An Investigation of Unexplained Infant Deaths in Houses Contaminated with Methyl Parathion

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In Lorain County, Ohio, unexplained infant deaths in homes sprayed with methyl parathion (MP), an organophosphate (OP) pesticide, prompted an investigation to determine whether infants living in treated homes are at higher risk for unexplained death. A case was defined as any death of an infant (≤12 months of age) in Lorain County between 1 January 1990 and 31 December 1994, attributed to sudden infant death syndrome (SIDS) or other unknown natural causes. For each case infant, birth certificate data were used to identify two control infants matched with regard to date of birth, sex, city of residence, and maternal race and educational level. Wipe samples from the home address listed on the birth certificate of control infants or the death certificate of case infants were analyzed for MP. Birth certificates provided additional risk factor information. The relationship between MP contamination and unexplained death was analyzed by exact conditional logistic regression. Wipe samples were collected from the residences of 34 case infants and 72 control infants. MP (>0.02 mg/100 cm²) was detected in five homes, three of which had been occupied by case infants. Case infants were 4.6 times more likely than control infants to have lived in MP-treated homes, but the confidence interval (CI) was wide (95% CI: 0.2, 274.7) and included 1. Maternal smoking, young maternal age, and the presence of other siblings in the family were each independently predictive of case status. In a multivariate model adjusting for these other variables and the matching variables, the estimated risk associated with MP exposure was 13.0 (95% CI: 0.2, 2685.0). Although this association was not statistically significant and should be interpreted cautiously, it suggests an increased risk for unexplained death among infants living in MP-contaminated homes. The relationship between children’s health and exposure to OP pesticides including MP should be evaluated further. Key words: infants, methyl parathion, organophosphate, pesticides, SIDS, sudden infant death syndrome. Environ Health Perspect 110(suppl 6):1053–1056 (2002). http://ehpnet1.niehs.nih.gov/docs/2002/suppl-6/1053-1056wasley/abstract.html

Methyl parathion (MP) is an organophosphate (OP) pesticide that the U.S. Environmental Protection Agency designates as having category 1 toxicity, with a lethal oral dose between 7 drops and 1 teaspoon (5–50 mg/kg) for a 70-kg adult (7). It is usually used only on field crops, particularly on cotton (2). When used outdoors, MP is rapidly degraded by microbes in the environment and to a lesser extent by exposure to sunlight (1,2). However, when used indoors, the chemical remains stable for long periods and consequently is not approved for such use.

MP is readily absorbed via all routes of exposure (oral, dermal, inhalation) and is rapidly distributed to body tissues (2). The known health effects of MP, which acts by inhibiting the enzyme acetylcholinesterase, are typical of those induced by OP pesticides. Acute effects of exposure include headaches, loss of coordination, salivation, nausea, and muscle fasciculations (1–5). The chronic effects of exposure have been less well characterized.

Most reported cases of MP poisoning have occurred in an occupational setting (4–8). However, although MP is not approved for indoor use, several reports have documented OP poisoning in children and adults after in-home use of MP (9,10) or similar compounds (11–13). In Mississippi, 7 of 13 members of a family became seriously ill after their home had been sprayed with MP; one person died (9). In another incident, two children died and four other siblings in the same family were hospitalized when their home was treated with MP (10). Notably, in both incidents, adults living in the same house as the ill children showed no apparent symptoms of pesticide poisoning.

Consequently, when it was discovered in November 1994 that more than 400 homes in Lorain County, Ohio, had been sprayed with MP by an unlicensed exterminator working in the area, there was considerable concern about the potential health consequences for people living in contaminated homes.

An initial investigation was conducted to evaluate exposure levels among residents and to determine what, if any, adverse health effects had been caused by that exposure. In that investigation, both biological and environmental sampling were used to confirm residents’ exposures to MP. In the liver, MP is metabolized and detoxified through a series of hydrolysis, demethylation, and dearylation reactions (1,2,14). p-Nitrophenol (PNP), a product of this series of reactions, is excreted in the urine and can be used as a measure of exposure (15). In Lorain County the median urinary level of PNP among 142 tested residents was 138 ppb (extrapolated dose from biomonitoring), more than 200 times greater than that reported in a National Health and Nutrition Examination Survey (NHANES) reference population (16).

Despite this documented exposure and numerous reports of ill effects among residents, the investigation identified no ongoing excess of acute health effects that could be linked to the exposure (17). However, during the course of that investigation, reports were received of two unexplained infant deaths that had occurred in sprayed homes. Both deaths were classified as due to sudden infant death syndrome (SIDS). One of the infants was only 8 days of age at the time of death; most SIDS deaths occur among infants 2–6 months of age (18). Evidence from previous investigations (19) and from animal studies (20–22) supported the concern that infants may be more susceptible to the effects of some OP pesticides and that, despite the apparent lack of health effects in adults, the health of infants remaining in contaminated homes was in jeopardy.

In response to that concern we conducted a case-control investigation to determine whether infants who died of undetermined causes were more likely to have been exposed to MP in their homes than were similar control infants.

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Materials and Methods

Case identification. Using death certificate data, we defined a case as the death of any infant 12 months of age or less that occurred in Lorain County between 1 January 1990, and 31 December 1994, and was attributed to either SIDS or unknown natural causes. We included cases from 1990 because the applicator was known to have been working in the Lorain area since that time.

Selection of control infants. For each identified case infant, two matched control infants were selected from computerized birth certificate records. Matching was done on the following characteristics: city of residence, maternal level of education, and maternal race. These characteristics were known or suspected to be associated with increased risk of both unexplained infant death and exposure to MP. Matching allowed adjustment for the potentially confounding effect of these characteristics on any association between MP exposure and unexplained infant death. Control infants were also matched to cases on sex and as closely as possible with regard to the date of birth. Starting with the birth certificate of the case infant, the next two infants born that met the other matching criteria were selected as controls.

Assessing exposure to methyl parathion. The MP exposure of case and control infants was estimated from the MP levels of environmental samples collected from the home address listed on the birth certificate of the control infants or the death certificate of the case infants. Although our ability to measure MP exposure directly was limited because biological samples such as tissue or urine were not available for testing, experience in the earlier investigation of known exposure showed that the results obtained from environmental sampling correlated well with those from biological samples. In addition, that investigation also showed that MP was stable indoors and could be detected at least as long as 3 years after being sprayed. Consequently, we believe this method was a justifiable way of estimating exposure.

Because it is hypothesized that the effect of MP is acute, we decided that the relevant site to evaluate for possible exposure among case infants would be the house where they died. Similarly, because the present exposure status of control infants is less relevant to this investigation, qualitative samples taken from these areas were the most predictive of whether a house had been sprayed with MP, and that results correlated well not only with the overall level of household MP contamination but also with results obtained from biologic samples (23). The samples were analyzed by gas chromatography at the Ohio Department of Agriculture for the presence of both MP and PNP.

These environmental swipe results were used to qualitatively classify homes as being contaminated. In contrast to the earlier investigation of homes known to be MP contaminated, in this investigation it was expected that most of the tested homes would be negative for MP. Furthermore, in houses positive for MP, it was not known when the house was sprayed, how the environmental conditions in the house affected the stability of the chemical, and when the infant lived there relative to the timing of the spraying. Consequently, because the relationship between current PNP levels and those that would have been found in the house at the time when the case/control infant lived there was unknown, the value of doing extensive quantitative assessments to estimate the exposure of the infants was limited. For the purposes of this investigation, qualitative assessment of whether MP had been ever used in the home was sufficient to classify the home and its residents as exposed. No correlation between the quantitative level of MP contamination in those sites and the likelihood or magnitude of infant exposure was made.

Information on other known and suspected risk factors for sudden unexplained infant death was obtained from the electronic birth certificate files. This included information about the infant’s sex, birth weight, and gestational age at birth, as well as information about the mother and details of the pregnancy. Informed consent was obtained from residents living in the sampled homes.

Statistical analysis. The relationship between each predictor variable and the occurrence of unexplained infant death was evaluated after adjusting for the matching variables using exact conditional logistic regression (Table 2). In an analysis of the relationship between household contamination with MP and unexplained infant deaths, an odds ratio (OR) of approximately 5 suggested an association but with a confidence interval (CI) that overlapped 1, this relationship was not statistically significant.

Among the other variables tested, several were significantly associated with unexplained infant deaths. The strongest predictor was maternal smoking during pregnancy (OR = 7). Other factors associated with an increased risk were young maternal age (<25 years), low birth weight (<2,500 g), and early gestational age of the infant, as well as the occurrence of complications during labor. In addition, infants whose mothers reported 10 or fewer prenatal medical visits were more

Results

Of 39 decedents that met the case definition (Table 1), 23 (59%) were male, 32 (82%) were white, and 7 (18%) were black. In comparison, the overall population composition of Lorain County is 89% white, 8% black, and 3% other. The geographic distribution of the cases roughly reflects the population distribution of the county, with 15 (39%) of cases occurring in the city of Lorain, 12 (31%) in Elyria, and 12 (31%) in other towns in the county. The mean age of these infants at the time of death was just under 3 months and ranged from 8 days to 6 months.

The homes of 34 of these decedents were evaluated for MP. Of these, 3 (8.8%) had detectable (>0.02 mg/100 cm²) levels of the pesticide, whereas evidence of MP was found in only 2 (2.7%) of the 73 control homes tested. It was not possible to collect samples from the homes of 5 of the case subjects because the residents either were not at home at the time of investigators’ visits or refused to permit access to their house.

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likely to die of undetermined cause than were infants of mothers who reported more visits. Finally, the presence of other siblings in the family was also associated with an infant’s increased risk of dying of undetermined causes. The following factors were not found to be associated with unexplained infant death: Aggar score (a scoring method with a range of 0–10 for describing the physical condition of a newborn infant shortly after delivery), medical risk factors associated with the pregnancy, and maternal use of alcohol during pregnancy.

Taking the subset of variables associated with unexplained infant death in single-variable models, we used stepwise conditional logistic regression to construct a multivariate model appropriate for matched data (Table 3). We included MP exposure in the model to evaluate whether the estimate of association would be affected by adjusting for the potentially confounding effects of other variables. In addition to the term for MP exposure, the final model identified maternal smoking (OR 5.5; 95% CI: 1.4, 21.6), young maternal age (OR 5.9; 95% CI: 1.4, 21.6), and the presence of siblings (OR 7.9; 95% CI: 1.5, 37.3) as being independently predictive of unexplained infant death. The estimated risk attributed to MP exposure was increased in the multivariate model to 13, but again, the CI was very large and overlapped 1.

Discussion

The population exposed to MP as the result of this widespread, illegal misapplication of MP in Lorain County, Ohio, was the largest ever to have been evaluated. Although the initial investigation of the misapplication in Lorain County found no evidence, even among children, of any ongoing excess of any adverse health effects that could be linked to exposure to the pesticide, anecdotal reports of serious unexplained illness among residents around the time the pesticide was sprayed, as well as reports of deaths among domestic and wild animals, suggested that the effects of exposure might have been greater when the pesticide was initially sprayed. Consequently, when it was reported that two infants had died of undetermined causes in homes known or suspected to have been sprayed with MP, there was concern that despite the apparent absence of health effects among adults living in contaminated houses, the health of children living in those homes may have been at risk.

Several observations support this idea that infants and small children are more sensitive to the toxic effects of OP pesticides.

First, there are physiologic differences between infants and adults that may influence how they react to OP pesticide exposure. Infants have more rapid metabolic rates than adults and also differ in their ability to activate, detoxify, and excrete xenobiotic compounds (26). The toxic effect of acetylcholinesterase-inhibiting compounds such as MP may also be greater in infants who, relative to adults, have lower baseline levels of acetylcholinesterase and plasma pseudocholinesterase activity (27). In addition, because their kidney and liver functions have not yet completely developed, infants are less able to detoxify and excrete harmful substances. The clinical picture of an infant with OP poisoning is not the same as that for an adult (19). They do not always present with the pinpoint pupils that are the pathognomonic sign of OP poisoning in adults; the presence of other symptoms is even more variable (19). Results from animal studies also suggest differential susceptibility of immature and mature animals (21,22,28). In another study, young rats were more susceptible to the toxic effects of MP than adult animals (2). Because of their greater surface:body-mass ratio, infants may also absorb a toxic dose of OP faster than adults. Behavioral factors such as putting fingers and other objects in their mouths may make infants more likely to become exposed to OP pesticides. These factors, as well as the fact that infants spend more time indoors than children or adults, mean that they may be more likely to be exposed to toxic levels of a pesticide than adults living in the same environment.

SIDS is a multicausal, heterogeneous diagnosis; we do not suggest that pesticides are a principal cause of SIDS. Only three of the decedents’ homes had detectable levels of MP; thus, the proportion of SIDS deaths potentially attributable to MP is small. However, one can imagine a mechanism by which OP exposure could result in a death that might be mistaken for a SIDS death. The usual cause of death following acute OP poisoning is respiratory failure due to paralysis of the muscles of the respiratory system. Similarly, an unexplained cessation of breathing is the hallmark of a SIDS death. Although many hypotheses have been proposed (29), the mechanism for this respiratory failure remains unknown, as do the exposures (if any) that precipitate it. Factors suggested to play a role include incomplete development of the respiratory system (prematurity is a risk factor for SIDS) or a precipitating respiratory infection (29).

One of the difficulties associated with the investigation in Lorain County is the applica-
tor did not keep records of the homes he had treated. Thus, without a mechanism for accurately determining the number or location of houses sprayed with MP or the number of infants living in those contaminated homes, it was not clear whether two unexplained deaths among infants is more than would be expected in this group. At the county level, SIDS rates were not elevated for the years in question. However, given the limited number of children “at risk” of dying in an MP-contaminated home, it is unlikely, even if such children face a significantly increased SIDS death rate, that the increased numbers of deaths in such a small population would affect the rate in the overall population. SIDS is a relatively rare outcome, with a baseline incidence at the time of this investigation of less than 2/1,000 live births (30). Thus, assuming a mechanism had been available for identifying infants who had lived in those homes, a retrospective cohort study based of the 400 sprayed homes that had been identified would have had extremely limited power to assess any relationship between SIDS and MP exposure. Consequently, a case-control study in which we determined whether the deceased children were more likely to have lived in sprayed homes was identified as the only feasible approach for addressing this question.

Because of the circumstances under which it was done, this investigation had several unavoidable limitations. First was the small sample size. In addition to SIDS being a rare outcome, MP is also a rare exposure that only occurs in relation to sporadic events like this misapplication. Consequently, the population of infants who may have been exposed was restricted to both a particular area (Lorain County) and a particular period (1990 through 1994). Given that the possibility of exposure was documented for only three SIDS cases, one of which was an index case, the power of the investigation was limited. Second, because biological samples such as tissue or urine were not available for testing, we had limited ability to assess MP exposure. However, in the earlier investigation of exposure, results obtained from environmental sampling correlated well with those from

Table 2. Potential risk factors for unexplained infant death: exact conditional logistic regression, single-variable models.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP exposure</td>
<td>4.6 (0.2, 27.4)</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>7.2 (2.3, 23.8)</td>
</tr>
<tr>
<td>Other children</td>
<td>5.0 (1.8, 20.9)</td>
</tr>
<tr>
<td>Birth weight &lt; 2,500 g</td>
<td>3.7 (1.0, 12.6)</td>
</tr>
<tr>
<td>Maternal age &lt; 25 years</td>
<td>3.3 (1.1, 11.9)</td>
</tr>
<tr>
<td>Gestational age &lt; 38 weeks</td>
<td>3.2 (1.0, 12.4)</td>
</tr>
<tr>
<td>Prenatal visits &lt; 10</td>
<td>2.8 (1.1, 8.2)</td>
</tr>
<tr>
<td>Labor complications</td>
<td>2.1 (0.9, 5.4)</td>
</tr>
</tbody>
</table>

Table 3. Risk factors for unexplained infant death: multivariate exact conditional logistic regression, final model.

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP exposure</td>
<td>13.0 (0.2, 2686.5)</td>
</tr>
<tr>
<td>Maternal smoking</td>
<td>5.5 (1.4, 31.6)</td>
</tr>
<tr>
<td>Maternal age &lt; 25 years</td>
<td>5.9 (1.4, 39.7)</td>
</tr>
<tr>
<td>Other children</td>
<td>7.9 (1.5, 73.4)</td>
</tr>
</tbody>
</table>
biological samples. In addition, that investigation also showed that MP was stable indoors and could be detected at least as long as 3 years after being sprayed. Consequently, we believe that this method was a justifiable way of estimating exposure.

Finally, because we were estimating past exposure status on the basis of measurements made in the present and relating that status to cases that happened as much as 5 years ago, it was not always possible to be certain of the temporal relationship between exposure and outcome. For example, it is possible that even though a house where a child had died of unknown causes was found during the investigation to be contaminated with MP, it is not necessarily clear whether that contamination existed at the time of the death or whether it occurred later. However, this risk of misclassification is greater for deaths that occurred further in the past than it is for more recent deaths. Because two of the three case infants died within 18 months of when the environmental testing was done (dates of death were in December 1993 and November 1994), we believe the risk of misclassification is minimal.

These limitations prevent us from making conclusive statements about the risk to infants exposed to MP. However, we believe the results of this investigation provide valid and useful information that, in combination with the results from other similar investigations, can be used to assess the potential hazards associated with the use of OP pesticides.

Although the focus of our investigation was to assess the health hazard that MP exposure poses for infants rather than to identify risk factors for SIDS in general, our findings were interesting in that they corroborated much of what is known about risk factors for SIDS. Two factors (maternal age less than 25 and maternal smoking during pregnancy) that we found to be statistically significantly associated with unexplained infant death have been previously identified (18,29,33) as risk factors for SIDS. The presence of other siblings in the family, which was the third statistically significant predictor of case status in our investigation, has also been previously reported as a risk factor for SIDS (18).

Our findings suggest that infants living in MP-contaminated homes may face an increased risk for unexplained death; however, this risk was not statistically significant. This may have been because of the small number of cases and controls exposed to the pesticide. Although this association must be interpreted cautiously, given its lack of statistical significance as well as the other limitations of the investigation, we believe that the findings presented provide sufficient evidence to warrant further evaluation of the relationship between exposure to OP pesticides and unexplained infant death. Although indoor exposure to MP is an uncommon occurrence, the household use of other OP pesticides is more widespread, and the evidence from this investigation and others suggests that the effects of these substances on the health of infants and young children should be more thoroughly investigated. In a study done in Missouri, 98% of families reported using pesticides in their homes at least once a year, and 66% reported using them more than 5 times a year (32). Eighty percent reported using them in the house during a pregnancy. OPs are estimated to be responsible for 80% of acute pesticide poisonings that require hospitalization (33). Spraying or foggling of insectsicides in homes has resulted in the hospitalization of infants and children for OP poisoning (34,35). In an investigation in Paraguay, 30% of 37 patients with acute flaccid paralysis diagnosed as Guillain-Barre syndrome were noted to have had definite or possible exposure to OP pesticides (36). It was also noted that the peak use of these pesticides coincided with the peak incidence of Guillain-Barre syndrome.

Efforts should be made to increase public awareness of the potential hazards of inappropriate pesticide use. In particular, the importance of using only licensed exterminators should be re-emphasized, and people should be encouraged to be cautious in their use of OP pesticides in homes where young children are present.

REFERENCES AND NOTES

17. Rubin C. Personal communication.
23. Esteban E. Personal communication.