The pharmacokinetics and placentental transfer of a single dermal 10.0 mg (10μCi/kg dose of uniformly phenyl-labeled [14C] methyl parathion (0,0-diethyl 0-4-nitrophenyl phosphorothioate) were investigated in pregnant Sprague-Dawley rats at 14–18 days of gestation. Three rats were killed at each time interval: 1, 2, 4, 12, 24, 48, 72, and 96 h after dosing. Radioactivity disappeared biexponentially from the administration sites, which retained 50% and 3% of the dose after 1 h and 96 h, respectively. Most of the absorbed radioactivity was excreted in the urine (91%). Only 3% of the 14C was recovered in the feces. One h after the administration, radioactivity was detected in all tissues, including fetal tissue. The peak maternal plasma concentration of radioactivity (ng methyl parathion equivalent/ml) was 1005 at 2 h, compared to 318 ng for fetal plasma at 12 h. The maximum concentrations of radioactivity (ng methyl parathion equivalent/g), detected in most tissues within 12 h of dosing, were, in descending order: adipose tissue (67,532), kidney (1571), spleen (1256), spinal cord (1004), heart (729), liver (706), brain (546), placenta (389), and fetus (256). The metabolism studies showed that methyl parathion, detected by HPLC, was the major compound identified in plasma and tissues. The maximum concentration detected was in plasma, at 513 ng/ml, and in the following tissues (ng/g fresh tissue): kidney (819), fetus (668), placenta (394), liver (375), and brain (282). The metabolite methyl paraaxon was detected in material brain and liver at maximum concentrations (ng/g fresh tissue) of 135 and 64 after 12 h and 4 h respectively, while p-nitrophenol was only detected in liver at a maximum concentration of 21 ng/g 72 h after dosing. Pharmacokinetic studies showed that methyl parathion disappeared monoeXponentially from plasma and tissues. The half-life of elimination of methyl parathion from plasma was 11 h corresponding to a constant rate value of 0.06 h−1. The results indicate that skin and placenta are poor barriers against methyl parathion permeability, resulting in a rapid and extensive dermal absorption of this insecticide and extensive placentental transfer. This is indicated by the relative residence (Rd) of methyl parathion in the plasma, which was largest in the placenta followed by the fetus. This study suggests that pregnant women and fetuses may be at risk of cholinergic toxicity following dermal exposure to methyl parathion.

Key Words: Methyl parathion; acetylcholinesterase inhibition; organophosphorus insecticide; metabolic activation; cytochrome P450.

Methyl parathion (0,0-diethyl 0-4-nitrophenyl phosphorothioate) is a highly toxic organophosphorus insecticide that is safely used on agricultural crops, particularly cotton, because it degrades and dissipates quickly in the environment (WHO, 1993). Although it is approved only for agricultural crops, it has been used illegally in other areas because it is cheap and effective in controlling insects. In November 1994, an episode of indoor methyl parathion use was reported in Lorain, Ohio (ATSDR, 1997). Since then, home pesticide applicators and residents have sprayed methyl parathion in hundreds of houses in Alabama, Arkansas, Illinois, Louisiana, Michigan, Mississippi, Tennessee, and Texas. Methyl parathion exerts its insecticidal toxicity by inhibiting acetylcholinesterase in the central and peripheral nervous systems (Abou-Donia, 1994). Some residents, including children in these homes, exhibited signs of cholinergic stimulation such as sweating, dizziness, vomiting, diarrhea, convulsions, cardiac arrest, respiratory arrest, and even death; some pets also died (ATSDR, 1997).

There are several data gaps regarding the risk assessment for methyl parathion in such areas, as to its pharmacokinetics and pharmacodynamics during pregnancy. The pharmacokinetic profile of organophosphorus insecticides is affected by factors such as route of administration (Carver and Riviere, 1989) and animal species (Qiao et al., 1994). These insecticides are lipid-soluble and are capable of penetrating biological membranes, including the skin (Baynes and Bowen, 1995; Carver and Riviere, 1989; Draper and Street, 1981; Nolan et al., 1984; Wester et al., 1993) and the placenta, and into the fetus (Salama et al., 1992 a,b; Villeneuve et al., 1972). Physiological and biochemical changes associated with pregnancy may result in alterations in the pharmacokinetics of methyl parathion, with subsequent modifications of its pharmacodynamics and toxicity. During pregnancy, there is a reduction of several metabolism enzymes and xenobiotic-binding proteins that may influence the toxicity of methyl parathion. This insecticide undergoes metabolic activation and detoxification by: (a) hepatic and extrahepatic miosomal cytochrome P450 (Chambers...
et al., 1991; Hollingworth et al., 1967; Nielsen et al., 1991; Norman and Neal, 1976; Sultatos, 1987), (b) esterases (Aldridge, 1953), and (c) glutathione S-transferase (Hollingworth et al., 1973). Pregnancy-induced suppression of these enzymes may change methyl parathion metabolism and disposition, resulting in its increased concentration in circulation and enhanced delivery to the maternal brain and the fetus. These events result in greater acetylcholinesterase inhibition and elevated cholinergic stimulation in both the mother and the fetus.

We report the results of an investigation into the pharmaco-kinetics, metabolism, and placental transfer of a single dermal 10.0 mg/kg (0.15 \( \times \) LD\(_{50}\)) of \(^{14}C\)methyl parathion in pregnant Sprague-Dawley rats. Dermal application was used because it is a major route of entry for the test compound in residences, following indoor application.

**MATERIALS AND METHODS**

**Chemicals.** Uniformly phenyl-labeled \(^{14}C\)methyl parathion (0.0-dimethyl 0–4-nitrophenyl phosphorothioate), specific activity of 13.8 mCi/mole, and \(p\)-nitrophenol were obtained from Sigma Chemical Co. (St. Louis, MO). Unlabeled methyl parathion and methyl paraxon (0.0-dimethyl 0–4-nitroph- enyl phosphate) were obtained from Chem. Service Co. (West Chester, PA). The scintillation cocktail Permaflour-V and the Carbosorb II were purchased from Packard Instrument Co. All solvents used for HPLC analysis were HPLC grade.

**Experimental animals.** Pregnant Sprague-Dawley rats (240–350 g), at 14–18 days of gestation, were purchased from Charles River Laboratories (Raleigh, NC). The animals were kept in a 12-h light/dark cycle (temperature 21–23°C) and were provided with a free supply of feed (Rodent Laboratory Chow, Ralston Company, St. Louis, MO), as well as tap water. The animals were kept in plastic metabolism cages that allowed the separation of urine and feces.

**Treatment of animals.** Radiolabeled and unlabeled methyl parathion were dissolved in acetone to obtain the desired specific radioactivity. A single dose of 10 mg (10 \( \mu \)Ci)/kg in 0.1 ml acetone was applied with a micropipette to an unprotected 1 cm\(^2\) area of pre-clipped skin on the back of each animal’s neck. The acetone was rapidly evaporated by gentle blowing. The dosage chosen was 15% of the dermal LD\(_{50}\), so that it would not produce maternal or fetal toxicity. Eight groups of 3 rats each were killed at time intervals of 1, 2, 4, 12, 24, 48, 72, and 96 h.

**Animal handling.** After methyl parathion application, each rat was placed individually in a metabolism cage, and urine and feces were collected daily. At each time interval, the rats were anesthetized with an ip injection of sodium pentobarbital (50 mg/kg) and killed by heart exsanguination. Blood was collected via heart puncture with a heparinized syringe and centrifuged at 200 rpm for 15 min at 5°C to separate red blood cells from plasma. Selected tissues (Table 1) were excised rapidly and stored at −70°C until analysis.

**Assay of radioactivity.** Duplicate samples (50–200\(g\)) from fresh tissues were combusted in a Packard tri-carb model 306B sample oxidizer, using 10 ml of the trapping solution Carborosorb and 12 ml scintillation cocktail Permaflour V (Packard Instrument Co., Downers Grove, IL). Plasma and urine were combusted after being pipetted (0.1 ml aliquots) in duplicate onto absorbent combustion caps held in combustion cones. A Beckman LS 6500 Multi-purpose liquid scintillation spectrometer (Beckman Instruments Corporation, Palo Alto, CA) was used to assay \(^{14}C\) radioactivity at 5°C. Counts were corrected for dilution, quenching, background, and counting efficiency. Counting efficiencies were determined to be above 70%.

**Extraction of methyl parathion and metabolite.** Tissue samples (500 mg), plasma (0.1 ml), and urine (1 ml) were homogenized in 6 ml of a 1:1 mixture of \(n\)-hexane and ethyl acetate containing 1 ml of 0.1% phosphoric acid. Homogenates were centrifuged at 2500 rpm for 10 min and the organic layers were separated. The aqueous layer and precipitated protein were re-extracted with one additional volume of the solvent, and the organic layer was added to the original extract. The combined solvent extracts were concentrated by a gentle blowing of nitrogen. The residue was dissolved in 0.5 ml of \(n\)-hexane prior to HPLC analysis.

**High performance liquid chromatography (HPLC).** The HPLC system used for analysis of methyl parathion and metabolites consisted of a Model 660 solvent programmer equipped with two Model 600A pumps, a Beckman 165 variable wavelength detector, a V-6k injector, and an RCM-100 radial compression separation system with C\(_8\) cartridge (Waters Associates, Inc., Milford, MA), a guard column filled with C\(_{18}\) \( \mu \) Bondapack, and a Millipore Waters 740 Data Module. Millipore membrane filters, type HA or HF, pore size 0.45 mm (Millipore, Bedford, MA), were used to filter the solvents. Tissue and plasma extracts were injected in 10-\(\mu\)l volumes and eluted from the column by gradient elution. We used initial solvent (A) consisting of 38%

**TABLE 1**

Concentration of Radioactivity (ng equivalent/g) in the Tissues of Pregnant Sprague-Dawley Rats following a Single Dermal Dose of 10 Mg/kg of \(^{14}C\)Methyl Parathion

<table>
<thead>
<tr>
<th>Tissue</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>12</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>222 ± 38</td>
<td>1005 ± 104</td>
<td>412 ± 23</td>
<td>439 ± 19</td>
<td>278 ± 57</td>
<td>49 ± 9.2</td>
<td>2 ± 0.6</td>
<td>1.0 ± 0.1</td>
</tr>
<tr>
<td>Liver</td>
<td>225 ± 39</td>
<td>489 ± 126</td>
<td>706 ± 85</td>
<td>703 ± 291</td>
<td>469 ± 228</td>
<td>174 ± 153</td>
<td>52 ± 0.4</td>
<td>118 ± 23</td>
</tr>
<tr>
<td>Kidney</td>
<td>287 ± 185</td>
<td>1349 ± 334</td>
<td>1238 ± 244</td>
<td>1571 ± 391</td>
<td>574 ± 182</td>
<td>228 ± 181</td>
<td>125 ± 106</td>
<td>ND(^4)</td>
</tr>
<tr>
<td>Heart</td>
<td>150 ± 54</td>
<td>371 ± 42</td>
<td>729 ± 12</td>
<td>418 ± 194</td>
<td>210 ± 82</td>
<td>88 ± 47</td>
<td>37 ± 25</td>
<td>ND</td>
</tr>
<tr>
<td>Brain</td>
<td>153 ± 48</td>
<td>261 ± 82</td>
<td>299 ± 97</td>
<td>546 ± 239</td>
<td>74 ± 16</td>
<td>58 ± 50</td>
<td>56 ± 12</td>
<td>14 ± 7.4</td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>1444 ± 6447</td>
<td>18334 ± 7526</td>
<td>22405 ± 7600</td>
<td>67532 ± 22697</td>
<td>34436 ± 2163</td>
<td>6479 ± 2943</td>
<td>2108 ± 443</td>
<td>10350 ± 2547</td>
</tr>
<tr>
<td>Fetus</td>
<td>65 ± 41</td>
<td>180 ± 141</td>
<td>256 ± 72</td>
<td>137 ± 92</td>
<td>136 ± 39</td>
<td>69 ± 25</td>
<td>33 ± 25</td>
<td>34 ± 25</td>
</tr>
<tr>
<td>Fetal Plasma</td>
<td>ND</td>
<td>104 ± 25</td>
<td>213 ± 113</td>
<td>318 ± 241</td>
<td>181 ± 123</td>
<td>37 ± 22</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Placenta</td>
<td>81 ± 26</td>
<td>316 ± 139</td>
<td>389 ± 39</td>
<td>219 ± 86</td>
<td>339 ± 44</td>
<td>83 ± 76</td>
<td>28 ± 25</td>
<td>47 ± 14</td>
</tr>
<tr>
<td>Spleen</td>
<td>136 ± 54</td>
<td>493 ± 118</td>
<td>1256 ± 169</td>
<td>470 ± 269</td>
<td>142 ± 40</td>
<td>129 ± 31</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>110 ± 22</td>
<td>318 ± 49</td>
<td>1004 ± 229</td>
<td>329 ± 21</td>
<td>245 ± 63</td>
<td>355 ± 78</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

Note. Results are expressed as mean ± SD of 6 samples from 3 animals (2 samples/animal). ND, not detectable.
water that contained 1 ml of 1% phosphoric acid and 62% methanol for 8 min, followed by solvent (B) consisting of 65% water that contained 1ml of 1% phosphoric acid and35% methanol for 15 min at a flow rate of 2 ml/min. The UV absorbance of the column elutes was monitored at 280 nm to detect and quantify methyl parathion and metabolites. A standard curve was obtained by injecting known amounts of each chemical and measuring the peak area. The retention time, peak areas, and percentage of each peak in the chromatogram were measured by the data processor.

**Kinetic analysis.** The kinetic analysis of methyl parathion and metabolites in plasma and tissues were performed using a kalideograph for Macintosh program (Abou-Donia et al., 1983, 1995). The terminal half-life of methyl parathion and metabolites was calculated from the elimination rate constant, \( \beta \), that was obtained by linear regression of the terminal linear exponential decline in concentration, using the expression:

\[
\text{t}_{1/2} = \frac{0.693}{\beta}
\]

The total area under the compound concentration vs. time curves for plasma, AUC \(_{\text{plasma}}\), and tissues, AUC \(_{\text{organ}}\), was calculated by the trapezoidal rule and extrapolated to infinity by using the last data point and the respective terminal linear experimental decline. The relative residence (\( R_R \)) of methyl parathion in specific tissues with respect to plasma was calculated according to the equation:

\[
R_R = \frac{\text{AUC}_{\text{organ}}}{\text{AUC}_{\text{plasma}}}
\]

where the AUC’s are as defined above. Thus, the \( R_R \) values reflect the relative accumulation of methyl parathion in specific organs or the relative exposure of individual organs to methyl parathion. The use of \( R_R \) avoids the time-dependent changes in concentration ratios for various compounds with time.

**RESULTS**

**Clinical and Necropsy Observations**

A single topical application of 10 mg/kg, 15% of the dermal acute LD\( _{50} \) dose, did not cause cholinergic toxicity. Both control and treated animals consumed comparable amounts of feed and water. There were no differences in the weight, size, shape, or color of various tissues of treated animals compared with tissues of the control rats.

**Recovery of Radioactivity**

At the end of the 96-h experiment, the total radioactivity recovered from excreta, tissues, and application site was 98% of the applied dose. Radioactivity disappeared rapidly from the application site. The \( ^{14} \)C content of the application site decreased biexponentially with time to 50% and 3% of the applied dose at one and 96 h, respectively. The apparent overall skin disappearance rate constants were 0.35 h\(^{-1}\) and 0.03 h\(^{-1}\) corresponding to half-lives of 2 h and 22 h, for the initial and terminal phase, respectively.

**Radioactivity in Excreta**

Radioactivity was rapidly excreted in urine. One h after application, 14% of the \( ^{14} \)C was recovered in the urine. Urinary content of \( ^{14} \)C reached a peak of 30% at 4 h. By the end of the 96-h experiment, a total of 91% of the applied dose was excreted in the urine. In contrast, only 3% of the administered dose was detected in the feces.

**Tissue Distribution**

Table 1 shows the concentration of radioactivity in plasma and various tissues at different time intervals after a single application of \([^{14} \)C]methyl parathion to pregnant rats. Radioactivity was extensively distributed in all tissues. The highest concentration of \( ^{14} \)C was found in adipose tissue, followed by the kidney and liver. The nervous tissues from brain and spinal cord contained considerable concentrations of radioactivity, followed by the placenta and fetus.

**Tissue Metabolism of Methyl Parathion**

Qualitative and quantitative analyses of methyl parathion and metabolites were carried out using HPLC in plasma and tissues (Fig. 1). Methyl parathion was detected in all samples and accounted for most of the radioactivity throughout the experiment period (Table 2). The maximum methyl parathion concentration in tissues exceeded those of plasma 4–96 h after dosing, suggesting that analyzed tissues have greater affinity for methyl parathion than to plasma components. The kidney and liver contained the highest concentrations of methyl parathion after one and two h of dosing. The fetus had the highest concentration 4 and 12 h after the administration. Methyl paraoxon was detected in the liver and brain (Table 3), while \( p \)-nitrophenol was found only in the liver.

**Pharmacokinetics of Methyl Parathion and Metabolites**

Methyl parathion disappeared monoexponentially, both from plasma (Fig. 2) and from all tissues (Table 4). Liver had the longest half-life value (19.25 h), followed by placenta and
brain values. The half-life of methyl parathion in the fetus was 10.8 h. A striking result is the finding that placenta and fetus had the largest AUC values (15.8 and 12.9 μg/ml h, respectively) as well as the largest relative residence (RR) of methyl parathion of 2.35 and 1.92, respectively. The half-life values for methyl paraoxon and p-nitrophenol in liver were 27.7 and 53.3 h, respectively.

**DISCUSSION**

This study of pharmacokinetics, metabolism, and placental transfer of a topical dose of methyl parathion shows that the skin is an important port of entry for this insecticide, with subsequent placental transfer into the fetus. In the present study, no acute cholinergic toxicity was seen in treated animals. This result was expected, since the dose used (10 mg/kg) was 15% of the acute dermal LD50 dose of methyl parathion.

Dermal application was carried out with unprotected skin. In this study, we attempted to approximate conditions of human exposure where the skin is usually naked or covered with loosely fitted clothing. Furthermore, the use of acclusive dressing results in the reversible hydration of the skin and leads to increased rates of absorption of many compounds, exaggerating the toxic effect caused by skin contact (Wurster and Kramer, 1961). Although the animals were housed individually, the possibility that some oral absorption might have occurred through grooming cannot be discounted. Sartorelli et al (1997) demonstrated the in vitro percutaneous penetration of methyl parathion through the human skin. Similar results were obtained in experimental animals for dermal application of other organophosphorus insecticides such as leptophos (O-methyl O-4-bromo-2,5-dichlorophenyl phenylphosphonothioate; Abou-Donia, 1979) and EPN (O-ethyl O-4-nitrophenyl phenylphosphonothioate; Abou-Donia et al., 1983). Also, Knaak et al (1984) reported that 59% and 57% of dermally applied dose of parathion were absorbed through the skin of adult male and female rats, respectively. In the present study, methyl parathion was applied in 0.1-ml acetone. Since this solvent was rapidly evaporated by a gentle blowing, it is unlikely that it had a significant impact on the dermal absorption of the test compound. Although the rat is not a particularly good model of trans-dermal pharmacokinetics, it was used because a major aim of the study was the placental transfer that is usually investigated in pregnant rats.

The high solubility of methyl parathion in lipid solvents may explain its rapid absorption through the skin, considered to be by diffusion (Chang and Riviere, 1991; Scheuplein and Blank, 1971). This suggestion is consistent with the finding that 91% of the dermally applied dose was excreted in the urine. It is also

<table>
<thead>
<tr>
<th>Tissue</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>12</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>41.26</td>
<td>513.25</td>
<td>210.62</td>
<td>232.10</td>
<td>126.91</td>
<td>23.63</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Liver</td>
<td>32.13</td>
<td>289.60</td>
<td>374.97</td>
<td>355.68</td>
<td>135.81</td>
<td>86.45</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Kidney</td>
<td>175.16</td>
<td>818.64</td>
<td>208.20</td>
<td>230.55</td>
<td>166.24</td>
<td>51.86</td>
<td>12.34</td>
<td>2.74</td>
</tr>
<tr>
<td>Brain</td>
<td>37.71</td>
<td>208.18</td>
<td>281.79</td>
<td>211.05</td>
<td>94.61</td>
<td>32.23</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Fetus</td>
<td>66.74</td>
<td>141.71</td>
<td>562.04</td>
<td>667.71</td>
<td>129.28</td>
<td>25.32</td>
<td>22.50</td>
<td>ND</td>
</tr>
<tr>
<td>Placenta</td>
<td>162.64</td>
<td>207.24</td>
<td>365.46</td>
<td>394.37</td>
<td>327.19</td>
<td>134.61</td>
<td>46.32</td>
<td>ND</td>
</tr>
</tbody>
</table>

**Note.** Concentration is expressed as a mean of six samples from three animals (2 samples/animal). ND, not detectable. SD for all values was less than 10% of the value.

### TABLE 3

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Metabolite</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>12</th>
<th>24</th>
<th>48</th>
<th>72</th>
<th>96</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Methyl paraoxon</td>
<td>ND</td>
<td>ND</td>
<td>64.23</td>
<td>23.79</td>
<td>15.81</td>
<td>10.47</td>
<td>6.31</td>
<td>ND</td>
</tr>
<tr>
<td>Liver</td>
<td>p-Nitro phenol</td>
<td>ND</td>
<td>ND</td>
<td>15.02</td>
<td>16.59</td>
<td>18.41</td>
<td>20.64</td>
<td>21.29</td>
<td>13.24</td>
</tr>
<tr>
<td>Brain</td>
<td>Methyl paraoxon</td>
<td>ND</td>
<td>92.69</td>
<td>112.32</td>
<td>134.98</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

**Note.** Concentration is expressed as a mean of 6 determinations from 3 animals (2 samples/animal). ND, not detectable.
in agreement with the present finding that adipose tissue contained the highest concentration of radioactivity. Methyl parathion stored in adipose tissue may be released slowly into circulation, where it can be delivered to the nervous system and result in toxicity. Similar results were reported following oral administration of methyl parathion in rats (Garcia-Repetto et al., 1997).

The kidney plays an important role in the excretion of methyl parathion and its metabolites as indicated by its high content of radioactivity. Nonionic absorption and passive re-absorption of methyl parathion in the renal tubule (Milne et al., 1958) are probably enhanced by the chemical’s high lipid solubility. Similar results were reported for the ethyl analogue, parathion; a total of 85% of orally administered parathion to rats was recovered in urine, while more than 90% of the administered dose to pigs was detected in the urine (Nielsen et al., 1991).

Methyl parathion analyzed by HPLC distributed rapidly in all tissues, with adipose tissue, liver, and kidney having the highest concentrations (Sultatos et al., 1990). Similar results were obtained with parathion following both intravenous injection (iv) and oral administration in dogs (De Schryver et al., 1987), and after an iv injection in rabbits (Eigenberg et al., 1983), and in pigs (Nielsen et al., 1991). In this study, methyl parathion disappeared from the plasma, like that from other tissues, monoexponentially with a half-life of 11 h, similar to that of the fetus and kidney. Other tissues had longer half-life values with liver having the longest at 19.3 h, followed by placenta (16.5 h), and brain (13.6 h). The elimination half-life in dogs was 7.2 h for an iv injection of methyl parathion (Brackman et al., 1983) and 9.7 min for an ip injection of methyl paraoxon (De Schryver et al., 1987). In the present study, methyl parathion and metabolites were analyzed in the extracts of total fetal homogenates. It is realized, however, that methyl parathion concentrations in individual fetal tissues such as the brain may vary from the total compartment, but these data were not available.

Methyl parathion undergoes metabolic biotransformation by hepatic and extrahepatic phase I and phase II metabolism.

### TABLE 4
**Pharmacokinetic Parameters of Methyl Parathion and Its Metabolites in Plasma and Tissues of Pregnant Sprague-Dawley Rats following a Single Dermal Dose of 10 Mg/kg of [14C]methyl Parathion**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Compound</th>
<th>Half-life elimination rate (h)</th>
<th>Constant (h⁻¹)</th>
<th>AUC (ng/mlh)</th>
<th>Relative residence (Rₑ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>Methyl parathion</td>
<td>11.00</td>
<td>0.06</td>
<td>6732.54</td>
<td>1.00</td>
</tr>
<tr>
<td>Liver</td>
<td>Methyl parathion</td>
<td>19.25</td>
<td>0.04</td>
<td>9364.09</td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>Methyl paraoxon</td>
<td>27.72</td>
<td>0.03</td>
<td>1106.40</td>
<td>1.39</td>
</tr>
<tr>
<td></td>
<td>p-Nitrophenol</td>
<td>53.30</td>
<td>0.01</td>
<td>1763.71</td>
<td>1.39</td>
</tr>
<tr>
<td>Kidney</td>
<td>Methyl parathion</td>
<td>9.90</td>
<td>0.07</td>
<td>9228.04</td>
<td>1.37</td>
</tr>
<tr>
<td>Brain</td>
<td>Methyl parathion</td>
<td>13.59</td>
<td>0.05</td>
<td>5940.31</td>
<td>0.88</td>
</tr>
<tr>
<td>Placenta</td>
<td>Methyl parathion</td>
<td>16.50</td>
<td>0.04</td>
<td>15839.08</td>
<td>2.35</td>
</tr>
<tr>
<td>Fetus</td>
<td>Methyl parathion</td>
<td>10.82</td>
<td>0.06</td>
<td>12937.96</td>
<td>1.92</td>
</tr>
</tbody>
</table>

*Note.* All parameters are defined in Materials and Methods section.
Phase I reactions include methyl parathion desulfuration by cytochrome P450 (Norman and Neal, 1976; Norman et al., 1973; Sultatos and Murphy, 1983). Butler and Murray (1997) have recently shown the major involvement of CYP3A4 isozyme in the desulfuration of parathion. This reaction results in the formation of methyl paraoxon, the only active metabolite that is a more potent compound (Yamamoto et al., 1983; Zhang and Sultatos, 1991). Cytochrome P450 also catalyzes de-arylation of methyl parathion to $p$-nitrophenol and dimethyl phosphorothioic acid (Neal, 1967). The third phase I reaction is the hydrolysis of paraoxon by liver and plasma paraoxanase (Tyndall and Daniel, 1975). Phase II reactions include: (a) conjugation of methyl parathion with glutathione by glutathione S-aryl transferase to form $p$-nitrophenyl mercapturic acid (Hollingworth et al., 1973; Huang and Sultatos, 1993) and glutathione S-alkyl transferase to yield S-methyl glutathione (Abou-Donia, 1994; Radulovic and Kulkarni, 1987), b) $p$-nitrophenol is further conjugated with glucuronic acid and sulfuric acid (Neale and Parke, 1973).

Figure 3 presents a suggested scheme for the metabolism of a single dermal application of [14C]methyl parathion in pregnant rats. Methyl parathion was detected in all analyzed tissues, while methyl paraoxon was found in the liver and brain and $p$-nitrophenol was detected only in the liver. Methyl paraoxon had a longer half-life in the liver than that of its parent compound. The $R_\text{a}$ values of methyl parathion in various tissues relative to plasma reflect its accumulation and persistence, as well as its relative pool size, in these tissues when compared to plasma. Both kidney and liver had high $R_\text{a}$ values, reflecting their role in elimination of this insecticide. Fetal tissue had a higher $R_\text{a}$ value, while placenta exhibited the highest $R_\text{a}$ value of all tissues, suggesting that this tissue functions as a temporary depot for methyl parathion in the animal’s body. As time passes, methyl parathion is released from this storage tissue, mobilized and transferred into the fetus. The high $R_\text{a}$ values in placental and fetal tissues suggest that the fetus is vulnerable to methyl parathion toxicity following exposure to toxic levels. Similar patterns of disposition in pregnant rats were reported for methamidophos ($O,S$-dimethyl phosphoroamidothioate; Salama et al., 1992a), acephate ($O,S$-dimethyl acetylphosphoroamidothioate; Salama et al., 1992b) and chrolpyrifos ($O,O$-diethyl $O$-3,5,6-trichloro-2-pyridinyl phosphorothioate; Abdel-Rahaman et al., 1993).

This study shows that a single dermal application of methyl parathion in pregnant rats was rapidly absorbed and extensively distributed in tissues. It then crossed the placenta into the fetus and was quickly excreted, mostly as water-soluble metabolites, in the urine. Both methyl parathion and its more toxic metabolite, methyl paraoxon were present in the maternal brain and in the fetus. The results suggest that a pregnant woman and her fetus are both at risk following dermal exposure to methyl parathion (Benke and Murphy, 1975). This is particularly significant since several factors are influenced by pregnancy and may be responsible for the alterations of the pharmacokinetics and toxicity of methyl parathion. These factors include decreases of: (a) hepatic microsomal cytochrome P450 (Feuer, 1979; Weitman et al., 1983), (b) serum cholinesterase activity (Howard et al., 1978; Schneider, 1965); (c) serum paraoxanase (Tyndall and Darrel, 1975); (d) serum albumin (Stock et al., 1980); (e) glucuronyl transferase (Neale and Parke, 1973); (f) sulfate conjugation (Pulkkinen, 1966); and (g) glutathione conjugation (Combes and Stakelum, 1962). The
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depression of both the xenobiotic metabolizing enzymes and the drug-binding proteins that act as scavengers for organophosphorus esters, diminishes the body’s ability to detoxify methyl parathion as well as its active metabolite, methyl paraoxon, during pregnancy. Thus, toxic exposure to methyl parathion during pregnancy may lead to increased levels of the free insecticide and its active metabolite, methyl paraoxon (de Lima et al., 1996) in circulation. This results in a corresponding increase in their concentration in the maternal brain and the fetus, with subsequent increased cholinergic stimulation.

REFERENCES


