5.8 **CHLORPYRIFOS-METHYL (090)**

**TOXICOLOGY**

Chlorpyrifos-methyl is the ISO approved name for O,O-dimethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate (CAS No.5598-13-0). Chlorpyrifos-methyl is an organophosphorus compound that acts against insects. The mechanism of action is inhibition of acetylcholinesterase activity. Chlorpyrifos-methyl was evaluated previously by the JMPR in 1975, 1991 and 1992 when an ADI of 0–0.01 mg/kg bw was established. In 2001, the Meeting concluded that an ARfD for chlorpyrifos-methyl was not necessary. Chlorpyrifos-methyl was reviewed at the present Meeting as part of the periodic review programme of the CCPR. New studies of dermal and inhalation exposure in rats, genotoxicity in vivo, reproductive toxicity and inhibition of neuropathy target esterase (NTE) had been made available since the last full review in 1992.

Most of the pivotal studies met the basic requirements of the relevant Organisation for Economic Co-operation and Development (OECD) or national test guidelines, although the level of detail in some of the reports did not always match current requirements. A number of studies did not contain certificates of compliance with GLP. The available studies in human volunteers were considered to have been performed according to contemporary ethical standards. The overall database is considered adequate for deriving reference doses.

**Biochemical aspects**

Chlorpyrifos-methyl is rapidly and extensively absorbed in rats given a single oral dose at 16 or 30 mg/kg bw. Excretion was rapid (largely within 24 h) and primarily in the urine. Urinary metabolites were identified as the glucuronide conjugate of 3,5,6-trichloro-2-pyridinol (68.6%), the desmethyl metabolite O-methyl-O-(3,5,6-trichloropyridyl) phosphorothioate (17.8%) and free 3,5,6-trichloro-2-pyridinol (13.8%). Although these results were reported very briefly, they are broadly consistent with data for the closely-related compound chlorpyrifos (Annex 5, reference 86). The fate of the phosphorothioate moiety was not investigated.

**Toxicological data**

Chlorpyrifos-methyl is of low acute toxicity when administered orally, dermally (LD$_{50}$ > 2000 mg/kg bw) or by inhalation (LC$_{50}$ > 0.67 mg/L). Chlorpyrifos-methyl is a slight, transient irritant to skin and eye and has been found to produce skin sensitization in a Magnussen & Kligman maximization test, but not in a Buehler test.

Short-term studies of toxicity identified decreased cholinesterase activity and adrenal vacuolation as the most sensitive indicators of toxicity caused by chlorpyrifos-methyl. Studies did not show any consistent time-related progression in the inhibition of plasma or erythrocyte cholinesterase activity with repeated or prolonged administration of chlorpyrifos-methyl, suggesting that inhibition reaches a “steady state” relatively rapidly. There was evidence of significant but not complete recovery of cholinesterase activities after 2 or more weeks. In the 28-day study in mice, the NOAEL was 10 ppm, equal to 1.3 mg/kg bw per day, on the basis of reduced brain acetylcholinesterase activity and vacuation of the zona fasciculata of the adrenals. The same end-points were the basis for the NOAEL of 1 mg/kg bw per day in the 90-day study in rats. Decreased brain cholinesterase activity, decreased body-weight gain, clinical chemistry and haematological findings were noted at the highest dose of 50 mg/kg bw per day in a 90-day study in dogs, with a NOAEL of 10 mg/kg bw per day. No evidence of toxicity, including brain acetylcholinesterase activity, was reported in a 6-month study in Rhesus monkeys given doses of up to 5 mg/kg bw per day.

The potential genotoxicity of chlorpyrifos-methyl has been investigated in an adequate battery of tests in vitro and in vivo. No evidence of mutagenicity was noted; however, chlorpyrifos-
methyl was found to be clastogenic in Chinese hamster ovary cells in the presence of metabolic activation. Studies in vivo on micronucleus formation in bone marrow and on unscheduled DNA synthesis (UDS) gave negative results.

The Meeting concluded that chlorpyrifos-methyl is unlikely to be genotoxic.

No evidence of carcinogenicity was seen in long-term studies of toxicity/carcinogenicity with chlorpyrifos-methyl in rats or mice. Adrenal pathology (vacuolation of the adrenal cortex zona fasciculata consistent with lipid accumulation) was noted in rats and mice. Having considered the outcome of a pathology review by a group that re-examined the slides of adrenal tissues obtained in the study in rats, the Meeting concluded that the findings at 1 mg/kg bw per day were not adverse. Decreased brain acetylcholinesterase activity was found to be a consistent and sensitive indicator of chronic toxicity caused by chlorpyrifos-methyl. The inhibition of cholinesterase activity by chlorpyrifos-methyl seen in the long-term studies did not increase with duration of dosing. The NOAEL was 1 mg/kg bw per day in rats, and 3.9 mg/kg bw per day in mice. Toxicity in a limited 2-year study in dogs was limited to reduced body-weight gain at the highest dose of 3 mg/kg bw per day, with a NOAEL of 1 mg/kg bw per day.

The Meeting concluded that chlorpyrifos-methyl is not carcinogenic.

Marginal effects on fertility were seen at the highest dose of 3 mg/kg bw per day in an early three-generation study in rats; the NOAEL was 1 mg/kg bw per day. A subsequent, more extensive, two-generation study in rats found no effects on reproduction or pup development at 10 mg/kg bw per day; the NOAEL for parental toxicity was 1 mg/kg bw per day on the basis of findings in the adrenal gland. In an initial study of developmental toxicity in rats, there was no indication of teratogenicity at 200 mg/kg bw per day. Indications of delayed fetal development were seen at all doses (50 mg/kg bw per day and above) but without a clear dose–response relationship. In a range-finding study of developmental toxicity in rats, there was no indication of teratogenicity at 200 mg/kg bw per day, a dose producing salivation immediately after the second and subsequent doses and significant inhibition of cholinesterase activity. At 12.5 mg/kg bw per day, there was slight inhibition (10%) of brain acetylcholinesterase activity 1 day after the final dose. The NOAEL for maternal toxicity was considered to be 1 mg/kg bw per day. The Meeting considered that the salivation was unlikely to be a result of systemic toxicity as it occurred immediately after dosing, whereas the C_{max} was at 5 h, and there was evidence that chlorpyrifos-methyl tasted unpleasant at high concentrations. In a full study of developmental toxicity in rats, the NOAEL for maternal toxicity (brain cholinesterase activity 4 days after the final dose) and pup development (overall rate of anomalies) was 12.5 mg/kg w per day with a NOAEL for teratogenicity of 50 mg/kg bw per day, the highest dose tested. The only study of developmental toxicity in rabbits given chlorpyrifos-methyl was not performed to modern standards, but was considered adequate to assess the potential for teratogenicity. The NOAEL for maternal toxicity was 4 mg/kg bw per day on the basis of reductions in body-weight gain and food consumption. The NOAEL for teratogenicity and fetal developmental toxicity was 16 mg/kg w per day, the highest dose tested.

The Meeting concluded that chlorpyrifos-methyl caused developmental toxicity only at doses that were maternally toxic, but that it was not teratogenic.

The primary plant and mammalian metabolite of chlorpyrifos-methyl, 3,5,6-trichloropyridinol (TCP), was considered by the 1999 JMPR during the review of chlorpyrifos (Annex 5, references 86, 88). The acute oral toxicity of TCP is moderate, with LD_{50}s in the range of 380 to 1000 mg/kg bw. In studies of toxicity with repeated doses, the liver was the main target organ, with the lowest NOAEL of 12 mg/kg bw per day being identified in a study in dogs. TCP was not genotoxic in vitro or in vivo. There were no developmental effects at doses of up to 150 mg/kg bw per day in rats, but rabbits showed increased incidences of abnormalities, primarily dilatation of the cerebral ventricles and hydrocephaly at 100 mg/kg bw per day and above, and the NOAEL was 25 mg/kg bw per day.

Some histopathological evidence of neuropathy was noted in hens given a single potentially lethal dose of chlorpyrifos-methyl at 5000 mg/kg bw. Equivocal histopathological findings noted in a
short-term study of delayed neurotoxicity were considered to be similar to background findings and not consistent with delayed neuropathy. No assessment of neuropathy target esterase (NTE) activity was made in the studies of neurotoxicity, but a study in vitro showed that chlorpyrifos-methyl oxon had a potency for inhibiting acetylcholinesterase activity that was more than 100-fold that of NTE. This study also showed that chlorpyrifos-methyl oxon was less potent than chlorpyrifos oxon as an inhibitor of brain acetylcholinesterase activity in hens.

The Meeting concluded that chlorpyrifos-methyl was unlikely to produce delayed neuropathy in the absence of very severe cholinergic toxicity.

In two studies in human volunteers exposed orally to chlorpyrifos-methyl for 21 or 28 days, there were no adverse findings concerning clinical signs, clinical chemistry or cholinesterase activity. The NOAEL was 0.3 mg/kg bw per day over 21 days, the highest dose tested. A single oral dose of (the closely-related compound) chlorpyrifos of up to 1 mg/kg bw did not significantly inhibit erythrocyte acetylcholinesterase activity in human volunteers. The studies in human volunteers were considered to have been performed according to contemporary ethical standards.

There were no reports of adverse effects in production-plant workers.

The Meeting concluded that the existing database on chlorpyrifos-methyl was adequate to characterize the potential hazards to fetuses, infants and children.

**Toxicological evaluation**

The Meeting established an ADI of 0–0.01 mg/kg bw based on the NOAEL of 1 mg/kg bw per day identified on the basis of inhibition of brain acetylcholinesterase activity and adrenal vacuolation in the 2-year study of toxicity and carcinogenicity in rats and with a safety factor of 100. This value is supported by the NOAEL of 1 mg/kg bw per day for inhibition of parental brain acetylcholinesterase activity in the multigeneration study of reproductive toxicity in rats and by the NOAEL of 1 mg/kg bw per day for inhibition of maternal brain acetylcholinesterase activity in the study of developmental toxicity in rats. The Meeting did not consider changes observed in the adrenals of rats given a dose of 1 mg/kg bw per day in the 2-year study to be treatment-related, a conclusion that is consistent with that of the pathology review group. Limited studies in human volunteers, while not of sufficient quality (e.g. too few subjects, limited duration of treatment and the fact that no assessment of the adrenals was possible) to support their use in the derivation of an ADI, provide no basis for concern that the proposed ADI would not be adequately protective. In a number of studies, erythrocyte acetylcholinesterase activity was more sensitive than brain acetylcholinesterase activity to inhibition by chlorpyrifos-methyl. However, the Meeting noted that after oral administration the sensitivity of heart acetylcholinesterase activity to inhibition by chlorpyrifos-methyl was similar to that of brain acetylcholinesterase. It was further noted that the differential sensitivity of acetylcholinesterase was the same as that observed with the close structural analogue chlorpyrifos. In vivo, the sensitivity of the enzyme in peripheral neuronal tissue is similar to that in the brain, while the enzyme in erythrocytes is more sensitive. The Meeting therefore concluded that inhibition of brain acetylcholinesterase activity, not erythrocyte acetylcholinesterase activity, was the appropriate end-point for use in the risk assessment of chlorpyrifos-methyl.

The Meeting established an ARfD of 0.1 mg/kg bw based on the NOAEL of 1.0 mg/kg bw identified on the basis of the absence of inhibition of erythrocyte acetylcholinesterase activity in a single-dose study in human volunteers given the closely-related compound chlorpyrifos, and with a safety factor of 10. The Meeting discussed whether an ARfD was necessary for chlorpyrifos-methyl, given the absence of any clear indications of systemic toxicity after single exposures. In the absence

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of adequate single-dose studies with extensive investigations of cholinesterase activity and clinical signs, the Meeting considered that it was not able to discount the possibility that chlorpyrifos-methyl could produce acute effects. The Meeting considered basing the ARfD on the repeat-dose study in human volunteers given chlorpyrifos-methyl, in which an overall NOAEL of 0.3 mg/kg bw per day was identified. It was noted that this was somewhat inconsistent with the higher NOAEL of 1.0 mg/kg bw in a single-dose study in humans given the closely-related, but more potent, compound chlorpyrifos. Having considered data on the kinetics and acetylcholinesterase-inhibition characteristics of chlorpyrifos and chlorpyrifos-methyl, the Meeting concluded that, although likely to be conservative, it was appropriate to use data from the single-dose study in humans given chlorpyrifos to establish the ARfD for chlorpyrifos-methyl. No other potentially acute effect that might serve as the basis for derivation of an ARfD was identified in studies in experimental animals.

A toxicological monograph was prepared

### Levels relevant to risk assessment

<table>
<thead>
<tr>
<th>Species</th>
<th>Study</th>
<th>Effect</th>
<th>NOAEL</th>
<th>LOAEL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mouse</strong></td>
<td>Two-year study of toxicity and carcinogenicity&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Toxicity</td>
<td>50 ppm, equal to 3.9 mg/kg bw per day</td>
<td>500 ppm, equal to 41 mg/kg bw per day</td>
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<tr>
<td></td>
<td></td>
<td>Carcinogenicity</td>
<td>500 ppm, equal to 41 mg/kg bw per day&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
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<tr>
<td><strong>Rat</strong></td>
<td>Two-year studies of toxicity and carcinogenicity&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Toxicity</td>
<td>1 mg/kg bw per day</td>
<td>50 mg/kg bw per day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carcinogenicity</td>
<td>50 mg/kg bw per day&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Multigeneration study of reproductive toxicity&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Reproductive toxicity</td>
<td>10 mg/kg bw per day&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Parental toxicity</td>
<td>1 mg/kg bw per day</td>
<td>3 mg/kg bw per day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Offspring toxicity</td>
<td>10 mg/kg bw per day&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Developmental toxicity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Maternal toxicity</td>
<td>1.0 mg/kg bw per day</td>
<td>12.5 mg/kg bw per day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Embryo/fetotoxicity</td>
<td>12.5 mg/kg bw per day</td>
<td>50 mg/kg bw per day</td>
</tr>
<tr>
<td><strong>Rabbit</strong></td>
<td>Developmental toxicity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Maternal toxicity</td>
<td>4 mg/kg bw per day</td>
<td>12–16 mg/kg bw per day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Embryo/fetotoxicity</td>
<td>16 mg/kg bw per day&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td><strong>Dog</strong></td>
<td>90-day study</td>
<td>Toxicity</td>
<td>10 mg/kg bw per day</td>
<td>50 mg/kg bw per day</td>
</tr>
<tr>
<td></td>
<td>Two-year study of toxicity&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Toxicity</td>
<td>1 mg/kg bw per day</td>
<td>3 mg/kg bw per day</td>
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<tr>
<td><strong>Rhesus monkey</strong></td>
<td>26-week study of toxicity&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Toxicity</td>
<td>5 mg/kg bw per day&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td><strong>Humans</strong></td>
<td>28-day study of toxicity&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Toxicity</td>
<td>0.2 mg/kg bw per day&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>21-day study of toxicity&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Toxicity</td>
<td>0.3 mg/kg bw per day&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Single-dose study of toxicity with chlorpyrifos&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Toxicity</td>
<td>1.0 mg/kg bw&lt;sup&gt;c&lt;/sup&gt;</td>
<td>—</td>
</tr>
</tbody>
</table>

<sup>a</sup> Dietary administration.
Estimate of acceptable daily intake for humans

0–0.01 mg/kg bw

Estimate of acute reference dose

0.1 mg/kg bw

Information that would be useful for the continued evaluation of the compound

Results from epidemiological, occupational health and other such observational studies of human exposure

Critical end-points for setting guidance values for exposure to chlorpyrifos-methyl

Absorption, distribution, excretion and metabolism in mammals

<table>
<thead>
<tr>
<th>Rate and extent of oral absorption</th>
<th>Rats: rapid and extensive, &gt;80%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermal absorption</td>
<td>Low: &lt; 5%, concentrated and diluted, rat epidermis in vitro</td>
</tr>
<tr>
<td>Distribution</td>
<td>Widely distributed.</td>
</tr>
<tr>
<td>Potential for accumulation</td>
<td>No potential for accumulation.</td>
</tr>
<tr>
<td>Rate and extent of excretion</td>
<td>Rapid and almost complete, within 72 h, mainly via urine (83–85%), after a single dose.</td>
</tr>
<tr>
<td>Metabolism in animals</td>
<td>Extensively metabolized. De-methylation, hydrolysis, conjugation, oxidative desulfuration</td>
</tr>
<tr>
<td>Toxicologically significant compounds (animals, plants and the environment)</td>
<td>Parent and oxon</td>
</tr>
</tbody>
</table>

Acute toxicity

| Rat, LD₅₀, oral | 2814 mg/kg bw |
| Rat, LD₅₀, dermal | > 2000 mg/kg bw |
| Rat, LC₅₀, inhalation | > 0.67 mg/L air (nose only) |
| Rabbit, dermal irritation | Slight, transient irritant |
| Rabbit, ocular irritation | Slight, transient irritant |
| Guinea-pig, dermal sensitization (test method used) | Negative results in Buehler test; positive results in Magnussen & Kligman maximization test |

Short-term studies of toxicity

| Target/critical effect | Inhibition of acetylcholinesterase activity, adrenal vacuolation |
| Lowest relevant oral NOAEL | 1 mg/kg bw per day (rat) |
| Lowest relevant dermal NOAEL | 10 mg/kg bw per day (systemic) |
| Lowest relevant inhalation NOAEC | 18 ppb (approximately 100 µg/m³) |
Genotoxicity

No genotoxic potential in vivo

**Long-term studies of toxicity and carcinogenicity**

<table>
<thead>
<tr>
<th>Target/critical effect</th>
<th>Inhibition of acetylcholinesterase activity, adrenal vacuolation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest relevant NOAEL</td>
<td>1 mg/kg bw per day</td>
</tr>
<tr>
<td>Carcinogenicity</td>
<td>Not carcinogenic</td>
</tr>
</tbody>
</table>

**Reproductive toxicity**

<table>
<thead>
<tr>
<th>Reproduction target/critical effect</th>
<th>Not toxic to reproduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest relevant reproductive NOAEL</td>
<td>10 mg/kg bw per day</td>
</tr>
<tr>
<td>Developmental target/critical effect</td>
<td>Not teratogenic. Delayed fetal development, slight increase in abnormalities at maternally toxic doses.</td>
</tr>
<tr>
<td>Lowest relevant developmental NOAEL</td>
<td>12.5 mg/kg bw per day (rat)</td>
</tr>
</tbody>
</table>

**Neurotoxicity/delayed neurotoxicity**

| Neurotoxicity/delayed neurotoxicity | Histopathological indications of neuropathy at 5000 mg/kg bw. No indications of delayed neuropathy at 500 mg/kg bw per day for 13 weeks. Very weak inhibitor of neuropathy target esterase (NTE) in vitro |

**Other toxicological studies**

| Studies in human volunteers          | No adverse effects at doses of up to 0.3 mg/kg bw per day for 21 days |
| Single-dose study in human volunteers given chlorpyrifos | No adverse effects at doses of up to 1.0 mg/kg bw |

**Medical data**

| Medical data | No adverse effects in production-plant workers |

**Summary**

<table>
<thead>
<tr>
<th>Summary</th>
<th>Value</th>
<th>Study</th>
<th>Safety factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADI</td>
<td>0–0.01 mg/kg bw</td>
<td>Rat, 2-year, dietary, Rat, reproductive toxicity, Rat, developmental toxicity, Dog, 2-year</td>
<td>100</td>
</tr>
<tr>
<td>ARfD</td>
<td>0.1 mg/kg bw</td>
<td>Single-dose study in human volunteers given chlorpyrifos</td>
<td>10</td>
</tr>
</tbody>
</table>

**RESIDUE AND ANALYTICAL ASPECTS**

Chlorpyrifos-methyl, an organophosphate insecticide has been evaluated by the JMPR several times since 1975. The compound was listed at the Thirty-ninth Session of the CCPR for periodic review by the 2009 JMPR for both toxicology and residues. An ADI of 0–0.01 mg/kg bw and a ARfD of 0.1 mg/kg bw was established by the Meeting. The manufacturer submitted data on metabolism of chlorpyrifos-methyl in farm animals and plants, environmental fate, methods of analysis, GAP information, supervised residue trials on citrus, pome fruit, stone fruits, cherries, grapes, strawberries, kiwi fruit, onion, tomato, peppers, sugar beet, potato, carrot, artichoke, green beans, oilseed rape, cotton and cereals, and processing studies on various crops. Additionally, metabolism studies on
chlorpyrifos in plants and of TCP and TMP in soils were submitted. The structure of the parent compounds and main metabolites are shown below.

| ![Structure of chlorpyrifos-methyl and its metabolites] |
|-----------------|-----------------|-----------------|-----------------|
| ![Structure of chlorpyrifos-methyl] (O,O-dimethyl O-3,5,6-trichloro-2-pyridinyl phosphorothioate) | ![Structure of OXm-Chlorpyrifos-methyl oxon] | ![Structure of TCP] | ![Structure of TMP] |
| ![Structure of DEM] Des-methyl chlorpyrifos-methyl | ![Structure of TCP] 3,5,6-trichloro-2-pyridinol | ![Structure of TMP] 2-methoxy-3,5,6-trichloropyridine |

**Animal metabolism**

The metabolism of chlorpyrifos-methyl in rats was evaluated by the WHO panel at the present Meeting. The compound was found to be rapidly and extensively absorbed in the rat following a single oral dose (16 or 30 mg/kg bw). Excretion was rapid (largely within 24 hours) and primarily in the urine. Urinary metabolites were identified as the glucuronide conjugate of TCP (68.6%), free TCP (13.8%) and DEM (17.8%). The fate of the phosphorothioate moiety was not investigated.

Two lactating goats were fed $[^{14}C]$chlorpyrifos-methyl at 32 mg/kg feed, administered in gelatin capsules, twice a day for 7 days then sacrificed 14 h after the final dose and samples taken. Liver, kidney, fat and milk fat were extracted with acetonitrile (ACN), the extract partitioned with hexane and the ACN layer analysed by radio TLC and HPLC. The non-extracted residue (NER) was subject to base hydrolysis. Recovery was > 91% of administered dose and approximately 95% of recovered radioactivity was in the urine (~22 mg/kg chlorpyrifos-methyl eq.). Highest total radioactive residues (TRR) were found in kidney and liver (0.62 and 0.40 mg/kg chlorpyrifos-methyl eq., respectively). Residues in fat and skeletal muscle were 0.14 and 0.047 mg/kg, respectively. In milk, residues concentrated in milk fat (0.115 mg/kg), with levels over 4 times that found in whole milk. The majority of the residues found in liver and kidney were TCP, 66.7% TRR (0.24 mg/kg) and 74.2% TRR (0.45 mg/kg) respectively. In fat and milk fat, the parent compound was predominant (55.3 and 61.8% TRR, respectively), at levels of 0.06 mg/kg. The S-methyl isomer and DEM were also detected in all matrices, at levels < 10% TRR each. Base extracts of liver and kidney showed no parent compound and only TCP as metabolite (10.56% TRR in liver and 6.8% TRR in kidney). Base extracts of insoluble tissue showed traces of chlorpyrifos-methyl (up to 0.2% TRR), TCP plus S-methyl isomer (up to 9% TRR) and up to 1% TRR of DEM in kidney.

Four laying hens received a daily dose of labelled $[^{14}C]$chlorpyrifos-methyl at a dietary intake level equivalent to 25 mg/kg feed for 10 days. The birds were sacrificed approximately 16 h after the tenth dose for tissue collection. Tissue and egg samples were extracted using ACN, the extracts partitioned with hexane and analysed by TLC and HPLC. The unextracted residues in egg yolk and kidney were subjected to base hydrolysis and the extracts analysed by LSC. The majority of the radioactivity (approximately 70% applied radioactivity) was present in the excreta. Radioactivity was low in tissues, exceeding 0.1 mg/kg only in fat (0.07–0.35 mg/kg chlorpyrifos-methyl eq.), kidney (0.09–0.15 mg/kg) and egg yolk (< 0.01–0.10 mg/kg). The highest level in muscle was 0.02 mg/kg. The majority of the residues present in kidney were the TCP (approximately 77% TRR) and DEM...
metabolites (22% TRR). Fat contained mainly the parent (approximately 75% TRR) and egg yolk contained roughly equal quantities of all three components (16 to 23% TRR).

In summary, chlorpyrifos-methyl is metabolized in goats and hens primarily to TCP (over 60% TRR). Residues concentrated in fat tissue and milk fat. This metabolic pathway was also found in rats.

**Plant metabolism**

The Meeting received plant metabolism studies with chlorpyrifos-methyl on tomato and cereal grains, and chlorpyrifos on citrus, cabbage, peas and radish.

Structurally, chlorpyrifos (O,O-diethyl O-3,5,6-trichloro-2-pyridinyl phosphorothioate) differs from chlorpyrifos-methyl (O,O-dimethyl O-3,5,6-trichloro-2-pyridinyl phosphorothioate) only in the phosphorothioester moiety, as the first is a diethyl and the second a dimethyl ester. Consequently, knowledge of chlorpyrifos metabolism in plants is useful in determining the relevant residues of chlorpyrifos-methyl, for enforcement purposes.

**Chlorpyrifos-methyl**

In a tomato study $[^{14}C]$chlorpyrifos-methyl was applied to plants at a rate equivalent to 0.99 kg ai/ha, within the seasonal label rate range of 0.5 to 3.0 kg ai/ha. Fruit and leaf samples were collected at 0, 5, 13, 26 and 42 days after application (DAT), rinsed first with dichloromethane (DCM) and then with ACN. A concentrate of the 26 DAT fruit extracted aqueous phase was subjected to treatment using β-glucosidase. The stability of DEM during extraction was evaluated by adding $[^{14}C]$/DEM (76% purity) to a 5 DAT rinsed control tomato fruit sample. An aliquot of a $[^{14}C]$/DEM solution (74.8% purity) was also subjected to the enzyme procedure. In rinsed fruit, the radioactivity decreased from 86.7% TRR at 0 DAT to 0.8% TRR at 26 DAT. TRR values also declined over the time in leaves. By 13 DAT, 15% remained in the tissues. About 100% of the $[^{14}C]$/DEM radioactivity was recovered during the procedure. Up to 5 DAT, most of the residues were identified as chlorpyrifos-methyl, which was metabolized primarily to TCP (11.3% TRR at 13 DAT) and polar residues (19.6% TRR at 13 DAT). For all fruit samples, no more than 2.5% of TRR was found in the region where DEM was expected to elute. TMP, the S-methyl isomer, and OXN were not detected in any sample. The β-glucosidase treatment liberated 6.5% TRR, eluting in the TCP region. About 62 and 24% TRR of $[^{14}C]$/DEM solution submitted to the enzyme procedure eluted in the DEM and TCP regions, respectively; about 17% of the radioactivity was lost during the procedure. As was found for fruit extracts, chlorpyrifos-methyl was metabolized in leaf rinses primarily to TCP and to polar residues.

An EC formulation of $[^{14}C]$chlorpyrifos-methyl was applied to wheat and maize grain at a rate equivalent to 32.4 mg ai/kg grain with samples of the treated grain stored at 25±1 °C for 180 days. At the end of the experiment, the parent compound represented about ⅓ of the applied radioactivity (AR) in maize and 45% in wheat. TCP and DEM represented 39 and 24% AR in maize, respectively; about 17% of the radioactivity was lost during the procedure. As was found for fruit extracts, chlorpyrifos-methyl was metabolized in leaf rinses primarily to TCP and to polar residues.

**Chlorpyrifos**

A single orange tree (Washington navel) was sprayed with $[^{14}C]$chlorpyrifos at a rate equivalent to 3.97 kg ai/ha. TRR levels in both leaves and fruit declined by 50% or more after 21 days after treatment. Over 99% of the whole fruit TRR remained associated with the peel, mostly as chlorpyrifos. OXON, TCP and DES were found at low levels (up to 0.5% TRR; 0.22 mg/kg chlorpyrifos eq.). Enzyme hydrolysis of the leaf aqueous soluble fraction, approximately 60% of the sample radioactivity was extracted into organic solvent, being 32.0% TCP. A base hydrolysis of this same fraction showed 80% of the residues as TCP. About 5% of NER was solubilised by enzyme digestion, 15% by acid hydrolysis; approximately 85% of the bound radioactivity remained
associated with the acid detergent fibre. About 90% of the leaf NER was solubilised by base hydrolysis. Subsequent partitioning of the aqueous phase from this step resulted in the extraction of 82.9% of the solubilised radioactivity into organic solvent, composed of at least seven components, with TCP representing 36.7% TRR.

**Cabbage** plants received one foliar spray application of $[^{14}C]$chlorpyrifos at a rate equivalent to 1.43 kg ai/ha. Plants were sampled at 0, 7, 14, 21 and 42 days after application (DAT) with TRR values declining over the 42 days. At 7 DAT, organic extracts contained 42% of TRR, mostly as chlorpyrifos. TCP levels increased from 2% TRR at 7 DAT to 6.1% TRR at 21 DAT. The maximum level of DES was found at 14 DAT (5.3% TRR). Chlorpyrifos appears to be metabolized to TCP, which is extensively conjugated with glucose and malonic acid.

**Potted pea** plants were treated with one application of $[^{14}C]$chlorpyrifos, applied at a rate equivalent to 1.9 kg ai/ha, with samples collected weekly up to 28 DAT. Radioactivity declined rapidly during the first 7 days; in pods, the levels had reached 0.25% of TRR at the end of the study. There was a steady decrease of chlorpyrifos over time (from 89.6% of TRR at 0 DAT to 3.8% of TRR by day 28 in pea pods), while TCP and TCP conjugates increased during this period (8.7 and 42.5% of TRR, respectively). Conjugates consisted of at least five different sugar or sugar plus malonic acid conjugates of TCP.

A single foliar spray of $[^{14}C]$chlorpyrifos was applied to radish plants at rate equivalent to 1.92 kg ai/ha then sampled weekly up to 35 days DAT. TRR in the rinsed tops decreased from 58.7 mg/kg chlorpyrifos eq. on Day 0 to 1.6 mg/kg at 35 DAT. Whereas the levels in roots remained relatively unchanged during the course of the study at about 2 mg/kg. Residues in the aqueous phase increased during the course of the experiment (from 0.06 to 38.5% of TRR in roots), representing mostly TCP conjugates. Chlorpyrifos residues decreased to 14.8% TRR in tops and 41.5% of TRR in roots at 35 DAT, while TCP reached 2.5% of TRR in tops at the end of the experiment. Enzyme digestion was more effective at releasing NER residues (up to 20% of TRR), with over 80% of this radioactivity being aqueous soluble.

In summary, metabolism studies conducted with chlorpyrifos-methyl and chlorpyrifos in plants indicates a single primary metabolic pathway that involves hydrolysis of the phosphate ester to give primarily TCP and polar residues, mainly TCP conjugates of glucose and malonic acid.

**Environmental fate**

The Meeting received information on soil aerobic metabolism and soil photolysis.

In four agricultural soils $[^{14}C]$Chlorpyrifos-methyl, at a rate equivalent to 0.5 kg ai/ha, was incubated under aerobic conditions at 40% moisture-holding capacity (MHC) and 20 °C. Samples were taken at regular intervals up to 100 DAT, extracted with solvent and analysed by LSC and HPLC. The initial degradation product in all soils was TCP, accounting for up to 65% of applied radioactivity (AR) within 7 days, which was subsequently mineralised to $^{14}CO_2$ (23–69% of AR at 100 days, depending upon soil type). Nine minor degradation products were also observed (up to 16% of AR), one of which at approximately 2% of AR co-chromatographed with TMP. Levels of NER reached 17–26% of AR at 100 days, and little or no organic volatiles were observed. Soil half-lives, estimated by best-fit kinetics, ranged from 0.63 days (sandy clay loam) to 3.6 days (loamy sand).

The route of aerobic degradation of $[^{14}C]$TCP was investigated in the laboratory in four European soils treated at 250 g/ha in a soil depth of 5 cm and a soil bulk density of 1.5 g/cm$^3$, adjusted to 40% maximum water holding capacity (WHC$_{max}$) and incubated at 20 °C in the dark. The amounts of TCP and its degradation products in the extracts were determined by HPLC and confirmed by TLC. For the non-sterile soils, the overall recovery ranged between 83.1 and 103.7% of AR, one of which at approximately 2% of AR co-chromatographed with TMP. Levels of NER reached 17–26% of AR at 100 days, and little or no organic volatiles were observed. Soil half-lives, estimated by best-fit kinetics, ranged from 0.63 days (sandy clay loam) to 3.6 days (loamy sand).
TCP was the major component present in all soil extracts, dropping to about 32% of AR after 120 days in the Marcham sandy clay loam soil. At this time, TMP level reached 13% of AR.

In top soil taken from three USA sites, \[^{14}\text{C}]\text{TMP} was assayed at a concentration of approximately 1.0 mg/kg of soil at 100% or 35% moisture content, \(\frac{1}{3}\) bar soil moisture tension and 25 °C. Extensive mineralization to \(\text{CO}_2\) (in the order of 70% of AR) was observed in the two silty soils but not in the sandy soil, a known poor degrader, where TMP accounted for about 70% of AR after 300 days. Low levels of TCP (about 10% of AR) were observed in all three soils.

The aerobic degradation of \[^{14}\text{C}]\text{Chlorpyrifos-methyl} was investigated in sandy loam and clay loam water/sediments treated at 0.5 kg ai/ha. The samples were incubated under an aerobic/anaerobic gradient in the dark at 17–20 °C. \[^{14}\text{CO}_2\] and other volatile organic compounds accounted for up to 11% of AR. The radioactivity associated with surface water declined from about 80% at time zero to 21–38% at the end of the experiment. Degradation of chlorpyrifos-methyl was rapid in both systems with less than 2% of AR remaining after 100 days. DT\(_{50}\) values in the sandy loam and clay loam systems were 2.6 and 25.4 days, respectively. The principal degradation product was TCP, which was detected at maximum levels of 83 and 62% in 30 day sandy loam and clay loam samples, respectively.

The aqueous photolytic degradation rate and quantum yield of \[^{14}\text{C}]\text{chlorpyrifos-methyl} solutions (8.8–13.7 mg/L) in water/ACN (9:1) were determined at 20 °C irradiated under a 450 W Xenon high-pressure lamp at 290 nm for periods of up to eight hours. Chlorpyrifos-methyl degraded with a calculated quantum yield of \(2.6 \times 10^{-3}\) and DT\(_{50}\) varying according to season and weather conditions, from 1.8 days to 3.8 months.

In summary, chlorpyrifos-methyl is degraded in soils and sediments to TCP, which is either directly mineralized to \(\text{CO}_2\), or via TMP.

**Methods of residue analysis**

The Meeting received data on analytical methods for chlorpyrifos-methyl in various plant and animal commodities. In general, for plant commodities the methods involved extraction with acetone/water. The extract was partitioned into hexane and quantified by GC/FPD or cleaned-up with C\(_{18}\) SPE and quantified by HPLC/MS/MS or GC/NCI-MS. The methods were satisfactorily validated at a LOQ of 0.01 mg/kg, with a LOD of 0.002 or 0.003 mg/kg.

In kidney, liver, milk, muscle and egg the compound was extracted with acetone, the extract cleaned-up in a C\(_{18}\) SPE and chlorpyrifos-methyl quantified by GC/NCI-MS. LOQ for chlorpyrifos-methyl was 0.01 mg/kg.

Although a multiresidue method to analyse chlorpyrifos-methyl was not provided, the Meeting is aware of the availability of multiresidue methods that include the compound.

**Stability of pesticide residues in stored analytical samples**

The Meeting received data on the stability of residues in various plant and animal commodities.

In one study conducted with oranges, grapes, wine, tomato, tomato juice and wheat fortified at 0.10 mg/kg chlorpyrifos-methyl, from 80 to 106% of the compound remained after 90 days of storage at -20 °C. Another study on various plant commodities, fortified at 0.10 mg/kg, chlorpyrifos-methyl was shown to be stable for up to 18 months when stored at -18 °C, with over 70% of the compound remaining on completion of the study.

In a study conducted with cattle tissues and milk, chlorpyrifos-methyl remained stable (75–85% remained) in samples fortified at 0.10 mg/kg after 90 days under frozen conditions (-20 °C). Almost half of chlorpyrifos-methyl present in fortified egg samples was lost during storage, suggesting instability of the compound in this matrix.
**Definition of the residue**

Chlorpyrifos-methyl was shown to metabolize in animals and plants primarily to TCP. This metabolite is the major residue in goat liver and kidney and hen kidney; it represented over 20% TRR in tomato 26 days after the last treatment and 39% TRR in maize after 180 days of storage. TCP is also the main metabolite in plants treated with chlorpyrifos.

Residues of chlorpyrifos-methyl were found to concentrate in fat tissue and milk fat. The compound has a log $K_{ow}$ of 4.

Even though TCP can be a significant part of the residues in plant and animals treated with chlorpyrifos-methyl, it is also a major metabolite formed following the application of chlorpyrifos. As a consequence, TCP is not considered as a specific residue marker of the use of chlorpyrifos-methyl.

TCP lacks the phosphate ester moiety, responsible for the cholinesterase inhibiting capacity of chlorpyrifos-methyl. Data from repeated dose studies show that TCP is about 10 times less toxic than the parent compound. Also, TCP levels in crops and animal products are generally not higher than those of the parent compound. As a consequence the Meeting agreed that dietary human exposure to this metabolite is not considered of toxicological concern.

The current residue definition for chlorpyrifos-methyl in plant and animal commodities, for both enforcement and dietary risk assessment purposes is: *Chlorpyrifos-methyl (fat-soluble).*

The Meeting agreed to confirm this residue definition of chlorpyrifos-methyl: *Chlorpyrifos-methyl.*

The residue is fat soluble.

**Results of supervised trials on crops**

The NAFTA calculator was used as a tool in the estimation of the maximum residue level from the selected residue data set obtained from trials conducted according to GAP. As a first step, the Meeting reviewed all relevant factors related to each data set in arriving at a best estimate of the maximum residue level using expert judgment. The NAFTA calculator was then employed. If use of the statistical calculation spreadsheet resulted in the derivation of a different value from that recommended by the JMPR, a brief explanation of the deviation is provided.

As no chlorpyrifos-methyl residue trial data was submitted for the following crops; cabbage head, Chinese cabbage, common beans, date, lettuce head, mushrooms, radish, rice and tea green black, the Meeting withdrew its previous maximum residue level recommendations.

**Citrus fruits**

Chlorpyrifos-methyl is registered in oranges, mandarins, clementines and lemons in Italy at a GAP rate of 0.055 kg ai/hL. In Spain, the approved rate is 0.068–0.09 kg ai/hL. In both countries the PHI is 15 days. Residue data from 51 trials conducted on various citrus fruits conducted from 1991 to 2006 were submitted.

Fifteen trials were conducted in Italy in oranges, mandarins and clementines. In seven trials conducted according to maximum Spanish GAP rate, residues (whole fruit) at 15 days PHI in mandarins and clementines were 0.18, 0.23 and 0.52 mg/kg and in oranges 0.16, 0.26, 0.58 and 0.89 mg/kg. Residues in mandarin pulp were < 0.01 (< LOD of 0.003 mg/kg) and 0.01 mg/kg. Eight trials did not match GAP.

Thirty six trials were conducted in Spain in lemons, oranges, mandarins and clementines. In eight trials conducted according to the maximum Spanish GAP rate, residues at 15 days PHI (whole fruit) were 0.09, 0.21, 0.33 and 0.69 mg/kg in mandarins and 0.09, 0.11, 0.11 and 0.18 mg/kg in
Chlorpyrifos-methyl

oranges. Residues were < 0.01 (< LOD of 0.003 mg/kg) and 0.01 mg/kg in mandarin pulp. Twenty eight trials did not match GAP.

The Meeting noted that the residue populations of chlorpyrifos-methyl in mandarins, clementine and oranges from 15 trials conducted according to Spanish GAP are within the same range and agreed to use a combined data set of: 0.09, 0.09, 0.11, 0.11, 0.16, 0.18, 0.18, 0.21, 0.23, 0.26, 0.33, 0.52, 0.58, 0.69 and 0.89 mg/kg. Residues in pulp from four trials were < 0.01 (2) (< LOD of 0.003 mg/kg) and 0.01 (2) mg/kg.

There is no current GAP for chlorpyrifos-methyl covering the citrus crop group; however the GAPs for the individual crops within the group are comparable. The Meeting agreed that as the registered uses cover the main crops within the group an estimate could be done for citrus crop group.

The Meeting estimated a maximum residue level of 2 mg/kg for chlorpyrifos-methyl in citrus fruit. The Meeting also estimated a HR of 0.01 mg/kg and a STMR of 0.01 mg/kg based on the residue data in citrus pulp.

A maximum residue level estimate of 1.4 mg/kg was derived from the use of the NAFTA calculator. The Meeting applied the JMPR procedure of using one significant figure for residues below 10 mg/kg.

The Meeting withdraws its previous recommendation of 0.5 mg/k for chlorpyrifos-methyl in oranges.

Pome fruits

Chlorpyrifos-methyl is registered in apples and pears in Italy (maximum rate of 0.077 kg ai/hL), in pome fruit in Spain (maximum rate of 0.09 kg ai/hL) and in Hungary (maximum rate of 0.76 kg ai/ha; 800–1000 L/ha), with a 15 day PHI. It is also approved for use in pome fruit in Switzerland, (maximum rate of 0.76 kg ai/ha), Poland (maximum rate of 0.6 kg ai/ha; 500–750 L/ha) and Greece (maximum rate of 0.056 kg ai/hL), with a PHI of 21 days. A total of 72 trials conducted in Europe from 1999 to 2007 in apple and pears were submitted. Decline studies showed that residues were still decreasing between 15 and 21 days after application

In two trials conducted in Austria, residues were 0.02 mg/kg in apple at 21 days PHI, matching GAP in Poland, and 0.05 mg/kg in pear at 14 days PHI, matching GAP in Hungary.

Two trials conducted in Belgium did not match GAP.

Thirty six trials were conducted in France (north and south). In 14 trials conducted in the south matching Spanish GAP, residues at 15 days PHI were: < 0.01 (< LOD of 0.003 mg/kg), 0.03 and 0.16 mg/kg in pears and 0.02, 0.03, 0.04, 0.07 (2), 0.08, 0.10 (2), 0.19, 0.20, 0.22 mg/kg in apples. In 13 trials matching Swiss or Polish GAP, residues at 21 days PHI were: < 0.01 (< LOD of 0.003 mg/kg), < 0.01, 0.02, 0.03, 0.05, 0.07 and 0.08 mg/kg in pears and 0.02, 0.03, 0.04, 0.08, 0.09 and 0.15 mg/kg in apples. Eighteen trials did not match any GAP.

Seven trials were conducted in Germany in apples. In four trials matching Hungarian GAP, residues within 15 days PHI were 0.02 (2), 0.05 and 0.56 mg/kg. One trial matched Swiss GAP with residues at 21 days PHI of 0.03 mg/kg. Two trials did not match GAP.

Four trials were conducted in Greece matched Spanish GAP. Residues at 15 days PHI were 0.02 and 0.04 mg/kg in pear and 0.15 and 0.19 mg/kg in apple.

Seven trials were conducted in Italy. In five trials matching Spanish GAP, residues at 15 days PHI were 0.02 (2) mg/kg in pears and 0.03, 0.06 and 0.08 mg/kg in apple. Two trials did not match GAP.

In three trials conducted in Poland according to GAP, residues at 21 days PHI were < 0.01 (< LOD of 0.003 mg/kg) and 0.01 mg/kg in apple and 0.02 mg/kg in pears.
Nine trials were conducted in Spain. In two trials conducted according to GAP, residues at 15 days PHI were 0.03 mg/kg in apple and 0.08 mg/kg in pears. Seven trials did not match GAP.

Two trials conducted in the United Kingdom did not match GAP.

Residues in pears from nine trials with a PHI of 15 days were: < 0.01 (< LOD of 0.003 mg/kg), 0.02 (3), 0.03, 0.04, 0.05, 0.06, 0.07 (3), 0.08 (2), 0.10 (2), 0.15, 0.19 (2), 0.20, 0.22 and 0.56 mg/kg

Residues in apples from 21 trials conducted at a 15 day PHI were: 0.02 (2), 0.03 (3), 0.04, 0.05, 0.06, 0.07 (3), 0.08 (2), 0.10 (2), 0.15, 0.19 (2), 0.20, 0.22 and 0.56 mg/kg

Residues in pears from nine trials conducted at a 21 day PHI were: < 0.01 (< LOD of 0.003 mg/kg), < 0.01, 0.02 (3), 0.03, 0.05, 0.07 and 0.08 mg/kg

Residues in apples from nine trials conducted at a 21 day PHI were: < 0.01 (< LOD of 0.003 mg/kg), 0.01, 0.02, 0.03 (2), 0.04, 0.08, 0.09 and 0.15 mg/kg.

The Meeting decided that data from trials in apples and pears, done according to GAP, were from different populations (Mann-Whitney U test) and could not be combined. The Meeting agreed that the residue data from apples at a PHI of 15 days, which had the highest residues and reflected the critical GAP in Europe, could be used for the estimation for pome fruits.

The Meeting estimated a maximum residue level of 1 mg/kg, a HR of 0.56 mg/kg and a STMR of 0.07 mg/kg for chlorpyrifos-methyl in pome fruits.

The maximum residue level estimate derived from use of the NAFTA calculator was 0.6 mg/kg. The Meeting noted that the majority of trials were conducted at the lower 25% range of the GAP rate, including the trial that gave rise to the highest residue (0.56 mg/kg). As a consequence the Meeting considered that the estimate derived from the calculation using the NAFTA spreadsheet may not accommodate all uses of chlorpyrifos-methyl in pome fruit that followed GAP.

The Meeting agreed to withdraw its previous recommendations of 0.5 mg/kg for chlorpyrifos-methyl in apple

**Stone fruits**

Chlorpyrifos-methyl is registered in Italy peaches and in Spain in peaches and nectarines at a maximum rate of 0.09 kg ai/h, with a PHI of 15 days. In Bulgaria, the rate is up to 0.055 kg ai/hL for stone fruits with a PHI of 14 days. In Greece, the PHI for stone fruit is 21 days (0.056 kg ai/hL) and 30 days (0.6 kg ai/ha) in Hungary for peaches and apricots. A total of 34 European trials were submitted for peaches and apricots completed between 1992 and 2007. Decline studies showed that residues were still decreasing between 15 and 21 days after application.

Ten trials were conducted in southern France. In five trials matching Spanish GAP, residues in whole fruit at 14–15 days PHI were < 0.01 and 0.02 mg/kg in apricots and < 0.01, 0.01 and 0.02 mg/kg in peaches; residues in pulp (pitted fruit) were < 0.01 (2), 0.01 and 0.02 (2) mg/kg. Three trials matched GAP in Greece, with residues in whole fruit and pulp of apricots (1 trial) and peaches at 21 days PHI of < 0.01 (3) mg/kg. Two trials did not match GAP

From five trials conducted in Greece, according to Italian GAP, residues in whole fruit at a PHI of 15 days were: < 0.01 (< LOD of 0.003 mg/kg), 0.01 and 0.04 mg/kg in apricots and < 0.01 and 0.17 mg/kg in peaches. Residues in pulp were < 0.01 (< LOD of 0.003 mg/kg), 0.01 and 0.04 mg/kg in apricot and < 0.01 mg/kg in peaches.

Eleven trials were conducted in Italy. In eight trials conducted according to GAP, residues at a PHI of 15 days were: < 0.01 mg/kg in apricots and 0.01, 0.02 (3), 0.06, 0.07 and 0.08 mg/kg in peaches; residues in pulp were < 0.01 mg/kg in apricot and 0.01, 0.02 (3), 0.06, 0.07 and 0.09 mg/kg in peaches. One trial matching Greek GAP, residues at a PHI of 21 days was < 0.01 mg/kg in peach whole fruit and pulp.
Chlorpyrifos-methyl

Eight trials were conducted in Spain. In three trial matching GAP, residues in whole fruit at a PHI of 15 days were: < 0.01 mg/kg (< LOD of 0.003 mg/kg) in apricots and 0.02 and 0.23 mg/kg in peaches; in pulp, residues were < 0.01 mg/kg (< LOD of 0.003 mg/kg) in apricots and 0.02 and 0.26 mg/kg in peaches. Five trials matched Greek GAP with residues at a PHI of 21 days of < 0.01 (2) (< LOD of 0.002 mg/kg) and < 0.01 in apricots and 0.02 and 0.03 mg/kg in peaches; in pulp, residues were < 0.01 (2) (< LOD of 0.002 mg/kg), < 0.01 and 0.02 mg/kg.

Residues in whole fruit and pulp of apricots from seven trials matching GAP with a PHI of 15 days were: < 0.01 (2) (< LOD of 0.003 mg/kg), < 0.01 (2), 0.01, 0.02 and 0.04 mg/kg.

Residues in whole fruit of peaches from 14 trials matching GAP with a PHI of 15 days were: < 0.01 (2), 0.01 (2), 0.02 (5), 0.06, 0.07, 0.08, 0.17 and 0.23 mg/kg. In pulp (pitted fruit), residues were: < 0.01 (3), 0.01 (2), 0.02 (5), 0.06, 0.07, 0.09 and 0.26 mg/kg.

Residues in whole fruit and pulp of apricots from four trials according to GAP at 21 days PHI were: < 0.01 (2) (< LOD of 0.002 mg/kg) and < 0.01 (2) mg/kg.

Residues in peaches from five trials matching GAP at a PHI of 21 days were: < 0.01 (3), 0.02 and 0.03 mg/kg. In pulp, residues were < 0.01 (2) (< LOD of 0.002 mg/kg), < 0.01 (2) and 0.02 mg/kg.

Chlorpyrifos-methyl is registered for use in cherries in Hungary at 0.6 kg ai/ha and 800–1000 L/ha (0.048–0.072 kg ai/hL) with a 30 day PHI. Eleven trials were conducted in Austria, Germany, Hungary and Poland in 2006/2007. Decline studies showed that residues declined rapidly during the first 5 days following application then relatively slowly thereafter. Consequently, data from samples collected 21 days after application (30% shorter PHI than GAP of 30 days) were accepted as being comparable to GAP. Residues from the 11 trials were < 0.01 (9) (< LOD of 0.003 mg/kg) and < 0.01 (2) mg/kg in whole fruit and pulp.

The Meeting agreed that the residue population from trials conducted at a PHI of 15 days in peaches had the highest residues and could be used for the estimation of a maximum residue level for stone fruit.

The Meeting estimated a maximum residue level of 0.5 mg/kg for chlorpyrifos-methyl in stone fruits. Based on the residue data in peach pulp (pitted fruit), the Meeting also estimated a HR of 0.26 mg/kg and a STMR of 0.02 mg/kg.

The maximum residue level estimate derived from use of the NAFTA calculator was 0.15 mg/kg. However, the Meeting noted that most of the trials were conducted at the lower 25% range of the GAP rate, including the trial that gave rise to the highest residue (0.23 mg/kg). The Meeting considered that the estimate derived from the NAFTA spreadsheet calculation may not accommodate all uses of chlorpyrifos-methyl in stone fruit that followed maximum GAP.

The Meeting withdraws its previous recommendations of 0.5 mg/kg for chlorpyrifos-methyl in peaches.

Grapes

Chlorpyrifos-methyl is registered in grapes in Italy at a rate up to 0.045 kg ai/hL and in Spain at up to 0.09 kg ai/hL, both with a PHI of 15 days. In France, the PHI is 21 days (0.338 kg ai/ha) and in Hungary 30 days (0.52–0.60 kg ai/ha; 800–1000L/ha). In Chile, the compound is recommended as a post-harvest treatment. Data was submitted from 63 trials conducted in red and white grapes (table and wine) from 1998 to 2007.

Three trials were conducted in Austria, from which one matched French GAP, with residues at a PHI of 21 days of < 0.01 mg/kg.

One trial conducted in Chile using foliar application did not matched GAP.
Chlorpyrifos-methyl

Twenty three trials were conducted in France. In two trials conducted in the south according to Spanish GAP, residues at a 15 day PHI were: < 0.01 and 0.07 mg/kg. Nine trials matched the French or Hungarian GAP, and residues were: < 0.01 (2) (< LOD of 0.003 mg/kg), < 0.01 (2), 0.01 (2), 0.03, and 0.04 mg/kg at a 21 day PHI and < 0.01 mg/kg at a 30 day PHI. The remaining trials did not match GAP.

Eleven trials were conducted in Germany, from which seven matched the French or Hungarian GAP, where residues found were: < 0.01 (2), 0.01 and 0.02 (3) mg/kg at a 21 day PHI and < 0.01 mg/kg at a 30 day PHI. The remaining trials did not match GAP.

Five trials were conducted in Greece, two matched the Italian GAP with residues at a 15 day PHI of 0.03 and 0.07 mg/kg. One trial matching French GAP gave residues at a 21 day PHI of < 0.01 mg/kg (< LOD of 0.003 mg/kg). Two trials did not match southern European GAP.

Two trials were conducted in Hungary, one matching French GAP, with residues at a PHI of 21 days of 0.01 mg/kg. One trial did not match any GAP from northern Europe.

Six trials were conducted in Italy, of which four matched GAP, where residues found at a PHI of 15 days were: < 0.01 (< LOD of 0.003 mg/kg), < 0.01, 0.01 and 0.12 mg/kg. One trial conducted in the north matched French GAP with residues at a 21 day PHI of < 0.01 mg/kg. One trial did not match GAP.

One trial was conducted in Poland according to French GAP with residues at a 21 day PHI of 0.04 mg/kg.

Twelve trials were conducted in Spain. In nine trials conducted according to GAP, residues at a 15 day PHI were: < 0.01 (< LOD of 0.003 mg/kg) (3), < 0.01 (< LOD of 0.003 mg/kg), < 0.01 (2), 0.04, 0.05 and 0.53 mg/kg. The remaining three trials did not match GAP.

Residues in grapes from 17 combined trials matching GAP at a 15 day PHI were: < 0.01 (4) (< LOD of 0.003 mg/kg), < 0.01 (< LOD of 0.002 mg/kg), < 0.01 (4), 0.01, 0.03, 0.04, 0.05, 0.07 (2), 0.12 and 0.53 mg/kg

Residues in grapes from 20 trials according to GAP at PHIs of 21 and 30 days could be also combined resulting in residues of: < 0.01 (3) (< LOD of 0.003 mg/kg), < 0.01 (8), 0.01 (4), 0.02 (3), 0.03 and 0.04 mg/kg

The residue populations from trials conducted according to 15 days PHI gave the highest levels and were used as the basis for the maximum residue level estimation for grapes.

The Meeting estimates a maximum residue level of 1 mg/kg, a HR of 0.53 mg/kg and a STMR of 0.01 mg/kg for chlorpyrifos-methyl in grapes.

The maximum residue level estimate derived from use of the NAFTA calculator was 0.70 mg/kg. The Meeting noted that most of the trials were conducted at the lower 25% range of the GAP rate, including the trial that gave rise to the highest residue (0.53 mg/kg). The Meeting considered that the estimate derived from the NAFTA spreadsheet calculation may not accommodate all uses of chlorpyrifos-methyl in grapes following the critical GAP.

Strawberries

Chlorpyrifos-methyl is registered for use in strawberries at a rate of 0.068–0.09 kg ai/hL in Italy and Spain, with PHIs of 15 and 5 days, respectively. No GAP information for northern Europe was provided. Data from 23 European trials were submitted.

Of five trials conducted in France, three were conducted in the south and matched Spanish GAP, residues found were: < 0.01 and 0.02 (2) mg/kg at 5 days PHI. Two trials conducted in northern France gave residues in the same range. Eight trials conducted in Italy and Spain at GAP rate, resulted in residues at 5 days PHI of: < 0.01 (< LOD of 0.003 mg/kg), < 0.01 (2), 0.02 (2), 0.01 (2),
and 0.04 mg/kg. Ten trials were conducted in northern Europe (Austria, Germany, Hungary, Poland and the UK) matching southern Europe GAP, giving residues in the same range.

From 11 trials conducted in southern Europe matching Spanish GAP residues found were: < 0.01 (< LOD of 0.003 mg/kg), < 0.01 (3), 0.01 (2), 0.02 (4) and 0.04 mg/kg.

The Meeting estimated a maximum residue level of 0.1 mg/kg, a HR of 0.04 mg/kg and a STMR of 0.01 mg/kg for chlorpyrifos-methyl in strawberries.

The maximum residue level estimate derived from use of the NAFTA calculator (> 10% of non-detects; maximum likelihood estimation (MLE) approach) was 0.08 mg/kg. The Meeting noted that all the trials were conducted at the lower 25% range of the GAP rate, including the one that gave rise to the highest residue (0.04 mg/kg). The Meeting considered that the estimate derived using the NAFTA spreadsheet calculator may not accommodate all uses of chlorpyrifos-methyl in strawberries following critical GAP.

Kiwifruit

Four European trials were submitted where 2 applications of chlorpyrifos-methyl were made at a rate of 0.049 kg ai/hL. Residues after 15 days ranged from 0.07 to 0.30 mg/kg and dropped to < 0.01 mg/kg (< LOD of 0.003 mg/kg) after 21 days. However, chlorpyrifos-methyl is currently not approved for use on kiwifruit in Europe.

As there was no GAP provided to support the trials, the Meeting could not estimate a maximum residue level for chlorpyrifos-methyl in kiwifruit.

Onions

Chlorpyrifos-methyl is registered for use in onions at a rate of 0.48 kg ai/ha in Hungary (PHI of 30 days) and at 0.36 kg ai/ha in Poland (PHI of 21 days). Six trials in onions were submitted however none were according to GAP.

As there was no GAP information provided to support the trials, the Meeting could not estimate a maximum residue level for chlorpyrifos-methyl in onions.

Tomatoes

Chlorpyrifos-methyl is registered in Italy, at a rate of 0.028–0.04 kg ai/hL (PHI of 15 days) and in Spain at up to 0.068–0.09 kg ai/hL (PHI of 5 days). Fifty five field and protected trials were conducted in Europe from 1999 to 2007. Ten trials were conducted in France. In seven trials conducted in southern France matching the Spanish GAP rate, residues at a PHI of 5 days were: 0.06, 0.20 and 0.42 mg/kg in field trials and 0.03, 0.08, 0.13 and 0.20 mg/kg in protected cropping trials. Three trials did not match GAP.

In four field trials conducted in Greece matching Spanish GAP, residues at a PHI of 5 days were: 0.03 (2), 0.06 and 0.31 mg/kg.

Seventeen trials were conducted in Italy. In nine trials conducted matching Spanish GAP, residues at 5 days PHI were: 0.05 (2), 0.07 (3), 0.08 and 0.92 mg/kg in field trials and < 0.01 and 0.05 mg/kg in protected cropping trials. Six trials did not match any GAP.

Fourteen trials were conducted in Spain. In six trials matching GAP, residues at 5 days PHI were: 0.01, 0.02, 0.04, 0.05 and 0.06 mg/kg in field trials and 0.03 mg/kg in protected cropping trials. Eight trials did not match GAP.

Ten trials conducted in northern Europe (the Czech Republic, Hungary, Germany, Poland and the UK) could not be evaluated due to the lack of an approved GAP for the region.
Residues on tomato from 19 trials conducted according to GAP in the field at 5 days PHI were: 0.01, 0.02, 0.03 (2), 0.04, 0.05 (3), 0.06 (3), 0.07 (3), 0.08, 0.20, 0.31, 0.42 and 0.92 mg/kg.

Residues on tomato from eight trials conducted matching GAP in the protected cropping at 5 days PHI were: < 0.01 (2), 0.03 (2) and 0.05 (2), 0.13 and 0.20 mg/kg.

Trials conducted matching Spanish GAP in field and protected cropping situations were not similar (Mann-Whitney U test) and could not be combined. The Meeting agreed that the residues coming from the field trials, having the highest residue population, could be used for the maximum residue level estimation.

The Meeting estimates a maximum residue level of 1 mg/kg, a HR of 0.92 mg/kg and a STMR of 0.06 mg/kg for chlorpyrifos-methyl in tomato.

The maximum residue level estimate derived from use of the NAFTA calculator was 0.90 mg/kg. The Meeting noted that most of the trials were conducted at the lower 25% range of the most critical GAP rate and that the NAFTA calculator value was lower than the highest residue found in the trials (0.92 mg/kg). The Meeting agreed that the value derived from the use of the NAFTA calculator spreadsheet may not accommodate all uses of chlorpyrifos-methyl in tomatoes where chlorpyrifos-methyl is applied according to critical GAP.

**Peppers**

Chlorpyrifos-methyl is registered to be used in peppers and egg plant in Italy at a rate of 0.34–0.45 kg ai/ha (PHI of 15 days) and 0.068–0.09 kg ai/L in Spain for peppers (PHI of 5 days). Twenty four trials were conducted in Europe from 1999 to 2007 in the field and protected cropping.

Three trials were conducted in southern France, with one in protected cropping matching Spanish GAP, with residues of 0.14 mg/kg at a 5 day PHI.

Five trials were conducted in Greece. In three protected cropping trials matching Spanish GAP, residues at 5 days PHI were 0.03 and 0.16 (2) mg/kg. Three trials conducted at double rate gave residues in the same range.

Five trials were conducted in Italy. In two protected cropping trials matching Spanish GAP, residues at 5 days PHI were 0.04 and 0.06 mg/kg.

Fourteen trials were conducted in Spain. Five protected trials matching GAP gave residues at a PHI of 5 days were: 0.03, 0.04, 0.06, 0.52 and 0.72 mg/kg and three field trials conducted at GAP gave residues of 0.01, 0.04 and 0.09 mg/kg. Six trials conducted at double rate or higher PHI gave residues in the same range.

Residues from protected cropping trials, conducted according to Spanish GAP were: 0.03 (2), 0.04 (2), 0.06 (2), 0.14, 0.16 (2), 0.52 and 0.72 mg/kg.

Residues found from field trials, conducted according to Spanish GAP, were: 0.01, 0.04 and 0.09 mg/kg.

Trials conducted according to Spanish GAP in the field and protected cropping were not similar (Mann-Whitney U test) and could not be combined. The Meeting agreed that as the residues coming from the protected cropping had the highest residue population, they be used for the maximum residue level estimation.

The Meeting estimated a maximum residue level of 1 mg/kg, a HR of 0.72 mg/kg and a STMR of 0.06 mg/kg for chlorpyrifos-methyl in peppers.

The maximum residue level estimate derived from use of the NAFTA calculator was 0.5 mg/kg. The Meeting noted that most of the trials were conducted at the lower 25% range of the most critical GAP rate and that NAFTA calculator value was lower than the highest residue found in the trials (0.72 mg/kg). The Meeting agreed that value derived from the use of the NAFTA calculator
Chlorpyrifos-methyl might not accommodate all uses in peppers where chlorpyrifos-methyl is applied according to critical GAP.

Using the default dehydration factor of 10 to extrapolate from peppers to dried chilli peppers, the Meeting estimated a maximum residue level of 10 mg/kg (based on a highest residue of 7.2 mg/kg) and a STMR of 0.6 mg/kg for chlorpyrifos-methyl in Peppers, chilli dried.

In Italy, the approved GAP is for both peppers and egg plant. The Meeting agreed to use the residue data in peppers and estimates a maximum residues level of 1 mg/kg, a HR of 0.72 mg/kg and a STMR of 0.06 mg/kg for chlorpyrifos-methyl in egg plants.

The Meeting withdraws its previous chlorpyrifos-methyl recommendations of 5 mg/kg in peppers, chilli dry and of 0.1 mg/kg in egg plant.

**Green beans and peas**

The Meeting received data from six residue trials in green beans and peas conducted in Europe at a rate of $2 \times 0.20$ to 0.52 kg ai/ha. Residues at 10 or 15 days after the last application ranged from $< 0.01$ (< LOD of 0.002 mg/kg) to 0.02 mg/kg.

However, as there was no GAP information provided to support the trials, the Meeting could not estimate a maximum residue level for chlorpyrifos-methyl in green beans or peas.

**Carrot**

The Meeting received data from four trials conducted in carrots in France, Italy and Spain, at a rate of $2 \times 0.48$ to 0.52 kg ai/ha. Residues after 3 days of the last application ranged from $< 0.01$ to 0.07 mg/kg.

However, as there was no GAP information provided to support the trials, the Meeting could not estimate a maximum residue level for chlorpyrifos-methyl in carrots.

**Potatoes**

Chlorpyrifos-methyl is approved for use in potatoes in Italy at a rate up 0.045 kg ai/hL or 0.45 kg ai/ha and in Spain up to 0.09 kg ai/hL. In both countries the PHI is 15 days. Data from 21 trials conducted in Europe from 2000 to 2007 were provided to the Meeting.

Seven trials were conducted in South of France. In two trials matching Spanish GAP, residues at a PHI of 15 days were: $< 0.01$ mg/kg (2) (< LOD of 0.003 mg/kg). No residues were detected in trials conducted at double rate (two trials), lower (one trial) or higher PHI (two trials).

Five trials were conducted in Italy. In three trials matching either the Italian or Spanish GAP rate, residues at a PHI of 15 days were: $< 0.01$ (2) (< LOD of 0.002 mg/kg) and $< 0.01$ mg/kg (< LOD of 0.003 mg/kg). No residues were detected in two trials conducted at doubled rate or one at a lower PHI.

Three trials were conducted in Spain. One trial matching GAP, resulted in residues at the 15 day PHI of $< 0.01$ mg/kg (< LOD of 0.003 mg/kg). No residues were detected in two trials conducted at lower or higher PHIs.

Six trials were conducted at 0.07 kg ai/hL in northern Europe (Germany, Poland, Hungary and the UK), for which no GAP information was provided. No residues were detected at any sampling point (0 to 21 days).

In six trials conducted in southern Europe according to GAP residues found were: $< 0.01$ (< LOD of 0.002 mg/kg) and $< 0.01$ (4) mg/kg (< LOD of 0.003 mg/kg). In all trials submitted, no residues were detected at the day of the last application, indicating that it is unlikely the use of chlorpyrifos-methyl, at the GAP rate, will leave detectable residues in potato tubers.
The Meeting estimated a maximum residue for chlorpyrifos-methyl of 0.01(*) mg/kg and a HR and STMR of 0 for chlorpyrifos-methyl in potato.

The NAFTA calculator was not used to derive an estimate as all residue values considered by the Meeting were below the LOQ, making its application unsuitable.

**Sugar beet**

Chlorpyrifos-methyl is registered for use on sugar beet in Poland at a rate of 0.36 kg ai/ha (PHI of 30 days) and up to 0.05 kg ai/hL in Spain (PHI of 15 days). Data from four trials conducted in Italy and Spain in 2000/2001 were submitted where sampling occurred at more than harvest interval of greater than 100 days.

As no trials were conducted that matched GAP, the Meeting could not estimate a maximum residue level for chlorpyrifos-methyl in sugar beet.

**Artichoke (globe)**

No GAP information on the use of chlorpyrifos-methyl in artichokes was provided to the Meeting. Four trials were conducted in Greece and Spain, at a 1 kg ai/ha. Residues at a PHI of 5 days ranged from 0.11 to 1.2 mg/kg.

As there is no GAP to support the trials, the Meeting could not estimate a maximum residue level for chlorpyrifos-methyl in artichoke.

The Meeting withdraws its previous recommendations of 0.1 mg/kg for chlorpyrifos-methyl in artichoke, globe

**Cereal grains – post-harvest use**

Chlorpyrifos-methyl is registered for use as a grain storage treatment in a number of countries. The application rate for cereal grains ranges from 2.5 g ai/tonne seed (storage interval of 21 days in Hungary to 120 days in Belgium) to 4.5 g ai/tonne seed (storage interval of 90 days) in the UK. In Spain, the GAP for wheat, barley and maize is 2.2 g ai/tonne seed with no storage interval specified.

Twelve trials were conducted in barley in Europe from 1994 to 1995. The formulation was applied to the grain in a rotary mixer using hand-held trigger application equipment at the GAP use rates and timings. Nine trials conducted at 4.5–5 g ai/tonne seed, gave residues within 90 days storage interval of 1.6, 1.9, 2.3, 2.6, 2.9, 3.0, 3.1, 3.2 and 3.3 mg/kg. One trial conducted at the GAP rate gave a large variation of residues during the period of storage, starting with 6.2 mg/kg at the day of treatment, reaching a highest residue of 10 mg/kg at 99 days of storage and dropping to 6.7 mg/kg after 182 days. The highest value from this trial is twice the application rate (5g ai/tonne), an unexpected in large scale post-harvest application in cereals. The Meeting agreed that this variation indicates a lack of homogeneity in mixing during treatment and the trial should not be considered in the estimation.

In two trials conducted at 2.5 g ai/tonne seed matching Spanish GAP, samples were collected from 0 to 181 days after the treatment; the highest residues were found after 7 days at 2.0 (2) mg/kg.

Twelve trials were conducted in wheat in Europe. Ten trials conducted at 4.5–5 g ai/tonne seed, gave residues within 90 days storage interval of 1.9, 2.2, 2.4, 2.9, 3.0, 3.1, 3.2 (2), 3.5 and 4.7 mg/kg.

In two trials conducted at 2.5 g ai/tonne seed matching Spanish GAP, samples were collected from 0 to 181 days after the treatment; the highest residues were found at 0 days were 2.2 (2) mg/kg.

Residue data from 19 trials conducted at the highest application rate in barley and wheat can be combines as follow: 1.6, 1.9 (2), 2.2, 2.3, 2.4, 2.6, 2.9 (2), 3.0 (2), 3.1 (2), 3.2 (3), 3.3, 3.5 and 4.7 mg/kg.
Residues from trials conducted in wheat and barley at 2.5 g ai/tonne seed are 2.0 (2) and 2.2 (2) mg/kg.

Based on the residue data from the highest application rate, the Meeting estimated a maximum residue level of 5 mg/kg, a HR of 4.7 mg/kg and a STMR of 3.0 mg/kg for chlorpyrifos-methyl in cereal grain group, post-harvest.

Long-term dietary risk assessment indicates an exceedance of the ADI for 10 of the 13 GEMS/Food Consumption Cluster Diets (up to 260 % ADI).

Taking the alternative GAP approach, the Meeting considered the residue data set coming from trials conducted according to Spanish GAP in wheat and barley for maximum residue level estimation. The Meeting estimated a maximum residue level of 3 mg/kg, a HR of 2.2 mg/kg and a STMR of 2.1 mg/kg for chlorpyrifos-methyl in wheat, barley and maize, post-harvest.

The maximum residue level estimate derived from use of the NAFTA calculator was 2.5 mg/kg. The normal JMPR procedure is to use one significant figure for maximum residue levels below 10 mg/kg. Rounding up the value obtained from the calculator results in 3 mg/kg which corresponds to the recommendation of the current Meeting.

The Meeting withdraws its previous recommendations of 10 mg/kg for chlorpyrifos-methyl in wheat and sorghum, post-harvest.

**Maize**

Chlorpyrifos-methyl is registered to be used in maize in Italy (0.06 kg ai/hL) and Spain (0.068–0.09 kg ai/hL), with a 15 days PHI.

Eight trials were conducted with maize in France, Italy and Spain in 2007 at a rate of 0.84–0.94 kg ai/ha (0.225 kg ai/hL). Samples collected from 22 to 93 days after the application gave residues < 0.01 mg/kg (< LOD of 0.003 mg/kg).

As no trial was conducted according to GAP, the Meeting could not estimate a maximum residue level for chlorpyrifos-methyl in maize.

**Cotton**

Chlorpyrifos-methyl is registered to be used in cotton in Spain (up to 0.09 kg ai/hL, 15 days PHI) and in Greece (up to 0.67 kg/ha; 500–800 L/ha with a 21 day PHI). Twelve trials were conducted in Greece and Spain in 2006/2007 at the Greek GAP rate, with residues in cotton seed ranging from < 0.003 to 0.02 mg/kg 15 days after the last application (eight trials) and < 0.01 mg/kg (< LOD of 0.003 mg/kg) 28 days after the last application.

As no trial was conducted according to GAP, the Meeting could not estimate a maximum residue level for chlorpyrifos-methyl in cotton seed.

**Rape seed**

The Meeting received no information on registered GAP for chlorpyrifos-methyl in rape seed. Data was submitted from 16 trials conducted in 2006/2007 where chlorpyrifos was applied at a rate of 0.45 to 0.49 kg ai/ha, which resulted in no detectable residues in samples collected at harvest intervals of 31 to 120 days.

As there was no GAP provided to support the trials, the Meeting could not recommend a maximum residue level for chlorpyrifos-methyl in rape seed.
**Animal feed**

Chlorpyrifos-methyl is registered for pre-harvest use in maize in Italy (0.06 kg ai/hL) and Spain (0.068–0.09 kg ai/hL), with a PHI of 15 days. In 28 trials conducted in Europe, samples of cobs, whole plant and stover (rest of the plant) were analysed. In four trials conducted in southern France and Spain, matching Spanish GAP, residues in maize whole plant, at a PHI of 15 days were: < 0.01, 0.04, 0.16 and 1.4 mg/kg. Twenty four trials were conducted at double rate and or samples were collected 28 days after the last application, i.e., did not match GAP.

The trials matching GAP with chlorpyrifos-methyl in maize were considered insufficient for making estimations for chlorpyrifos-methyl in animal feed.

In two trials conducted in cotton in Spain, matching Greek GAP, residues in cotton, whole plant, at a 15 day PHI were: 0.86 and 1.6 mg/kg.

The trials conducted with chlorpyrifos-methyl in cotton were considered insufficient to make estimations for chlorpyrifos-methyl in animal feed.

In 16 trials conducted with rape seed, samples of animal feed were analysed. As no registered GAP information for use in rape seed was provided, the trials could not be evaluated. Four trials were conducted in sugar beet and samples of animal feed were analysed (tops/leaves and whole plant).

As no registered GAP information was provided to support the trials, the Meeting could not make estimations for chlorpyrifos-methyl in animal feed from sugar beet.

**Fate of residues during processing**

Two processing studies on oranges were conducted in Spain in 2004–2005. Orange trees received 2 applications of chlorpyrifos-methyl at 2.7 kg ai/ha. The fruit was harvested 21 days after the second application and underwent processing that simulated standard industrial procedures. Residues of chlorpyrifos-methyl in whole fruit were 0.13 and 0.24 mg/kg. Mean (n=2) processing factors (PF) for chlorpyrifos-methyl were calculated as 0.046 for orange juice and 40.2 for essential oil.

In three French studies, two applications were made to apple trees at 0.6 or 0.78 kg ai/ha with harvested fruit processed following standard commercial practices. Residues of chlorpyrifos-methyl in the fruit ranged from 0.02 to 0.07 mg/kg. No residues were detected in apple juice, PF estimated as < 0.05, < 0.04 and < 0.15 (mean of < 0.08). No residues of chlorpyrifos-methyl were detected in apple purée, with a mean PF of < 0.15.

In a study conducted in 2004 on peaches in France, trees received two applications of chlorpyrifos-methyl at 0.833 and 0.904 kg ai/ha. Treated fruit was sampled 28 days after the last application and processed to juice and purée according to commercial practices. Chlorpyrifos-methyl residues in whole fruit were < 0.01 mg/kg. No residues were found in juice and purée, but were detected in dry pomace at the LOQ level. No PF for chlorpyrifos-methyl could be estimated as no residues were detected in the raw commodity.

In seven studies conducted on grapes, chlorpyrifos-methyl was applied twice at 0.07 kg ai/hL. Samples were taken 21 or 28 days after the last application and were processed to raisins and wine according to commercial practices. Residues of chlorpyrifos-methyl in grapes ranged from < 0.01 to 0.11 mg/kg but were not detected in wine (PF < 0.15), raisins (PF < 0.09) and must (PF < 0.15). Residues concentrated in grape wet pomace (mean PF of 4.2, n=2) and in dry pomace (median of > 7.5, n=4).

Three processing studies were conducted in tomatoes in Italy and Spain. Tomatoes were treated with chlorpyrifos-methyl at 0.24 or 0.07 kg ai/hL with samples processed according to commercial practice. Residues in tomatoes ranged from 0.17 to 0.22 mg/kg but were not detected in the juice (mean PF < 0.033) or the canned tomato (mean PF < 0.025). Residues were reduced in purée, with a mean PF of 0.27 and in washed tomato (PF of 0.75).
Two processing studies were conducted during 2004–2006 on barley grain stored for 6 months after receiving chlorpyrifos-methyl at 5 g ai/tonne grain. Residues of chlorpyrifos-methyl in grain at 0 or 180 days after treatment ranged from 2.1 to 3.2 mg/kg and were not detected in beer (mean PF < 0.001).

In one processing study conducted in France, maize treated twice at 0.56 kg ai/ha was processed according to commercial practices to flour and oil. Residues in grain were not reported and no residues of chlorpyrifos-methyl (< LOD of 0.002 mg/kg) were detected in the processed commodities.

Four processing studies were conducted on wheat grain stored for up to 6 months after being treated with chlorpyrifos-methyl at 1.25 to 5 g ai/tonne grain. Residues of chlorpyrifos-methyl in grain after treatment ranged from 0.52 to 3.2 mg/kg. Residues were reduced in white flour (mean PF of 0.25; n=6), white bread (mean PF of 0.05; n=6) and wholemeal bread (mean PF of 0.48, n=3). Residues remained unchanged in wholemeal flour (n=3) and concentrated in wheat germ (mean PF=1.9; n=3) and in bran (mean PF=2.45 n=6).

One processing study was conducted cotton after the plant was treated twice with chlorpyrifos-methyl at 0.675 kg ai/ha. Seed samples were collected 56 days after the last application and processed according to commercial practices. No residues were detected in cotton seed, pressed cake, raw oil or refined oil.

Two processing studies were conducted in rape seed treated with chlorpyrifos-methyl at a rate of 0.45 kg ai/ha. Seed samples were collected 105 days after treatment and processed according to commercial practices. No residues were detected in seed, pressed cake, raw or refined oil.

Summary of processing factors from the processing of Raw Agricultural Commodities (RACs)

<table>
<thead>
<tr>
<th>Processed commodity</th>
<th>Processing factor</th>
<th>Residue in the raw commodity</th>
<th>STMR-P, mg/kg</th>
<th>HR-P, mg/kg</th>
<th>Maximum residue level, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange juice</td>
<td>0.046</td>
<td>0.21 (median, citrus)</td>
<td>0.01</td>
<td></td>
<td>-</td>
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<tr>
<td>Apple juice</td>
<td>&lt;0.08</td>
<td>0.07 (STMR, pome)</td>
<td>0.0056</td>
<td></td>
<td>-</td>
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<tr>
<td>Apple wet pomace</td>
<td>0.5</td>
<td>0.07 (STMR, pome)</td>
<td>0.455</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Apple dried pomace</td>
<td>3.1</td>
<td>0.56 (HR, pome)</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Grape pomace, wet</td>
<td>4.2</td>
<td>0.01 (STMR)</td>
<td>0.042</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Grape pomace, dry</td>
<td>&gt;7.5</td>
<td>0.53 (HR)</td>
<td>-</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Grape Wine</td>
<td>&lt;0.15</td>
<td>0.01 (STMR)</td>
<td>0.002</td>
<td></td>
<td>-</td>
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<tr>
<td>Raisins</td>
<td>&lt;0.09</td>
<td>0.01 (STMR)</td>
<td>0.001</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Tomato juice</td>
<td>&lt;0.033</td>
<td>0.06 (STMR)</td>
<td>0.002</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Beer</td>
<td>&lt;0.001</td>
<td>2.1 (STMR, barley)</td>
<td>0.002</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Wheat bran</td>
<td>2.45</td>
<td>2.1 (STMR, wheat) 2.2 (HR, wheat)</td>
<td>5.14</td>
<td>5.39</td>
<td>6</td>
</tr>
<tr>
<td>Wheat white flour</td>
<td>0.25</td>
<td>2.1 (STMR, wheat) 2.2 (HR, wheat)</td>
<td>0.525</td>
<td>0.55</td>
<td>-</td>
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<tr>
<td>Wheat germ</td>
<td>1.9</td>
<td>2.1 (STMR, wheat) 2.2 (HR, wheat)</td>
<td>3.99</td>
<td>4.18</td>
<td>5</td>
</tr>
<tr>
<td>Wheat wholemeal</td>
<td>1</td>
<td>2.1 (STMR, wheat) 2.2 (HR, wheat)</td>
<td>2.1</td>
<td>2.2</td>
<td>-</td>
</tr>
<tr>
<td>Wheat white bread</td>
<td>0.05</td>
<td>2.1 (STMR, wheat) 2.2 (HR, wheat)</td>
<td>0.105</td>
<td>0.11</td>
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<tr>
<td>Wheat wholemeal bread</td>
<td>0.48</td>
<td>2.1 (STMR, wheat) 2.2 (HR, wheat)</td>
<td>1.01</td>
<td>1.06</td>
<td>-</td>
</tr>
</tbody>
</table>
**Residues in animal commodities**

**Farm animal dietary burden**

The Meeting estimated the dietary burden of chlorpyrifos-methyl in farm animals on the basis of the diets listed in Annex 6 of the 2006 JMPR Report (OECD Feedstuffs Derived from Field Crops), the STMR or highest residue levels estimated at the present Meeting. Dietary burden calculations are provided in Annex 6. Only residue values for grain and fruit pomace, wet were available for use in the calculation of the dietary burden.

<table>
<thead>
<tr>
<th>Animal dietary burden for chlorpyrifos-methyl, ppm of dry matter diet</th>
<th>US-Canada</th>
<th>EU</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beef cattle</strong></td>
<td>max</td>
<td>3.95</td>
<td>3.59</td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td>3.77</td>
<td>3.42</td>
</tr>
<tr>
<td><strong>Dairy cattle</strong></td>
<td>max</td>
<td>3.69&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.95</td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td>3.52&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.85</td>
</tr>
<tr>
<td><strong>Swine breed</strong></td>
<td>max</td>
<td>5.04&lt;sup&gt;e&lt;/sup&gt;</td>
<td>4.31&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td>4.8</td>
<td>4.11&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Swine finish</strong></td>
<td>max</td>
<td>4.31</td>
<td>4.31</td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td>4.11</td>
<td>4.11</td>
</tr>
<tr>
<td><strong>Poultry broiler</strong></td>
<td>max</td>
<td>4.31&lt;sup&gt;e&lt;/sup&gt;</td>
<td>2.98</td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td>4.11&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.84</td>
</tr>
<tr>
<td><strong>Poultry layer</strong></td>
<td>max</td>
<td>3.68&lt;sup&gt;g&lt;/sup&gt;</td>
<td>1.97</td>
</tr>
<tr>
<td></td>
<td>mean</td>
<td>3.52&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.88</td>
</tr>
</tbody>
</table>

<sup>a</sup> Highest maximum cattle or swine dietary burden suitable for maximum residue level estimates for mammalian meat

<sup>b</sup> Highest mean cattle or swine dietary burden suitable for STMR estimates for mammalian meat.

<sup>c</sup> Highest maximum dairy cattle dietary burden suitable for MRL estimates for mammalian milk.

<sup>d</sup> Highest mean dairy cattle dietary burden suitable for STMR estimates for milk.

<sup>e</sup> Highest maximum poultry dietary burden suitable for MRL estimates for poultry meat and eggs.

<sup>f</sup> Highest mean poultry dietary burden suitable for STMR estimates for poultry meat and eggs.

<sup>g</sup> Highest maximum poultry dietary burden suitable for MRL estimates for eggs.

<sup>h</sup> Highest mean poultry dietary burden suitable for STMR estimates for eggs.

The chlorpyrifos-methyl dietary burdens for animal commodity MRL estimation (residue levels in animal feeds expressed on dry weight) reached a maximum of 5 ppm for swine and of 3.68 ppm for poultry. The chlorpyrifos-methyl dietary burdens for animal commodity STMR estimation (residue levels in animal feeds expressed on a dry weight basis) reached a maximum of 4.11 ppm for swine and of 3.52 ppm for poultry.

**Animal feeding studies**

In one feeding study conducted in dairy cows, the animals were fed 0, 1, 3, 10, 30, and 100 ppm chlorpyrifos-methyl in the diet starting at the lowest level and increasing the dosage every two weeks. The highest feeding level was followed by a two week period where no chlorpyrifos-methyl was added to the feed. In milk, chlorpyrifos-methyl was not detected 13 days after 3 and 10 ppm dosing but was detected at the LOQ level 9–11 days after dosing at 30 ppm. In milk cream, the levels detected at 30 ppm were 0.08–0.09 mg/kg. Cream samples from the 3 or 10 ppm dose levels were not analysed.

In another study, calves were fed rations containing 1, 3, 10, 30 and 100 ppm chlorpyrifos-methyl for 28 days. Residues of chlorpyrifos-methyl in fat samples were 0.01 mg/kg at 3 ppm,
0.03 mg/kg at 10 ppm and 0.09 mg/kg at 30 ppm. Muscle, liver and kidney samples were only analysed from the 30 or 100 ppm feeding level, and were not detected (< 0.01 mg/kg).

In a study on swine, animals were fed rations containing 1 to 100 ppm of chlorpyrifos-methyl for 28 days. In muscle, residues were only found above the LOQ (0.01 mg/kg) at the 30 ppm level or 100 ppm (0.03 and 0.14 mg/kg). No residues were found at any feeding level in liver or kidney. In fat, residues increased proportionally with the feeding level (mean/high levels at 3 ppm: 0.02/0.03 mg/kg; 10 mg/kg: 0.07/0.11 mg/kg).

In one study conducted with laying poultry, the birds were fed rations containing 1, 3, 10, 30 and 100 ppm chlorpyrifos-methyl for 28 days. No residues of chlorpyrifos-methyl were detected (< 0.01) in muscle, fat and eggs at or below the feeding level of 10 mg/kg. At 30 ppm, residues were detected only in fat at the LOQ and at 100 ppm in fat (0.15 mg/kg) and eggs (0.02 mg/kg).

Animal commodity maximum residue levels

<table>
<thead>
<tr>
<th>Dietary burden (mg/kg)</th>
<th>Chlorpyrifos-methyl residues, mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Milk</td>
</tr>
<tr>
<td>nrl cattle beef,</td>
<td>(4.2)</td>
</tr>
<tr>
<td>highest residue</td>
<td>[1; 3; 10; 30]</td>
</tr>
<tr>
<td>STMR cattle beef,</td>
<td>(3.8)</td>
</tr>
<tr>
<td>mean residue</td>
<td>[1; 3; 10; 30]</td>
</tr>
<tr>
<td>nrl milk, mean</td>
<td>(3.7)</td>
</tr>
<tr>
<td>residue</td>
<td>[3; 10; 30]</td>
</tr>
<tr>
<td>STMR milk, mean</td>
<td>(3.5)</td>
</tr>
<tr>
<td>residue</td>
<td>[3; 10; 30]</td>
</tr>
</tbody>
</table>

Feeding study and the dietary burden calculations for cattle were the basis for the estimations in milk. Based on the residues on milk cream (0.009 and 0.008 mg/kg) and the default assumption that milk cream is 50% fat, the Meeting recommends a maximum residue level of 0.02 mg/kg and a STMR of 0.016 mg/kg for chlorpyrifos-methyl in milk fats. The Meeting estimated a maximum...
residue level of 0.01(\textasteriskcentered) mg/kg in milks; assuming milk to contain 4\% fat, the Meeting estimated a STMR of 0.0006 mg/kg for chlorpyrifos-methyl in milks (4\% of milk fat STMR of 0.016 mg/kg).

Based on the feeding studies and the dietary burden calculations for swine, the Meeting recommends a maximum residue level of 0.01(\textasteriskcentered) mg/kg, a STMR and a HR of 0 mg/kg for chlorpyrifos-methyl in edible offal (mammalian); a maximum residue level of 0.1 mg/kg (fat) for meat (from mammalian other than marine mammals); a STMR of 0.03 mg/kg and HR of 0.055 mg/kg in the fat portion of the meat and a STMR and HR of 0 in the muscle portion of the meat.

Based on the feeding study and the dietary burden calculation for chickens, the Meeting estimates a maximum residue level of 0.01(\textasteriskcentered) mg/kg and a STMR and HR of 0 mg/kg for chlorpyrifos-methyl in eggs and poultry edible offal; a maximum residue level of 0.01 mg/kg in poultry meat (fat), a STMR and HR of 0.004 mg/kg in the fat portion of the poultry meat and a STMR and HR of 0 in the muscle portion of the poultry meat.

The Meeting withdraws its previous recommendations for chlorpyrifos-methyl in cattle fat, cattle meat, cattle edible offal, chicken fat, chicken meat, chicken edible offal, milks and eggs.

**DIETARY RISK ASSESSMENT**

**Long-term intake**

The ADI for chlorpyrifos-methyl is 0–0.01 mg/kg bw. The International Estimated Daily Intakes (IEDI) for chlorpyrifos-methyl was estimated for the 13 GEMS/Food Consumption Cluster Diets using the STMR or STMR-P values estimated by the current Meeting. The results are shown in Annex 3. The IEDI ranged from 20 to 140\% of the ADI. The information provided to the JMPR precludes an estimate that the long-term intake of residues of chlorpyrifos-methyl would be below the ADI.

The IEDI exceeded the maximum ADI for the Cluster diets C (110\% ADI) and H (140\% ADI), with 42.7 and 72.8\% of the total intake, respectively, coming from the consumption of maize. The estimation of a STMR made by the Meeting considered the alternative GAP approach. However, in the absence of suitable information this could not be done. To refine the long-term intake estimates information on expected residues in maize processed commodities, such as maize flour and cooked maize would need to be assessed. The ADI for chlorpyrifos-methyl was established by the present Meeting on the basis of a NOAEL of 1 mg/kg bw/d from a 2-year study in rats and a safety factor of 100. However, two other studies had LOAELs of 3 mg/kg bw/d, suggesting it is unlikely that the ADI itself could be refined.

**Short-term intake**

The ARfD for chlorpyrifos-methyl is 0.1 mg/kg bw. The International Estimated Short Term Intake (IESTI) for chlorpyrifos-methyl was calculated for the plant and animal commodities for which STMR(P)s and HR(P)s were estimated and for which consumption data were available. The results are shown in Annex 4. The IESTI ranged from 0 to 30\% of the ARfD for the general population and from 0 to 40\% for children. The Meeting concluded that the short-term intake of residues from the uses of chlorpyrifos-methyl considered by the Meeting is unlikely to present a public health concern.