UK childhood exposures to pesticides 2004–2007: a TOXBASE toxicovigilance study

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ABSTRACT
Objective: There are no systematic methods for toxicovigilance of non-medicinal products in the UK. This is particularly relevant for pesticides, where there is significant public concern about potential adverse effects. This study describes a prospective toxicovigilance scheme based on follow-up of enquiries to the National Poisons Information Service (NPIS) through its online poisons information system TOXBASE. These enquiries reflect acute exposures and the patterns of acute illness that result.

Results: A total of 10 061 pesticide-related enquiries were identified. After follow-up, data were gathered on 2364 suspected exposures, of which 1162 involved children. After exclusions, 1147 exposures are reported here. No deaths were reported and only 37 children were admitted to hospital. The majority were considered to have either minimal or no features (925, 80.6%). Symptoms for 38 children were unknown. Symptoms reported in the other 184 children included nausea or vomiting (58), eye irritation, pain or conjunctivitis (29), skin irritation (28), abdominal pain (24), mouth or throat irritation (18) and diarrhoea (15). Where age was recorded, 60.5% (680) of children involved in suspected pesticide exposures were aged 2 years or less. The most common scenario for acute accidental exposure to pesticide in children was exposure after application (329, 28.7%) or due to poor storage (228, 19.9%).

Conclusions: Areas of potential concern identified included storage, access of young children to “laid” baits and pesticides, and exposures as a result of medication errors, with liquid head lice preparations being confused with other medicines. Use of NPIS systems provides a potentially useful method of toxicovigilance.

METHODS
TOXBASE is the internet database of the NPIS.7 A list of pesticides of specific interest was agreed between the Pesticides Safety Directorate of the UK Health and Safety Executive and NPIS Edinburgh in 2004, and monographs for these pesticides were identified on TOXBASE. By March 2007, 324 TOXBASE entries for products and specific agents were being tracked. Users accessing these pesticides for a patient-related enquiry were requested to complete an online form. If they did not, a postal questionnaire based on that of Leverton and colleagues8 was sent, with a covering letter and prepaid return envelope. No postal questionnaires were sent to NHS Direct or NHS 24, because of the difficulties of identifying case details in their systems. Responses about the same exposure were combined.

All telephone enquiries to NPIS Edinburgh (>90% from Scotland) about pesticides received during the period were followed up. Thus the total number of questionnaires comes from three sources: electronic questionnaires, follow-up of TOXBASE users who did not complete an
The vast majority of children (1106, 96.4%) were not admitted to intensive care, required ventilation or were reported to have significant complications or longer-term effects from the exposure. There were no deaths reported in our study group, and only two prolonged prothrombin time.

Table 1  Gender and age group of 1123 children involved in acute accidental exposures whose specific age was recorded

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Boys exposed to pesticides</th>
<th>Girls exposed to pesticides</th>
<th>Gender not known</th>
<th>χ²</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%)</td>
<td>Ratio (95% CI)</td>
<td>No (%)</td>
<td>Ratio (95% CI)</td>
<td>No (%)</td>
</tr>
<tr>
<td>0–4</td>
<td>943 (54.3)</td>
<td>0.58 (0.55–0.61)</td>
<td>394 (42.0)</td>
<td>0.42 (0.39–0.45)</td>
<td>6</td>
</tr>
<tr>
<td>5–9</td>
<td>147 (49.7)</td>
<td>0.50 (0.42–0.58)</td>
<td>73 (50.3)</td>
<td>0.50 (0.42–0.58)</td>
<td>2</td>
</tr>
<tr>
<td>10–12</td>
<td>33 (57.6)</td>
<td>0.58 (0.41–0.73)</td>
<td>14 (42.4)</td>
<td>0.42 (0.27–0.59)</td>
<td>0</td>
</tr>
</tbody>
</table>

DISCUSSION
In contrast to the situation for drugs, there is at present no formal system for toxicovigilance for other products in the home or garden.

The active ingredients most frequently identified in these exposures of children were permethrin (insecticide), malathion (head lice treatment) and metaldehyde (slug killer) (table 2). Most exposures (94.4%) were to products for non-professional use in the home or garden.

The most common scenario for acute accidental exposure in children was that they were exposed as a consequence of use but not during application (529, 28.7%). These were often to bait-type products, or were due to unsatisfactory storage (228, 19.9%). Of the 529 cases where the exposure occurred after application, 119 (36.2%) involved rodenticides; 96 (29.2%), ant killers; and 83 (16.1%), slug killers. The most frequent route of exposure was ingestion (778, 69.1%). Multiple routes of exposure were found for 17.9% (201) of children.

Symptoms were absent in 925 (80.6%); for 38 the question was answered “unknown” or was not recorded; in the 184 children who had symptoms, these included nausea or vomiting (58), eye irritation (29), skin irritation (28), abdominal pain (24), mouth or throat irritation (18) and diarrhoea (15).

Of exposure to head lice treatments, therapeutic error accounted for 29 (16.5%) of 178, these products being mistaken for an oral medication (41.4% for paracetamol). Seven (24.1%) patients exposed because of therapeutic error had symptoms, similar to the prevalence of symptoms in head lice exposures overall (43, or 24.4%).

Of 259 patients exposed to rodenticides, 44 respondents recorded measuring the INR (international normalised ratio) or prothrombin time, although most (26) did not report the result. Of the 18 who did record the outcome, 16 found normal and only two prolonged prothrombin time.

Specific treatment was recorded as not required in 86.5% (608) of the 708 cases. In the 29 cases where a specific treatment was recorded, it involved eye irrigation (15), oral activated charcoal (5), skin decontamination (5), topical antibiotics to the eye (4), oral fluids (2), analgesia (2), gastric lavage (1), intravenous fluid (1), oral antihistamines (1), oral antibiotics (1) or topical emollient (1), in line with the advice provided on TOXBASE. No children were admitted to intensive care, required ventilation or were reported to have significant complications or longer-term effects from the exposure. There were no deaths reported in our study group, and the national data sets on mortality are not product specific and so do not assist further analysis in this regard.
These findings concur with those of previous studies on 5 years, with children aged 2 the most frequently exposed (fig 1). Patients with symptoms.

Exposures to anticoagulants, the results of clotting studies were tors) are best suited to this approach. Thus, of 18 children assays are not widely available. In this series, exposures to exposure to pesticides is challenging in routine practice, as laboratory confirmation was conducted. Confirmation of exposures reflect other experience in childhood poisoning where less likely.

The distribution of patient age and gender reported in this study reflects many of the patterns that have been found in previous epidemiological studies of general poisoning and study reflects many of the patterns that have been found in childhood poisoning where and suggests that the data collected reflect the overall pattern of exposure. These similarities support the concept that the surveillance approach we have used is likely to reflect overall patient exposure patterns, and while it is possible that this low response rate might bias the results, these similarities make it less likely.

It is unlikely that all patients were exposed to pesticide if exposures reflect other experience in childhood poisoning where laboratory confirmation was conducted. Confirmation of exposure to pesticides is challenging in routine practice, as assays are not widely available. In this series, exposures to anticoagulants and organophosphates (cholinesterase inhibitors) are best suited to this approach. Thus, of 18 children exposed to anticoagulants, the results of clotting studies were abnormal in only two. No assays were reported in relation to organophosphates, but assays are clinically indicated only in patients with symptoms.

Most exposures (84.0%) occurred in children under the age of 5 years, with children aged 2 the most frequently exposed (fig 1). These findings concur with those of previous studies on childhood poisoning. Most of the exposures reported either occurred after the pesticide, usually a bait-type compound, had been applied (28.7%) or were due to unsatisfactory storage (19.9%). Exposures through ingestion were common (in 69.1%), with rodenticides (22.5%), ant killers (20.8%) and slug killers (12.1%) being prominent.

Despite the large number of children presenting to healthcare professionals, most exposures did not produce symptoms (80.6% asymptomatic) and were considered of “minor” severity (76.2%) by the healthcare professional involved. Most of the children exposed (96.4%) either were not admitted to hospital or were discharged on the same day. No patients were reported as being admitted for more than 2 days. The cases in which an admission of 2 days was recorded followed exposure to rodenticides.

Head lice treatments accounted for 15.5% of exposures. There is potential to reduce therapeutic error through education, repackaging or improved storage. These products were either mistaken by children themselves or by carers as an oral pharmaceutical.

**CONCLUSIONS**

The effects of potentially toxic pesticides on health can be monitored using NPIS resources. Most suspected pesticide exposures of children resulted in no clear acute adverse health outcome and were considered of minor severity. No children were reported to have died or to have been admitted to intensive care. Nevertheless, issues such as safety of storage and care after application of bait-style products were highlighted. There would appear to be potential for reducing such exposures through health education and improved packaging and labeling.

**Acknowledgements:** This study was conceived by Professor DN Bateman and planned by Professor DN Bateman and Mrs Alison Good. Mr RD Adams and Mr D Lupton collected and analysed the data. Mr RD Adams drafted the manuscript and all authors contributed to the final version.

**Funding:** The UK Health and Safety Executive and the Pesticide Safety Directorate funded this study. The funding sponsor had no role in the design of the study other than to request a range of pesticides about which they were specifically interested in gathering exposure data. The study sponsor played no role in the collection, analysis or interpretation of data. The study sponsor also played no role in writing the report or the decision to submit the paper for publication.

**Competing interests:** None.

Mr Richard D Adams, Mr David Lupton, Mrs Alison M Good and Professor David Nicholas Bateman are all based at NPIS Edinburgh in the Royal Infirmary of Edinburgh, Scotland.

**REFERENCES**

Hyperinsulinism-hyperammonaemia syndrome

The hyperinsulinism-hyperammonaemia syndrome (HHS) was reported in a series of eight patients in 1988. Since then several series of up to 14 patients have been reported. The cause is an activating missense mutation in the GLUD1 gene at chromosome 10q23.3 that encodes glutamate dehydrogenase (GDH). The mutations occur either de novo or with dominant inheritance. The activity of GDH is enhanced by reduction of the inhibitory effect on GDH of guanosine triphosphate (GTP) and adenosine triphosphate (ATP). In HHS the biochemical disturbance affects the pancreas, the liver, and possibly the brain. The main clinical features are recurrent hypoglycaemia (it is a cause of leucine-induced hypoglycaemia) beginning in early infancy, and mild to moderate hyperammonaemia without lethargy, headaches or acute neurological disturbance. Now the neurological aspects of the syndrome have been emphasised in a report of 22 patients from 17 families from centres in France, Italy and Belgium (Nadia Bahi-Buisson and colleagues. Developmental Medicine and Child Neurology 2008;50:945–9; see also Commentary, ibid: 888). The series consisted of 12 males and 10 females aged 18 months to 40 years, all with HHS proved genetically or biochemically. Learning disability was present in 17 patients and 14 had childhood-onset epilepsy, often with atypical absences. Less frequent seizure types included focal motor seizures and generalised tonic–clonic seizures. Eleven patients responded well to anticonvulsant drugs. Two patients had pyramidal tract involvement and one had generalised dystonia.

Four patients had signs of hypoglycaemia within 3 days of birth, but the median age at recognition of hypoglycaemia was 5 months. Seventeen patients had hypoglycaemic seizures. The hypoglycaemia was usually well controlled with diazoxide or a leucine-restricted diet or cornstarch, but one patient needed partial pancreatectomy. Mean ammonia concentrations varied from 117 to 128 μmol/l in different groups, but did not differ significantly between patients with or without epilepsy or learning disability. GDH overactivity affects the pancreas (hypoglycaemia), the liver (hyperammonaemia) and the brain. Whether the neurological problems seen in HHS are a consequence of hypoglycaemia or hyperammonaemia, or reflect brain GDH activity remains uncertain, but there is a suggestion from this series that mutations in the GTP binding site of GDH might predispose to epilepsy. Brain GDH activity could be important in regulating neurotransmitters such as GABA.