate nutrition and other socio-economic factors on the effect of environmental factors will also be assessed. Although the research is still on-going, results are being published, a list of which is available on the Internet[b].

## 6.5 The Role of Metabolism in Influencing Susceptibility to Organophosphate Pesticide Toxicity in Man, University of Newcastle upon Tyne, UK

This study is investigating the role of metabolism in influencing susceptibility to OP pesticide toxicity in man and has focused on determining the extent of variation between individuals in their capacity to metabolise organophosphates and the influence of genetic makeup on these differences (personal communication, Dr Faith Williams, University of Newcastle Upon Tyne).

This work has shown the importance of the balance between activation (by various cytochromes P450) and detoxification (by A- and B-esterases) pathways in determining toxic effects. An extensive panel of characterised human liver microsomal preparations has been used to identify the P450 isoforms participating in the activation pathway(s) and to determine the extent of the detoxication of several OPs via esterase hydrolysis.

The study is currently being extended to investigate the capacity of a panel of foetal lvers to metabolise OPs. These studies will use the knowledge gained from the research with adult samples to determine the activation/detoxication balance for the unborn child. This research is necessary because the literature has suggested that young animals may be more susceptible to OP toxicity than adults, but it is uncertain whether this has a purely metabolic mechanism. These studies will determine the extent in which human foetal liver can metabolise OPs, since this could be used to assess the potential risk to the developing nervous system.

[a] Columbia University (2002) *Mission*, available [May 2002] at: http://cpmcnet.columbia.edu/dept/sph/ccceh/mission/index.html
[b] Columbia University (2002) *Publications*, available [May 2002] at: http://cpmcnet.columbia.edu/dept/sph/ccceh/publications/publications.html

# 7 Areas for Further Research

There is a surprising lack of epidemiological data on health effects in the fetus and child from exposure to OP pesticides. The few data that are available come mainly from the USA and focuses on reproductive effects. No studies have been conducted on developmental effects. There are two studies ongoing in the USA examining the adverse effects (including neurodevelopment and behavioural problems) in children from exposure to OP pesticides, the results of which will help assess the need for and/or determine priorities for further health-related research although a number of UK exposure-related areas could be progressed independently of this. With the exception of dietary sources there are also large data gaps for exposure to OP pesticides in the UK. Outlined below are some suggestions for future research.

- Children in the McConnell study (1999) continuously exposed to OP pesticides had significantly lower levels of cholinesterase than control children but did not demonstrate acute systemic effects. A follow-up to this study would provide an opportunity to observe developmental effects in the exposed children.

- If the studies in the USA do demonstrate adverse health effects a comprehensive review of the animal data in the literature might help to elucidate the mechanisms of action in relation to specific OPs.

- Research is required to fully assess the exposure of UK infants and children from all routes of exposure to OP pesticides. A biomonitoring survey of such exposures would prove informative, enable an assessment of whether measures need to be implemented to reduce exposure and provide valuable information to interpret the findings of the on-going US research (CHAMACOS and Mothers and Newborns Studies) in the light of UK exposures.

- Research would also be useful to better ascertain the contribution of non-dietary sources of exposure to OPs to total exposure. Particular UK data gaps include information on children's exposure from the use of OP pesticides in non-agricultural settings (e.g. the home); children's exposure to OP-containing head lice treatments along with data on the patterns and frequency of use of such products; the importance of para-occupational sources of exposure, and exposure to OPs from environmental sources (e.g. spray drift). Better understanding of these individual sources of exposure could highlight potentially high-exposed groups.

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# Annex 1: Search Strategy

Relevant descriptors* for organophosphorus pesticides (OP) were identified in the Medical Subject Heading thesaurus (MeSH) which is used by the National Library of Medicine (NLM) to index papers entered into Medline, Toxline and CancerLit. The terms used in Embase were also identified from the Emtree thesaurus produced by Elsevier Science (Table A1.1).

**Table A1.1 Literature search descriptors**

| Database | Pesticides descriptors | Population descriptors |
|---|---|---|
| Medline, Toxline and CancerLit | ORGANOPHOSPHORUS-COMPOUNDS<br>ORGANOTHIOPHOSPHORUS-COMPOUNDS<br>INSECTICIDES-ORGANOPHOSPHATE | CHILD, FETUS, EMBRYO, PARENTS, PREGNANCY |
| Embase | ORGANOPHOSPHATE-PESTICIDE | CHILD, FETUS, EMBRYO, ADOLESCENT, NEWBORN |
| Biosis, CA Search | 'ORGANOPHOSPHORUS or ORGANOPHOSPHATE' in the same sentence as 'PESTICIDE or INSECTICIDE' | CHILD, CHILDREN, EMBRYO, FETUS, ADOLESCENCE, ADOLESCENT, NEWBORN, PREGNANCIES OR PREGNANCY, PARENT(S) |

Medline indexes chemicals according to their chemical structure, as opposed to Embase which groups chemicals according to their activity.

The following MeSH terms for Medline were identified as being required for OPs:

- Organophosphorus compounds# - D2.705#
- Organothiophosphorus compounds# - D2.719#
- Insecticides-organophosphate# - D5.723.491.574#

The reason for this was that Dichlorvos - **D2.705**.190 (Figure A1) for example, is indexed under organophosphorus compounds# - **D2.705** (Figure A1) and not under organothiophosphorus compounds# - **D2.719** (Figure A2) where most of the other OP are indexed, or under insecticides-organophosphate# - **D5.723.491.574** (Figure A3).

Emtree for Embase is simpler than MeSH for the NLM databases, as all OPs are indexed under one heading: organophosphate pesticide# - D5.30.60.655# (Figure A4).

Descriptors for 'fetus', 'embryo' and 'children' were also identified for each database, as terms differ from database to database (Table A1.1).

For Medline and Embase, these terms were searched for in the descriptor field only, as the papers have been indexed by the NLM or Elsevier Science with these terms. Biosis and CA Search do not have such a rigid descriptor system as Medline and Embase and cannot be searched in the same way. Hence the terms were searched for in the *Titles*, *Descriptor* and *Abstract* fields.

* Different people use different phrases/words to describe a subject. Descriptors are the single terms added to a record in the descriptor field by indexers, which allows ALL records on a subject to be retrieved using a single term, without the need to search on all possible phrases/words for that subject.

In the search strategy, these terms were combined together in order to retrieve papers containing both descriptors/terms: ‘organophosphorus compounds’ AND ‘embryo’ OR ‘organophosphorus compounds’ AND ‘fetus’ OR organophosphorus compounds’ AND ‘adolescent’ and so on.

## Figure A1 MeSH Tree for organophosphorus compounds

**D2 - ORGANIC CHEMICALS**

| | | | |
|---|---|---|---|
| Organic Chemicals | | | |
| Organometallic Compounds | | | |
| Organomercury Compounds | | | |
| Merbromin | | | |
| Merbromin | D2.691.750.575 | | |
| Phenylmercury Compounds | D2.691.750.740 | | |
| Chloromercurinitrophenols | D2.691.750.740.225 | | |
| 4-Chloromercuribenzenesulfonate | D2.691.750.740.250 | D2.455.426. | D2.886.645. |
| Mercuribenzoates | D2.691.750.740.644 | D2.241.223. | |
| Chloromercuribenzoates | D2.691.750.740.644.261 | D2.241.223. | |
| p-Chloromercuribenzoic Acid | D2.691.750.740.644.261.275 | D2.241.223. | |
| Hydroxymercuribenzoates | D2.691.750.740.644.450 | D2.241.223.<br>D2.241.511. | D2.241.223.<br>D2.755.410. |
| Phenylmercuric Acetate | D2.691.750.740.760 | | |
| Organoplatinum Compounds | D2.691.800 | | |
| Carboplatin | D2.691.800.338 | | |
| Organotechnetium Compounds | D2.691.825 | | |
| Technetium Tc 99m Aggregated Albumin | D2.691.825.375 | D12.776.34. | |
| Technetium Tc 99m Diethyl-iminodiacetic Acid | D2.691.825.445 | D2.241.81.<br>D12.125.72. | D2.491.485. |
| Technetium Tc 99m Dimercaptosuccinic Acid | D2.691.825.468 | D2.241.81. | D2.886.489. |
| Technetium Tc 99m Disofenin | D2.691.825.475 | D2.241.81.<br>D12.125.72. | D2.491.485. |
| Technetium Tc 99m Exametazime | D2.691.825.562 | D2.92.570. | |
| Technetium Tc 99m Lidofenin | D2.691.825.710 | D2.241.81.<br>D12.125.72. | D2.491.485. |
| Technetium Tc 99m Medronate | D2.691.825.750 | D2.705.206. | |
| Technetium Tc 99m Mertiatide | D2.691.825.775 | D12.644.456. | |
| Technetium Tc 99m Pentetate | D2.691.825.875 | D2.92.782. | D2.241.81. |
| Technetium Tc 99m Sestamibi | D2.691.825.937 | D2.626.872 | |
| Organotin Compounds | D2.691.850 | | |
| Trialkyltin Compounds | D2.691.850.900 | | |
| Triethyltin Compounds | D2.691.850.900.910 | | |
| Trimethyltin Compounds | D2.691.850.900.950 | | |
| Sucralfate | D2.691.925 | D9.203.698. | |
| Tetraethyl Lead | D2.691.950 | | |
| Zineb | D2.691.975 | D2.241.81. | D2.886.706. |
| Organophosphorus Compounds | D2.705 | | |
| Aminoethylphosphonic Acid | D2.705.50 | | |
| Armin | D2.705.65 | | |
| Carbamyl Phosphate | D2.705.130 | D2.241.81. | |
| Chlorfenvinphos | D2.705.150 | | |
| Dichlorvos | D2.705.190 | | |
| Diphosphoglyceric Acids | D2.705.196 | D2.241.81.<br>D9.203.811. | D2.241.511. |
| 2,3-Diphosphoglycerate | D2.705.196.175 | D2.241.81.<br>D9.203.811. | D2.241.511. |
| Diphosphonates | D2.705.206 | | |
| Alendronate | D2.705.206.100 | | |
| Clodronic Acid | D2.705.206.200 | | |
| Etidronic Acid | D2.705.206.830 | | |
| Technetium Tc 99m Medronate | D2.705.206.885 | D2.691.825. | |
| Fosinopril | D2.705.275 | D12.125.72. | |
| Hempa | D2.705.320 | | |
| Isoflurophate | D2.705.364 | | |
| Mevinphos | D2.705.434 | | |
| Monocrotophos | D2.705.471 | | |
| Naled | D2.705.509 | | |
| Paraoxon | D2.705.569 | | |
| Phosphamidon | D2.705.614 | | |
| Phosphines | D2.705.621 | D1.695.525 | |
| Phosphinic Acids | D2.705.629 | D1.29.260. | D1.695.625. |
| Phosphonic Acids | D2.705.639 | D1.29.260. | D1.695.625. |
| Fosfomycin | D2.705.639.250 | | |
| Phosphonoacetic Acid | D2.705.639.590 | D2.241.81. | |
| Foscarnet | D2.705.639.590.500 | D2.241.81. | |
| Trichlorfon | D2.705.639.930 | | |
| Phosphoramide Mustards | D2.705.670 | D2.455.526. | |
| Cyclophosphamide | D2.705.670.243 | D2.455.526. | |

## Figure A2 MeSH Headings for organothiophosphorus compounds

**D2 - ORGANIC CHEMICALS**

| | | | |
|---|---|---|---|
| Organic Chemicals | | | |
| Organophosphorus Compounds | | | |
| Phosphoramide Mustards | | | |
| Cyclophosphamide | | | |
| Ifosfamide | | | |
| Ifosfamide | D2.705.670.243.250 | D2.455.526. | D3.383.533. |
| Phosphoranes | D2.705.671 | D1.695.550 | |
| Phosphoric Acid Esters | D2.705.673 | | |
| Phosphorous Acids | D2.705.676 | D1.29.260. | D1.695.625. |
| Phosphites | D2.705.676.700 | D1.248.497. | D1.695.625. |
| Polyisoprenyl Phosphates | D2.705.690 | D2.455.849. | |
| Dolichol Phosphates | D2.705.690.200 | D2.33.415. D2.455.849. | D2.455.849. D10.516.289. |
| Sarin | D2.705.785 | | |
| Soman | D2.705.860 | | |
| Tetrachlorvinphos | D2.705.890 | | |
| Tetraisopropylpyrophosphamide | D2.705.900 | | |
| Tritolyl Phosphates | D2.705.960 | D2.755.239. | |
| Organoselenium Compounds | D2.712 | | |
| Selenocysteine | D2.712.600 | D12.125.166. | |
| Selenomethionine | D2.712.700 | D12.125.166. | |
| Organosilicon Compounds | D2.715 | | |
| Silanes | D2.715.625 | D1.837.700 | |
| Siloxanes | D2.715.650 | D1.837.800 | D25.720.900 |
| Silicones | D2.715.650.700 | D25.720.900. | |
| Dimethylpolysiloxanes | D2.715.650.700.150 | D25.720.900. | |
| Simethicone | D2.715.650.700.150.750 | D25.720.900. | |
| Silicone Gels | D2.715.650.700.755 | D25.720.900. | |
| Silicone Oils | D2.715.650.700.800 | D25.720.900. | |
| Trimethylsilyl Compounds | D2.715.715 | | |
| Organothiophosphorus Compounds | D2.719 | | |
| Amifostine | D2.719.60 | | |
| Azinphosmethyl | D2.719.94 | | |
| Chlorpyrifos | D2.719.170 | | |
| Coumaphos | D2.719.199 | D3.438.150. | |
| Cystaphos | D2.719.208 | | |
| Diazinon | D2.719.220 | | |
| Dimethoate | D2.719.245 | | |
| Disulfoton | D2.719.270 | | |
| Echothiophate Iodide | D2.719.341 | | |
| Fenitrothion | D2.719.456 | | |
| Fenthion | D2.719.460 | | |
| Fonofos | D2.719.464 | | |
| Leptophos | D2.719.500 | | |
| Malathion | D2.719.639 | | |
| Parathion | D2.719.746 | | |
| Methyl Parathion | D2.719.746.500 | | |
| Phenylphosphonothioic Acid, 2-Ethyl 2-(4-Nitrophenyl) Ester | D2.719.750 | | |
| Phorate | D2.719.783 | | |
| Phosmet | D2.719.790 | | |
| Temefos | D2.719.900 | | |
| Thiophosphoric Acid Esters | D2.719.926 | | |
| Thiotepa | D2.719.950 | D3.383.97. | |
| Peroxides | D2.737 | D1.248.497. | D1.650.550. |
| Lipid Peroxides | D2.737.450 | D10.516.440 | |
| tert-Butylhydroperoxide | D2.737.825 | | |
| Phenols | D2.755 | | |
| Aminophenols | D2.755.50 | D2.92.146. | |
| Anisoles | D2.755.75 | D2.355.601. | D2.355.726. |
| Anethole Trithione | D2.755.75.100 | D2.355.601. | D2.355.726. |
| Butylated Hydroxyanisole | D2.755.75.241 | D2.355.601. | D2.355.726. |
| Guaiacol | D2.755.75.536 | D2.355.601. D2.755.166. | D2.355.726. |
| Guaiacol Glyceryl Ether | D2.755.75.536.400 | D2.355.601. D2.755.166. | D2.355.726. |
| Methocarbamol | D2.755.75.536.400.500 | D2.241.81. | D2.355.601. |
| Bisphenol A-Glycidyl Methacrylate | D2.755.100 | D2.241.81. D25.720.716. | D25.339.149. |
| Bithionol | D2.755.120 | | |

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**Figure A3 MeSH headings for insecticide organophosphorus**

**D5 – ENVIRONMENTAL POLLUTANTS, NOXAE, AND PESTICIDES**

**Environmental Pollutants, Noxae, and Pesticides**
**Pesticides**
**Herbicides**
**Herbicides, Triazine**

| | | |
|---|---|---|
| **Herbicides, Triazine** | D5.723.366.477 | D27.720.723. |
| **Herbicides, Urea** | D5.723.366.506 | D27.720.723. |
| **Insect Repellents** | D5.723.441 | D27.720.723. |
| **Insecticides** | D5.723.491 | D27.720.723. |
| **Insecticides, Botanical** | D5.723.491.324 | D27.720.723. |
| **Insecticides, Carbamate** | D5.723.491.408 | D27.720.723. |
| **Insecticides, Organochlorine** | D5.723.491.491 | D27.720.723. |
| **Insecticides, Organophosphate** | D5.723.491.574 | D27.720.723. |
| **Insecticides, Organothiophosphate** | D5.723.491.657 | D27.720.723. |
| **Molluscacides** | D5.723.596 | D27.720.723. |
| **Pesticide Residues** | D5.723.697 | G3.850.460. |
| **Pesticide Synergists** | D5.723.748 | D27.720.723. |
| **Rodenticides** | D5.723.853 | D27.720.723. |

**Figure A4 Emtree**



D5.30.60.440.725 **pyrethroid**
allethrin
bioallethrin
bioresmethrin
cipermethrin
cismethrin
cyfluthrin
cyhalothrin
cyphenothrin
deltamethrin
fenpropathrin
fenvalerate
flucythrinate
flumethrin
fluvalinate
permethrin
phenothrin
pyrethrin
resmethrin
tetramethrin
tralomethrin

D5.30.60.560 **molluscacide**
aridanin
4 bromo 2,5 dichlorophenol
clonitralide
metaldehyde
phosalone

D5.30.60.650 **organochlorine pesticide**
chlornitrofen
chlorobenzilate
chloropicrin
chlorothalonil
chlorthiamid
dacthal
dicofol
tetradifon

D5.30.60.650.440 **organochlorine insecticide**
aldrin
campheclor
chlordane
chlordecone
chlorphenotane
clofentezine
1,1 dichloro 2,2 bis(4 chlorophenyl)ethane
1,1 dichloro 2,2 bis(4 chlorophenyl)ethylene
1,2 dichlorobenzene
1,4 dichlorobenzene
dieldrin
endosulfan
endrin
heptachlor
heptachlor epoxide
alpha hexachlorocyclohexane
beta hexachlorocyclohexane
isobenzan
lindane
methoxychlor
mirex
nonachlor
oxychlordane
photomirex
1,1,1 trichloro 2 (2 chlorophenyl) 2 (4 chlorophenyl)ethane

D5.30.60.655 **organophosphate pesticide**
armin
clofenvinfos
edifenphos
fenamiphos
fenclofos
phenthoate
thiometon
vamidothion

D5.30.60.655.440 **organophosphate insecticide**
acephate
azinphos ethyl
azinphos methyl
chlorpyrifos
chlorpyrifos methyl
coumafos
crufomate
cyanofenphos
cythioate
dichlorvos
dicrotophos
dimethoate
dimpylate
disulfoton

. . ethion
. . ethoprop
. . etrimfos
. . fenitrothion
. . fensulfothion
. . fenthion
. . fonofos
. . formothion
. . isofenphos
. . leptophos
. . malaoxon
. . malathion
. . methamidophos
. . methidathion
. . metrifonate
. . mevinphos
. . mipafox
. . monocrotophos
. . naled
. . omethoate
. . paraoxon
. . parathion
. . parathion methyl
. . phenylphosphonothioic acid o ethyl o (4 nitrophenyl) ester
. . phorate
. . phosalone
. . phosmet
. . . . . pnospnamidon
. . . . . phoxim
. . . . . pyraclofos
. . . . . pyridaphenthion
. . . . . quinalphos
. . . . . stirofos
. . . . . temefos
. . . . . terbufos
. . . . . triazophos
. . . . . tributyl phosphorotrithioite

**D5.30.60.770** **. . . rodenticide**
. . . . ANTU
. . . . brodifacoum
. . . . bromadiolone
. . . . bromethalin
. . . . chlorophacinone
. . . . coumatetralyl
. . . . difenacoum
. . . . flocoumafen
. . . . muricide
. . . . thallium sulfate
. . . . vacor
. . . . warfarin

**D5.40** **. industrial chemical**
. . aluminosilicate calcium
. . amosite
. . amphibole
. . apatite
. . aroclor
. . aroclor 1242
. . aroclor 1248
. . aroclor 1254
. . aroclor 1260
. . asbestos
. . asbestos fiber
. . asphalt
. . cellulose acetate
. . chrysotile
. . coal tar
. . concrete
. . crocidolite
. . epoxy resin
. . ethylene oxide
. . food additive
. . food dye
. . food preservative
. . formaldehyde
. . freon
. . fuller earth
. . glass
. . glass fiber
. . gutta percha
. . hexachlorobiphenyl
. . 2,2',4,4',5,5' hexachlorobiphenyl
. . hydrochloric acid
. . Indian ink
. . industrial effluent
. . industrial enzyme
. . industrial toxic substance

# Annex 2

**Table A2.1 Summary of organophosphate residues in cereals and cereal products**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with | | Total number of samples |
|---|---|---|---|---|---|---|
| | | | | 1 OP residue | >1 OP residue | |
| Bread (ordinary) | 2000 | 10 | Malathion (<0.05, 0.06), Pirimiphos-methyl (<0.05, 0.07–0.2) | 3.7 | 0 | 216 |
| | 1999 | 10 | Malathion (<0.05, 0.05), Pirimiphos-methyl (<0.05, 0.06–0.3) | 5.5 | 0.7 | 144 |
| | 1998 | 10 | Pirimiphos-methyl (<0.05, 0.05–0.2) | 19.3 | 0 | 243 |
| | 1996 | 10 | Etrimfos (<0.05, 0.06–0.3), Pirimiphos-methyl (<0.05, 0.05–0.2) | 17.8 | 0.8 | 241 |
| Bread (speciality) | 1999 | 10 | Pirimiphos-methyl (<0.05, 0.06– 0.5) | 11.8 | 0 | 68 |
| | 1997 | 10 | Chlorpyrifos-methyl (<0.02, 0.02, 0.03), Malathion (<0.02, 0.03–0.05), Pirimiphos-methyl (<0.02, 0.02–0.3) | 26.3 | 0.4 | 240 |
| Breakfast cereals | 2001 | 9 | Pirimiphos-methyl (<0.05, 0.06–0.5) | 8.3 | 0 | 144 |
| | 1997 | 8 | Etrimfos (<0.05, 0.1) | 0.9 | 0 | 108 |
| Beer | 1999 | 10 | No organophosphate pesticide residues detected | 0 | 0 | 72 |
| Biscuits (crackers) | 1998 | 10 | Pirimiphos-methyl (<0.05, 0.07) | 2.3 | 0 | 44 |
| Biscuits (sweet) | 1998 | 10 | Pirimiphos-methyl (<0.05, 0.06–0.1) | 9.3 | 0 | 43 |
| Biscuits (sweet/savoury) | 1997 | 9 | Pirimiphos-methyl (<0.05, 0.06–0.06) | 7.0 | 0 | 43 |
| Cakes | 1998 | 10 | No organophosphate pesticide residues detected | 0 | 0 | 48 |
| Cereal bars | 2001 | 18 | Chlorpyrifos-methyl (<0.05, 0.07), Pirimiphos-methyl (<0.05, 0.06, 0.06) | 3.1 | 0 | 96 |
| Noodles | 2001 | 9 | No organophosphate pesticide residues detected | 0 | 0 | 48 |
| Nuts | 2000 | 0 | - | - | - | 47 |
| Nut butter | 2000 | 0 | - | - | - | 24 |
| Pasta | 1999 | 9 | No organophosphate pesticide residues detected | 0 | 0 | 58 |
| Pulses | 1996 | 15 | No organophosphate pesticide residues detected | 0 | 0 | 54 |

[a] Detected at or above the reporting limit
- samples in which OPs were not sought

**Table A2.1 Summary of organophosphate residues in cereals and cereal products (continued)**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with | | Total number of samples |
|---|---|---|---|---|---|---|
| | | | | 1 OP residue | >1 OP residue | |
| Rice | 2000 | 14 | Pirimiphos-methyl (<0.05, 0.07–1.0) | 3.1 | 0 | 96 |
| | 1996 | 0 | - | - | - | 44 |

Data from:

MAFF (2000) *Annual Report of the Working Part on Pesticide Residues: 1999 (from 2000 known as the Pesticide Residues Committee). Supplement to The Pesticides Monitor 2000.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1999) *Annual Report of the Working Part on Pesticide Residues: 1998. Supplement to The Pesticides Monitor 1999.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1998) *Annual Report of the Working Part on Pesticide Residues: 1997. Supplement to The Pesticides Monitor 1998.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1997) *Annual Report of the Working Part on Pesticide Residues: 1996. Supplement to The Pesticides Monitor 1997.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

Pesticides Residues Committee (2002) *Pesticide Residues Monitoring Report. Third Quarter Results. July-September 2001,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Second Quarter Results. April-June 2001*, available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Fourth Quarter Results. October-December 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Third Quarter Results. July-September 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Second Quarter Results. April-June 2000*, available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2000) *Pesticide Residues Monitoring Report. First Quarter Results. January-March 2000*, available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

[a] Detected at or above the reporting limit

- samples in which OPs were not sought

**Table A2.2 Summary of organophosphate residues in fruit**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with | | Total number of samples |
|---|---|---|---|---|---|---|
| | | | | 1 OP residue | >1 OP residue | |
| Apples | 2000 | 39 | Azinphos-methyl (<0.05, 0.05–0.1), Chlorpyrifos (<0.01, 0.01–0.3), Diazinon (<0.01, 0.02, 0.03), Dimethoate (<0.01, 0.02–0.04), Fenitrothion (<0.01, 0.01), Phosalone (<0.01, 0.01–0.2), Phosmet (<0.05, 0.2) | 42.4 | 4.9 | 144 |
| | 1999 | 38 | Azinphos-methyl (<0.05, 0.05–0.1), Chlorpyrifos (<0.01, 0.01–0.3), Dimethoate (<0.01, 0.02–0.09), Phosalone (<0.05, 0.07–0.7), Phosmet (<0.05, 0.07, 0.1) | 36.8 | 5.6 | 144 |
| | 1998 | 12 | Chlorpyrifos (<0.05, 0.05–0.3), Dimethoate (<0.05, 0.07), Phosalone (<0.05, 0.05–0.7) | 17.7 | 0 | 96 |
| | 1997 | 32 | Chlorpyrifos (<0.01, 0.02–0.1), Diazinon (<0.01, 0.03), Dimethoate (<0.01, 0.01–0.06), Phosalone (<0.05, 0.08–0.4) | 19.4 | 0 | 72 |
| | 1997[b] | 44 | Azinphos-methyl (<0.05, 0.08–0.2), Chlorpyrifos (<0.01, 0.01–0.2), Diazinon (<0.01, 0.01), Dimethoate (<0.01, 0.01–0.1), Omethoate (<0.02, 0.04), Phosalone (<0.05, 0.06–0.5), Phosmet (<0.05, 0.07) | 35.9 | 9.0 | 78 |
| | 1996[c] | 4 | Chlorpyrifos (<0.01, 0.01–0.1) | 46.7 | 0 | 30 |
| Apricots | 1996 | 27 | Azinphos-methyl (<0.05, 0.1), Phosalone (<0.05, 0.3), Phosmet (<0.05,0.8) | 12.5 | 0 | 24 |
| Bananas | 1997[c] | 17 | Chlorpyrifos (<0.05, 0.06) | 2.0 | 0 | 50 |
| | 1996 | 11 | Chlorpyrifos (<0.02, 0.02–0.07) | 5.5 | 0 | 72 |
| Blackberries | 1999 | 35 | No organophosphate pesticide residues detected | 0 | 0 | 21 |
| Cherries | 1997 | 29 | No organophosphate pesticide residues detected | 0 | 0 | 24 |
| Coconut | 1997 | 0 | - | - | - | 12 |
| Currants | 1999 | 35 | Chlorpyrifos (<0.05, 0.1) | 2.4 | 0 | 41 |

[a] Detected at or above the reporting limit
[b] Results of a survey of organophosphate and carbamate residues in apples
[c] Samples collected as part of the European Union co-ordinated programme
- samples in which OPs were not sought

**Table A2.2 Summary of organophosphate residues in fruit (continued)**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with | | Total number of samples |
|---|---|---|---|---|---|---|
| | | | | 1 OP residue | >1 OP residue | |
| Dried fruit | 1996 | 15 | Chlorpyrifos (<0.02, 0.02–0.05), Malathion (<0.02, 0.02–0.03), Monocrotophos (<0.01, 0.03), Parathion-methyl (<0.01, 0.01–0.04), Pirimiphos-methyl (<0.01, 0.01–0.08) | 15.3 | 10.2 | 39 |
| Fruit juices | 2000 | 40 | No organophosphate pesticide residues detected above reporting limit | 0 | 0 | 71 |
| Grapes | 2001 | 12 | Chlorpyrifos (<0.05, 0.3) | 1.9 | 0 | 54 |
| | 2000 | 35 | Chlorpyrifos (<0.05, 0.09–0.8), Chlorpyrifos-methyl (<0.05, 0.2, 0.4), Methamidophos (<0.01, 0.1–0.4), Parathion (<0.05, 0.1, 0.2), Phosalone (<0.05, 0.1), Pyrazophos (<0.02, 0.04–0.1) | 19.4 | 4.2 | 72 |
| | 1997 | 33 | Chlorpyrifos (<0.05, 0.1), Dimethoate (<0.05, 0.07, 0.06), Ethion (<0.01, 0.1), Fenitrothion (<0.05, 0.05), Omethoate (<0.02, 0.02), Parathion (<0.01, 0.02, 0.2), Parathion-methyl (<0.01, 0.09, 0.2), Phosmet (<0.05, 0.06), Pyrazophos (<0.05, 0.3, 0.3) | 16.7 | 8.3 | 36 |
| Gooseberry | 1996 | 6 | Chlorpyrifos (<0.05, 0.2–0.3) | 24.0 | 0 | 25 |
| Kiwi fruit | 2001 | 43 | Chlorpyrifos (<0.05, 0.1, 0.1), Parathion (<0.02, 0.02) | 6.4 | 0 | 47 |
| Lemons | 2001 | 19 | Chlorpyrifos (<0.05, 0.05, 0.2), Diazinon (<0.01, 0.02), Ethion (<0.02, 0.04, 0.07), Fenitrothion (<0.02, 0.07, 0.6), Fenthion (<0.02, 0.02-0.03), Methidathion (<0.05, 0.08-0.4), Parathion (<0.05, 0.05-0.07) | 33.3 | 23.8 | 21 |
| Mandarin and Clementine | 1997[b] | 22 | Azinphos-methyl (<0.02, 0.03–0.2), Chlorpyrifos (<0.02, 0.02-0.2), Chlorpyrifos-methyl (<0.02, 0.1–0.2), Dimethoate (<0.02, 0.02), Ethion (<0.02, 0.07, 0.2), Fenthion (<0.02, 0.03), Malathion (<0.02, 0.02–0.3), Methidathion (<0.02, 0.03–0.7), Pirimiphos-methyl (<0.02, 0.02–0.08) | 40.0 | 30.0 | 50 |
| Mango | 2001 | 30 | No organophosphate pesticide residues detected above reporting limit | 0 | 0 | 36 |
| Melons | 1999[b] | 34 | Diazinon (<0.02, 0.02, 0.07), Methamidophos (<0.01, 0.01–0.3) | 13.9 | 0 | 72 |

[a] Detected at or above the reporting limit

[b] Samples collected for the European Union co-ordinated programme

**Table A2.2 Summary of organophosphate residues in fruit (continued)**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with | | Total number of samples |
|---|---|---|---|---|---|---|
| | | | | 1 OP residue | >1 OP residue | |
| Oranges | 1999 | 18 | Chlorpyrifos (<0.05, 0.07–0.2), Diazinon (<0.01, 0.3), Dimethoate (<0.05, 0.06, 0.2), Ethion (<0.02, 0.04), Methidathion (<0.05, 0.06–1.0) | 29.2 | 5.6 | 72 |
| | 1998[b] | 14 | Chlorpyrifos (<0.01, 0.05–0.3), Chlorpyrifos-methyl (<0.05, 0.06), Malathion (<0.05, 0.07), Methidathion (<0.05, 0.07–0.7) | 39.4 | 3.0 | 66 |
| Orange juice | 1997 | 21 | No organophosphate pesticide residues detected | 0 | 0 | 72 |
| Passion fruit | 1999 | 35 | Methamidophos (<0.01, 0.02), Omethoate (<0.05, 0.8), Triazophos (<0.05, 0.07) | 14.3 | 0 | 21 |
| Peaches and nectarines | 2001 | 34 | Acephate (<0.2, 0.2, 0.4), Azinphos-methyl (<0.05, 0.08), Fenitrothion (<0.01, 0.010.3), Methamidophos (<0.01, 0.05, 0.01), Parathion (<0.05, 0.05), Parathion-methyl (<0.05, 0.05), Phosmet (<0.02, 0.02) | 11.1 | 13.9 | 36 |
| | 1998[b] | 14 | Acephate (<0.02, 0.02, 0.03), Chlorpyrifos (<0.05, 0.07), Dimethoate (<0.05, 0.1), Ethion (<0.02, 0.03), Methamidophos (<0.01, 0.02–0.07), Phosalone (<0.05, 0.05, 0.06) | 19.4 | 1.4 | 72 |
| | 1997 | 43 | Acephate (<0.05, 0.05–0.4), Chlorfenvinphos (<0.02, 0.2, 0.2), Chlorpyrifos (<0.02, 0.03–0.1), Chlorpyrifos-methyl (<0.02, 0.07), Dimethoate (<0.02, 0.1), Fenitrothion (<0.02, 0.1–0.2), Methamidophos (<0.05, 0.05–0.3), Parathion-methyl (<0.02, 0.05), Phosalone (<0.05, 0.05–0.5), Quinalphos (<0.02, 0.06) | 30.0 | 7.5 | 80 |
| | 1996 | 37 | Methamidophos (<0.05, 0.07, 0.08) | 8.3 | 0 | 24 |

[a] Detected at or above the reporting limit

[b] Samples collected for the European Union co-ordinated programme

**Table A2.2 Summary of organophosphate residues in fruit (continued)**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with | | Total number of samples |
|---|---|---|---|---|---|---|
| | | | | 1 OP residue | >1 OP residue | |
| Pears | 2000 | 40 | Azinphos-methyl (<0.05, 0.06–0.2), Chlorpyrifos (<0.01, 0.02–0.07), Chlorpyrifos-methyl (<0.01, 0.01), Dimethoate (<0.01, 0.6), Malathion (<0.05, 0.07, 0.1), Phosalone (<0.01, 0.01–0.1), Phosmet (<0.05, 0.05–0.5) | 14.0 | 2.2 | 136 |
| | 1999 | 0 | - | - | - | 97 |
| | 1998 | 35 | Azinphos-methyl (<0.05, 0.09, 0.1), Dimethoate (<0.05, 0.07, 0.1), Fenitrothion (<0.02, 0.05), Phosalone (<0.05, 0.06–0.6), Phosmet (<0.02, 0.02–0.1) | 12.5 | 2.1 | 48 |
| | 1997 | 31 | Dimethoate (<0.05, 0.07, 0.09), Phosalone (<0.05, 0.2, 0.5), Phosmet (<0.05, 0.1–0.4) | 13.0 | 0 | 54 |
| | 1997[b] | 44 | Dimethoate, (<0.01, 0.04, 0.2), Omethoate (<0.01, 0.02, 0.07), Phosmet (<0.01, 0.06, 0.07), Phosalone (<0.01, 0.05–0.4) | 8.0 | 12.0 | 25 |
| Pears (oriental) | 1997 | 31 | Azinphos-methyl (<0.05, 0.05), Monocrotophos (<0.01, 0.02) | 15.4 | 0 | 13 |
| Pick your own soft fruit | 1996 | 12 | Fenitrothion (<0.05, 0.09) | 3.8 | 0 | 26 |
| Pineapples | 1997 | 0 | - | - | - | 23 |
| Plums | 2000 | 39 | Chlorpyrifos (<0.01, 0.03, 0.06), Dimethoate (<0.01, 0.08), Isazophos (<0.01, 0.02, 0.05), Parathion (<0.01, 0.06), Phosalone (<0.01, 0.01–0.2) | 18.2 | 2.3 | 44 |
| Raspberries | 1997 | 29 | No organophosphate pesticide residues detected | 0 | 0 | 24 |
| Star fruit | 2001 | 34 | Chlorpyrifos (<0.05, 0.06, 0.09), Monocrotophos (<0.02, 0.03) | 15 | 0 | 20 |
| Strawberries | 1999 | 35 | No organophosphate pesticide residues detected | 0 | 0 | 45 |
| | 1997 | 33 | Malathion (<0.02, 0.02–0.09) | 8.3 | 0 | 48 |
| | 1996[c] | 4 | Chlorpyrifos (<0.01, 0.01, 0.1) | 6.7 | 0 | 30 |

[a] Detected at or above the reporting limit
[b] Results of a survey of organophosphate and carbamate residues in pears
[c] Samples collected for the European Union co-ordinated programme
- samples in which OPs were not sought

**Table A2.2 Summary of organophosphate residues in fruit (continued)**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with | | Total number of samples |
|---|---|---|---|---|---|---|
| | | | | 1 OP residue | >1 OP residue | |
| Strawberries (Belgian/Dutch) | 2000[b] | 0 | - | - | - | 11 |
| Teas (fruit) | 1999 | 35 | No organophosphate pesticide residues detected | 0 | 0 | 36 |
| Wine | 1998 | 35 | No organophosphate pesticide residues detected | 0 | 0 | 72 |

Data from:

MAFF (2000) *Annual Report of the Working Part on Pesticide Residues: 1999 (from 2000 known as the Pesticide Residues Committee). Supplement to The Pesticides Monitor 2000.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1999) *Annual Report of the Working Part on Pesticide Residues: 1998. Supplement to The Pesticides Monitor 1999.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1998) *Annual Report of the Working Part on Pesticide Residues: 1997. Supplement to The Pesticides Monitor 1998.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1997) *Annual Report of the Working Part on Pesticide Residues: 1996. Supplement to The Pesticides Monitor 1997.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

Pesticides Residues Committee (2002) *Pesticide Residues Monitoring Report. Third Quarter Results. July-September 2001,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Second Quarter Results. April-June 2001,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Fourth Quarter Results. October-December 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Third Quarter Results. July-September 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Second Quarter Results. April-June 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2000) *Pesticide Residues Monitoring Report. First Quarter Results. January-March 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

[a] Detected at or above the reporting limit

[b] Results of a special survey of Belgian/Dutch strawberries for fungicide residues

- samples in which OPs were not sought

**Table A2.3 Summary of organophosphate residues in vegetables**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with | | Total number of samples |
|---|---|---|---|---|---|---|
| | | | | 1 OP residue | >1 OP residue | |
| Aubergine | 1998 | 35 | Methamidophos (<0.01, 0.04, 0.1) | 8.3 | 0 | 24 |
| Baby vegetables | 1997 | 33 | Chlorfenvinphos (<0.02, 0.05, 0.05), Triazophos (<0.02, 0.2) | 6.1 | 0 | 49 |
| Broccoli | 1996 | 13 | Chlorpyrifos (<0.05, 0.05, 0.08) | 6.5 | 0 | 31 |
| Broccoli/calabrese | 2000 | 35 | Chlorpyrifos (<0.05, 0.1), Methamidophos (<0.01, 0.03, 0.04) | 4.3 | 0 | 69 |
| Brussels sprouts | 1997 | 7 | Triazophos (<0.02, 0.03) | 4.2 | 0 | 24 |
| Cabbage | 1997 | 8 | No organophosphate pesticide residues detected | 0 | 0 | 24 |
| Cabbage (Chinese) | 1998 | 34 | No organophosphate pesticide residues detected | 0 | 0 | 21 |
| Cabbage (head cabbage) | 2000 | 32 | Dimethoate (<0.05, 0.08) | 1.4 | 0 | 72 |
| Carrots | 2000 | 15 | Chlorfenvinphos (<0.01, 0.01–0.9), Triazophos (<0.02, 0.04–0.3) | 9.9 | 0 | 71 |
| | 1999 | 14 | Chlorfenvinphos (<0.01, 0.01–0.09), Triazophos (<0.02, 0.04, 0.05) | 11.1 | 0 | 72 |
| | 1998[b] | 18 | Chlorfenvinphos (<0.01, 0.01–0.1), Phorate (<0.01, 0.07), Quinalphos (<0.01, 0.02-0.03), Triazophos (<0.02, 0.08, 0.1) | 19.7 | 0 | 66 |
| | 1997[c] | 4 | Chlorfenvinphos (<0.005, 0.006), Phorate (<0.005, 0.006–0.02), Quinalphos (<0.005, 0.02), Triazophos (<0.005, 0.02–0.2) | 66.7 | 27.8 | 18 |
| | 1996 | 5 | Chlorfenvinphos (<0.05, 0.03, 0.04) | 9.1 | 0 | 22 |
| Cauliflower | 1999[b] | 39 | No organophosphate pesticide residues detected | 0 | 0 | 71 |
| Celery | 1999 | 38 | Disulfoton (<0.05, 0.09,0.2), Heptenophos (<0.05, 0.03), Methamidophos (<0.01, 0.03) | 5.9 | 0 | 68 |
| | 1997 | 37 | Chlorpyrifos (<0.02, 0.02–0.06), Chlorpyrifos-methyl (<0.02, 0.02), Phorate (<0.02, 0.1, 0.3) | 13.9 | 1 | 36 |
| Cucumber | 2000 | 35 | No organophosphate pesticide residues detected | 0 | 0 | 59 |
| | 1996 | 9 | Methamidophos (<0.05, 0.07, 0.3) | 3.3 | 0 | 60 |
| Garlic | 2000 | 8 | No organophosphate pesticide residues detected | 0 | 0 | 24 |
| Green beans | 1997[b] | 34 | Dimethoate (<0.02, 0.1, 0.2), Omethoate (<0.02, 0.02, 0.07) | 0 | 3.7 | 54 |

[a] Detected at or above the reporting limit

[b] Samples collected for the European Union co-ordinated programme

[c] Results of a survey of pesticide residues in UK produced carrots of known treatment history

**Table A2.3 Summary of organophosphate residues in vegetables (continued)**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with | | Total number of samples |
|---|---|---|---|---|---|---|
| | | | | 1 OP residue | >1 OP residue | |
| Leek | 1996 | 7 | No organophosphate pesticide residues detected | 0 | 0 | 36 |
| Lettuce | 2000 | 35 | Acephate (<0.02, 0.06, 0.08), Dimethoate (<0.05, 0.06, 0.2), Methamidophos (<0.01, 0.02, 0.03), Tolclofos-methyl (<0.02, 0.03–0.2) | 15.5 | 4.2 | 71 |
| | 1999 | 9 | Acephate (<0.02, 0.05–0.1), Dimethoate (<0.05, 0.3), Methamidophos (<0.01, 0.03–0.06), Omethoate (<0.05, 0.08), Tolclofos-methyl (<0.02, 0.04–2.0) | 12.5 | 5.6 | 72 |
| | 1998 | 34 | Malathion (<0.05, 4.4), Tolclofos-methyl (<0.02, 0.04–3.1) | 24.0 | 4.0 | 25 |
| | 1996 | 1 | Tolclofos-methyl (<0.01, 0.01–2.8) | 65.2 | 0 | 66 |
| | 1996[b] | 4 | No organophosphate pesticide residues detected | 0 | 0 | 30 |
| Lettuce (winter) | 2000[c] | 1 | No organophosphate pesticide residue detected | 0 | 0 | 44 |
| | 1997 | 11 | Tolclofos-methyl (<0.01, 0.01–8.6) | 40.9 | 0 | 22 |
| Lettuce (winter, wholesale) | 1997 | 1 | Tolclofos-methyl (<0.01, 0.02–0.6) | 15 | 0 | 20 |
| Mushrooms | 1998 | 15 | No organophosphate pesticide residues detected | 0 | 0 | 47 |
| Olives | 1998 | 19 | No organophosphate pesticide residues detected | 0 | 0 | 24 |
| Onions | 2000 | 8 | No organophosphate pesticide residues detected | 0 | 0 | 48 |
| Parsnips | 2000 | 15 | No organophosphate pesticide residues detected | 0 | 0 | 36 |
| Peas | 2000 | 8 | No organophosphate pesticide residues detected | 0 | 0 | 27 |
| | 1998 | 35 | No organophosphate pesticide residues detected | 0 | 0 | 48 |
| Peas (edible, podded) | 1998 | 34 | Dimethoate (<0.05, 0.07), Methamidophos (<0.01, 0.01–0.1), Pyrazophos (<0.02, 0.03–0.04), Triazophos (<0.02, 0.02) | 20.8 | 0 | 48 |
| Peas (frozen) | 2000 | 8 | No organophosphate pesticide residues detected | 0 | 0 | 35 |

[a] Detected at or above the reporting limit

[b] Samples collected for the European Union co-ordinated programme

[c] Results of a special survey of UK-produced winter lettuce obtained from growers

**Table A2.3 Summary of organophosphate residues in vegetables (continued)**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with | | Total number of samples |
|---|---|---|---|---|---|---|
| | | | | 1 OP residue | >1 OP residue | |
| Peppers (sweet) | 2000[b] | 2 | No organophosphate pesticide residues detected | 0 | 0 | 24 |
| | 1999[c] | 2 | Acephate (<0.02, 0.1), Methamidophos (<0.01, 0.02–0.03) | 12.5 | 4.2 | 24 |
| | 1999[d] | 8 | Methamidophos (<0.01, 0.05–0.8) | 8.4 | 0 | 71 |
| | 1999[e] | 2 | Acephate (<0.02, 0.04), Methamidophos (<0.01, 0.01–0.4) | 37.5 | 4.2 | 24 |
| Potatoes | 2000 | 2 | No organophosphate pesticide residues detected | 0 | 0 | 144 |
| | 1999 | 2 | No organophosphate pesticide residues detected | 0 | 0 | 142 |
| | 1997 | 0 | - | - | - | 96 |
| | 1996 | 1 | No organophosphate pesticide residues detected | 0 | 0 | 152 |
| Potatoes (retail/farm gate) | 1997 | 0 | - | - | - | 30 |
| Potatoes (processed) | 2001 | 14 | No organophosphate pesticide residues detected | 0 | 0 | 48 |
| | 1998[c] | 2 | No organophosphate pesticide residues detected | 0 | 0 | 97 |
| Potatoes (salad) | 1996 | 4 | No organophosphate pesticide residues detected | 0 | 0 | 24 |
| Potatoes (speciality) | 1998 | 35 | No organophosphate pesticide residues detected | 0 | 0 | 47 |
| Radish | 1997 | 10 | Chlorfenvinphos (<0.02, 0.02) | 4.2 | 0 | 24 |
| Salad (mixed leaf) | 1998 | 35 | Acephate (<0.02, 0.07) | 4.2 | 0 | 24 |
| Salad crops | 1997[f] | 0 | - | - | - | 48 |
| Soya products | 1999 | 0 | - | - | - | 43 |
| Spinach | 1998[c] | 9 | Chlorpyrifos (<0.05, 0.05) | 1.5 | 0 | 66 |
| Spring greens | 1996 | 12 | No organophosphate pesticide residues detected | 0 | 0 | 5 |
| Spring Onions | 2000 | 8 | No organophosphate pesticide residues detected | 0 | 0 | 36 |

[a] Detected at or above the reporting limit
[b] Results of a special survey of sweet peppers obtained in December 2000–January 2001
[c] Samples collected for the European Union co-ordinated programme
[d] Results of a special survey of sweet peppers obtained in 2000
[e] Results of a special survey of sweet peppers obtained in 1999
[f] Results of a special survey of ambamectin in salad crops
- samples in which OPs were not sought

**Table A2.3 Summary of organophosphate residues in vegetables (continued)**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with | | Total number of samples |
|---|---|---|---|---|---|---|
| | | | | 1 OP residue | >1 OP residue | |
| Sprouted seeds | 1996 | 5 | No organophosphate pesticide residues detected | 0 | 0 | 36 |
| Swedes/turnips/kohlrabi/ salsify | 1999 | 10 | Chlorfenvinphos (<0.05, 0.06) | 1.4 | 0 | 70 |
| Sweetcorn | 1998 | 35 | No organophosphate pesticide residues detected | 0 | 0 | 48 |
| Tomatoes | 1998 | 34 | No organophosphate pesticide residues detected | 0 | 0 | 48 |
| Tomato products | 1996 | 18 | No organophosphate pesticide residues detected | 0 | 0 | 60 |
| Yam | 2000 | 0 | - | - | - | 42 |
| | 1998 | 35 | No organophosphate pesticide residues detected | 0 | 0 | 16 |

Data from:

MAFF (2000) *Annual Report of the Working Part on Pesticide Residues: 1999 (from 2000 known as the Pesticide Residues Committee). Supplement to The Pesticides Monitor 2000.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1999) *Annual Report of the Working Part on Pesticide Residues: 1998. Supplement to The Pesticides Monitor 1999.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1998) *Annual Report of the Working Part on Pesticide Residues: 1997. Supplement to The Pesticides Monitor 1998.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1997) *Annual Report of the Working Part on Pesticide Residues: 1996. Supplement to The Pesticides Monitor 1997.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

Pesticides Residues Committee (2002) *Pesticide Residues Monitoring Report. Third Quarter Results. July-September 2001,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Second Quarter Results. April-June 2001,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. First Quarter Results. January-March 2001,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Fourth Quarter Results. October-December 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/p rc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Third Quarter Results. July-September 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Second Quarter Results. April-June 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2000) *Pesticide Residues Monitoring Report. First Quarter Results. January-March 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

[a] Detected at or above the reporting limit

- samples in which OPs were not sought

**Table A2.4 Summary of organophosphate residues in animal products**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with one OP residue | Total number of samples |
|---|---|---|---|---|---|
| Bacon | 2000 | 7 | No organophosphate pesticide residues detected | 0 | 65 |
| Beef | 2000 | 7 | Phosmet (<0.005, 0.006) | 1.4 | 72 |
| | 1998 | 7 | No organophosphate pesticide residues detected | 0 | 48 |
| Butter | 2001 | 0 | - | - | 48 |
| | 1996 | 0 | - | - | 72 |
| Burgers | 1997 | 0 | - | - | 36 |
| Cheese (ewes/goats) | 1999 | 0 | - | - | 23 |
| Cheese (cows milk) | 1997 | 0 | - | - | 73 |
| Cheese | 1996 | 0 | - | - | 137 |
| Chicken | 2001 | 0 | - | - | 72 |
| | 1998 | 7 | No organophosphate pesticide residues detected | 0 | 48 |
| Chocolate (continental) | 1998 | 0 | | | 16 |
| Cooking ingredients | 1997 | 10 | No organophosphate pesticide residues detected | 0 | 60 |
| Cooking fats | 1997 | 0 | - | - | 33 |
| Cream | 2000 | 1 | No organophosphate pesticide residue detected | 0 | 48 |
| Duck | 2000 | 7 | No organophosphate pesticide residues detected | 0 | 36 |
| Eggs | 1997 | 0 | - | - | 72 |
| | 1996 | 0 | - | - | 73 |
| Geese | 1996 | 0 | - | - | 36 |
| Honey | 2001 | 43 | No organophosphate pesticide residues detected | 0 | 72 |
| Ice cream | 1997 | 0 | - | - | 36 |
| Kidney | 1998 | 0 | - | - | 48 |
| Lamb | 1999 | 7 | Diazinon (<0.05, 0.1, 0.3) | 2.8 | 72 |
| | 1997 | 18 | Diazinon (<0.05, 0.06) | 1.4 | 71 |
| | 1996 | 12 | Diazinon (<0.02, 0.05) | 1.4 | 70 |

[a] Detected at or above the reporting limit;
- samples in which OPs were not sought

**Table A2.4 Summary of organophosphate residues in animal products (continued)**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with one OP residue | Total number of samples |
|---|---|---|---|---|---|
| Liver | 1998 | 0 | - | - | 48 |
| Low fat spread | 1996 | 0 | - | - | 10 |
| Margarine | 1996 | 0 | - | - | 39 |
| Mayonnaise/Salad Cream | 2000 | 0 | - | - | 38 |
| Meat (canned/cooked) | 1998 | 0 | - | - | 48 |
| Milk | 2001 | 6 | No organophosphate pesticide residues detected | 0 | 158 |
| | 2000 | 0 | - | - | 212 |
| | 1999 | 0 | - | - | 214 |
| | 1998 | 0 | - | - | 216 |
| | 1997 | 0 | - | - | 216 |
| | 1996 | 0 | - | - | 376 |
| Milk, Goats/Ewes | 2001 | 0 | - | - | 37 |
| Pate, meat based | 1997 | 0 | - | - | 72 |
| Pies/Pastries/Sausage Rolls | 1999 | 7 | Pirimiphos-methyl (<0.02, 0.02–0.03) | 8.3 | 72 |
| Pork | 1999 | 7 | No organophosphate pesticide residues detected | 0 | 71 |
| Pork Produce (Chinese canned) | 1999 | 0 | - | - | 24 |
| Rabbit | 1997 | 0 | - | - | 36 |
| | 1996 | 0 | - | - | 30 |
| Rabbit (imported) | 1999 | 0 | - | - | 17 |
| | 1998 | 0 | - | - | 31 |
| Sausage | 1997 | 0 | - | - | 36 |
| Speciality meats | 1996 | 0 | - | - | 36 |
| Suet | 1996 | 0 | - | - | 36 |
| Turkey (breaded) | 1999 | 0 | - | - | 51 |
| Turkey (portions/joints) | 1999 | 7 | No organophosphate pesticide residues detected | 0 | 45 |

[a] Detected at or above the reporting limit
- samples in which OPs were not sought

**Table A2.4 Summary of organophosphate residues in animal products (continued)**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with one OP residue | Total number of samples |
|---|---|---|---|---|---|
| Veal | 1997 | 0 | - | - | 36 |
| Venison | 1996 | 0 | - | - | 36 |
| Yoghurt | 1997 | 0 | - | - | 36 |

Data from:

MAFF (2000) *Annual Report of the Working Part on Pesticide Residues: 1999 (from 2000 known as the Pesticide Residues Committee). Supplement to The Pesticides Monitor 2000.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1999) *Annual Report of the Working Part on Pesticide Residues: 1998. Supplement to The Pesticides Monitor 1999.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1998) *Annual Report of the Working Part on Pesticide Residues: 1997. Supplement to The Pesticides Monitor 1998.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1997) *Annual Report of the Working Part on Pesticide Residues: 1996. Supplement to The Pesticides Monitor 1997.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

Pesticides Residues Committee (2002) *Pesticide Residues Monitoring Report. Third Quarter Results. July-September 2001,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Second Quarter Results. April-June 2001,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. First Quarter Results. January-March 2001,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Third Quarter Results. July-September 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2000) *Pesticide Residues Monitoring Report. First Quarter Results. January-March 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

[a] Detected at or above the reporting limit

- samples in which OPs were not sought

**Table A2.5 Summary of organophosphate residues in fish and fish products**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with one or more OP pesticide residues | Total number of samples |
|---|---|---|---|---|---|
| Farmed fish | 1997 | 0 | - | - | 24 |
| | 1996 | 4 | No organophosphate pesticide residues detected | 0 | 29 |
| Fish oils | 1999 | 0 | - | - | 23 |
| Fish sticks | 1997 | 0 | - | - | 46 |
| Non-indigenous deep water fish | 1996 | 0 | - | - | 32 |
| Oily fish | 2000 | 0 | - | - | 36 |
| Pilchards | 1997 | 0 | - | - | 36 |
| Salmon, canned | 2001 | 0 | - | - | 48 |
| Sea fish | 1999 | 0 | - | - | 36 |
| Shellfish | 2000 | 0 | - | - | 48 |
| | 1996 | 0 | - | - | 16 |
| Tuna | 1998 | 0 | - | - | 52 |
| White fish | 1998 | 0 | - | - | 48 |

Data from:

MAFF (2000) *Annual Report of the Working Part on Pesticide Residues: 1999 (from 2000 known as the Pesticide Residues Committee). Supplement to The Pesticides Monitor 2000.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1999) *Annual Report of the Working Part on Pesticide Residues: 1998. Supplement to The Pesticides Monitor 1999.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1998) *Annual Report of the Working Part on Pesticide Residues: 1997. Supplement to The Pesticides Monitor 1998.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

MAFF (1997) *Annual Report of the Working Part on Pesticide Residues: 1996. Supplement to The Pesticides Monitor 1997.* MAFF Publications, available [May 2002] at: www.pesticides.gov.uk/committees/WPPR/wppr.htm

Residues Committee (2001) *Pesticide Residues Monitoring Report. Second Quarter Results. April-June 2001,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Third Quarter Results. July-September 2000,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

[a] Detected at or above the reporting limit

- samples in which OPs were not sought

**Table A2.6 Summary of organophosphate residues in miscellaneous foodstuffs**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s)[a] (reporting limit, concentration range; mg/kg) | Percentage of samples with one or more OP pesticide residues | Total number of samples |
|---|---|---|---|---|---|
| Crisps | 2001 | 4 | No organophosphate pesticide residues detected above reporting limit | 0 | 132 |
| Fast Food (burgers) | 2000 | 10 | No organophosphate pesticide residues detected | 0 | 72 |
| Pizza | 2001 | 11 | No organophosphate pesticide residues detected above reporting limit | 0 | 24 |
| Tea | 2001 | 9 | Ethion (<0.05, 0.08, 0.1) | 4.2 | 48 |

Data from:

Pesticides Residues Committee (2002) *Pesticide Residues Monitoring Report. Third Quarter Results. July-September 2001,* available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

Pesticides Residues Committee (2001) *Pesticide Residues Monitoring Report. Second Quarter Results. April-June 2000*, available [May 2002] at: www.pesticides.gov.uk/committees/PRC/prc.htm

[a] Detected at or above the reporting limit

**Table A2.7 Summary of animal products surveyed for organophosphate veterinary residues, 1998—2000[a]**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s) (concentration range; mg/kg) | Percentage of samples with one or more OP pesticide residues | Total number of samples |
|---|---|---|---|---|---|
| Bacon [b] | 1998 | 10 | No organophosphate residues detected | - | 22 |
| Beefburgers [b] | 1998 | 10 | No organophosphate residues detected | - | 22 |
| Cheese (organic UK and imported) [b] | 2000 | 8 | No organophosphate residues detected | - | 20 |
| Cheese (cheddar, goats and sheep) [b] | 1998 | 10 | No organophosphate residues detected | - | 65 |
| Concentrated meat extract [b] | 1998 | 10 | No organophosphate residues detected | - | 19 |
| Corned beef [b] | 1998 | 10 | No organophosphate residues detected | - | 23 |
| Cream (organic) [b] | 2000 | 8 | No organophosphate residues detected | - | 10 |
| Cream [b] | 1998 | 10 | No organophosphate residues detected | - | 26 |
| Ham [b] | 1998 | 10 | No organophosphate residues detected | - | 21 |
| Honey (imported and UK produced) [b] | 2000 | 8 | No organophosphate residues detected | - | 110 |
| | 1999 | 10 | No organophosphate residues detected | - | 60 |
| Kidney fat (cattle) | 2000 | 15 | No organophosphate residues detected | - | 264 |
| | 1999 | 15 | No organophosphate residues detected | - | 215 |
| | 1998 | 12 | No organophosphate residues detected | - | 231 |
| Kidney fat (pig) | 2000 | 15 | No organophosphate residues detected | - | 205 |
| | 1999 | 15 | No organophosphate residues detected | - | 319 |
| | 1998 | 12 | No organophosphate residues detected | - | 330 |
| Kidney fat (sheep) | 2000 | 15 | No organophosphate residues detected | - | 700 |
| | 1999 | 15 | Diazinon (0.02–0.15), Propetamphos (0.02–0.08) | 3.1 | 643 |
| | 1998 | 12 | Diazinon (2.3) | 0.2 | 610 |
| Milk | 2000 | 15 | No organophosphate residues detected | - | 7 |
| Pasties [b] | 1998 | 10 | No organophosphate residues detected | - | 21 |
| Pâté (chicken/pig liver) [b] | 1998 | 10 | No organophosphate residues detected | - | 24 |
| Pork (burgers and canned) [b] | 1998 | 10 | No organophosphate residues detected | - | 44 |

[a] Adapted from VMD 2001, 2000 and 1999

[b] Analysed as part of the non-statutory surveillance scheme

**Table A2.7 Summary of animal products surveyed for organophosphate veterinary residues, 1998–2000 (continued)[a]**

| Commodity | Year | Number of OPs sought | Organophosphate residue(s) (concentration range; mg/kg) | Percentage of samples with one or more OP pesticide residues | Total number of samples |
|---|---|---|---|---|---|
| Poultry (burgers and canned) [b] | 1998 | 10 | No organophosphate residues detected | - | 42 |
| Salmon (imported and farmed) | 2000 | 15 | No organophosphate residues detected | - | 64 |
| Salmon (farmed) | 1999 | 15 | No organophosphate residues detected | - | 22 |
| | 1998 | 12 | No organophosphate residues detected | - | 21 |
| Sausages (imported) [b] | 2000 | 8 | No organophosphate residues detected | - | 10 |
| Sausages (uncooked, beef and pork) [b] | 1998 | 10 | No organophosphate residues detected | - | 45 |
| Sea bass [b] | 2000 | 8 | No organophosphate residues detected | - | 10 |
| Stewing steak [b] | 1998 | 10 | No organophosphate residues detected | - | 22 |
| Tiger prawns [b] | 1998 | 10 | No organophosphate residues detected | - | 28 |
| Tilapia [b] | 1998 | 10 | No organophosphate residues detected | - | 21 |
| Trout (imported) [b] | 2000 | 8 | No organophosphate residues detected | - | 20 |
| Yoghurt (imported) [b] | 2000 | 8 | No organophosphate residues detected | - | 20 |

[a] Adapted from VMD 2001, 2000 and 1999

[b] Analysed as part of the non-statutory surveillance scheme