Sulphonylurea drugs

The sulphonylurea group of antidiabetic drugs includes tolbutamide, chlorpropamide, acetohexamide tolazamide, glibenclamide, glipizide, glimepiride and gliclazide. They are available in a range of tablet strengths, e.g. tolbutamide is available in 500 mg tablets, gliclazide is available as 80 mg tablets, while glibenclamide, glimepiride, glipizide, are available in tablets of 5 mg or less.

Sulphonylurea drug ingestion is not common in children and the clinical effects do not correspond well with the amount ingested. However, these drugs have the potential to cause severe toxicity. In addition, because of the non-specific signs and symptoms of hypoglycaemia, treatment may be delayed and long-term sequelae may result in severe hypoglycaemia. Although there is an antidote to sulphonylurea poisoning (octreotide) it has been used following overdose only within the last few years for either adults (Bui *et al.*, 2000; McLaughlin *et al.*, 2000) or children (Mordel *et al.*, 1998).

Sulphonylureas are thought to stimulate endogenous insulin secretion by producing a depolarizing of the pancreatic islet beta cell membrane resulting in release of the preformed insulin into the circulation. Sulphonylureas are rapidly absorbed and subjected to extensive hepatic metabolism. Some sulphonylureas have active metabolites, which may result in prolonged hypoglycaemia. There are two groups of sulphonylureas; the first generation tolbutamide, chlorpropamide, acetohexamide and tolazamide and the second generation glibenclamide, glipizide, glimepiride and gliclazide. The mechanism of action is the same but the second-generation sulphonylureas are more potent on an equimolar basis (Spiller, 1998). In children, NPIS (L) recommends observation in hospital for ingestion of any amount.

Clinical effects of poisoning

Sulphonylureas predominantly cause hypoglycaemia and this may be prolonged, particularly with those drugs, such as chlorpropamide, that have a long half-life. Children are more at risk of hypoglycaemia after ingestion of a sulphonylurea than adults because they have increased rates of glucose utilisation, and therefore deplete glucose stores more rapidly. This is because of their higher brain mass to body mass ratio and the greater energy requirement of brain tissue (Szlatenyi *et al.*, 1998). Children also have limited capacity for glucose synthesis through gluconeogenesis, glycogenolysis and metabolic fuel pathways (Szlatenyi *et al.*, 1998). Normal blood glucose is 60-100 mg/dL.

Epidemiology

Neither the AAPCC data nor the ONS data for England and Wales from 1993-1999, contained any reports of fatal cases involving ingestion of sulphonylureas by children under 5 years. There were no reports in the NPIS enquiry database between March 1997-December 2001 of children under 5 years with moderate or severe clinical effects due to ingestion of sulphonylureas alone.

The HASS sample of attendances by children under 5 years at 18 emergency departments resulting in hospital stay of one day or more between 1996 and 1999 included one case involving glibenclamide, three cases involving gliclazide and four cases involving unspecified antidiabetic preparations, out of a total of 452 solid drugs implicated in these incidents.

Cases in the literature

Case summaries

In the study reported by Quadrani *et al.* (1996) of sulphonylurea ingestion in children aged 1-16 years (mean 3.5 years) three drugs, chlorpropamide, glipizide and glibenclamide (glyburide), accounted for 95% of cases. Of the 93 cases reported, 27% became hypoglycaemic, the time to onset ranging from 0.5 to 16 hours post-ingestion. Half the children had hypoglycaemia within two hours of ingestion. Persistent hypoglycaemia occurred in nine children (10%). The authors found that ingestion of one tablet was sufficient to produce significant hypoglycaemia with delayed onset.

In another study of 185 children under 12 years (mean age 2.4 years) 30% developed hypoglycaemia (<60 mg/dL) which developed within 8 hours of ingestion in 96% of cases. Time to onset of minimum blood glucose concentration was 1-21 hours (mean 5.3 h). The mean hospital stay for those with hypoglycaemia was 28.2 hours compared to 21.6 hours for the children who did not develop hypoglycaemia. Enough data was available for 103 (58%) of 177 children who ingested glibenclamide or glipizide to calculate a toxic dose/weight ratio. However, risk assessment based on dose per kilogram body weight was unreliable. Of the 103 children, 31 of the 36 who ingested ≤0.3 mg/kg remained asymptomatic and 31 out of 67 who ingested >0.3 mg/kg had blood glucose concentrations <60 mg/dL (Spiller *et al.*, 1997).

Case reports

There are several case reports in the literature of hypoglycaemia in children following accidental ingestion of a sulphonylurea drug (Parker and Tisdell, 1963; Greenberg *et al.*, 1968, Graw and Clarke, 1970). In many cases the dose ingested is unknown. One 5 mg glipizide tablet caused hypoglycaemia (49 mg/dL) in a 2 year old child (13.2 kg) 11 hours after ingestion, even though he had been given activated charcoal within 40 minutes of ingestion and received intravenous dextrose with a normal diet. The blood glucose fell again (63 mg/dL) 20 hours post-ingestion (Frederick and Wang, 1994; Szlatenyi *et al.*, 1998). A 6 year old child presented in hospital with right-sided paresis and lethargy after ingestion of 6 glibenclamide tablets. Her blood glucose concentration was 34 mg/dL. She recovered without sequelae (Spiller *et al.*, 1998).

A boy aged 5 years and 9 months presented with status epilepticus and a blood glucose concentration of 12 mg/dL and developed recurrent hypoglycaemia despite receiving dextrose. It was discovered that he had been dispensed 5 mg glipizide instead of Adderall® (amphetamine and dextroamphetamine) for attention deficit hyperactivity disorder (ADHD). He had received 7.5 mg glipizide twice daily for three days with the last dose 14 hours before presentation. He was given octreotide and made a full recovery (Mordel *et al.*, 1998).

Hypoglycaemia may be prolonged following ingestion of a sulphonylurea drug. A 3.5 year old child had low blood glucose for four days following ingestion of an unknown quantity of chlorpropamide. He was not admitted until 36 hours post-ingestion and the blood glucose at this time was 28 mg/dL (Greenberg *et al.*, 1968). An adult was hypoglycaemic for 27 days following intentional ingestion of 5-10 g of chlorpropamide (Ciechanowksi *et al.*, 1999).

Some of these children developed neurological sequelae as a result of severe hypoglycaemia; this usually occurs in cases where treatment has been delayed. A 30 month old boy was admitted 48 hours after ingestion of an unknown number of glibenclamide tablets. His blood glucose was 7 mg/dL. He was discharged 12 days later with left third nerve palsy and decreased visual acuity in the left eye, but continued to experience epileptic seizures, some grand mal but mostly minor motor seizures (Sillence and Court, 1975). In another case an 11 month old child was admitted comatose with convulsions 12 hours after having been fed an unknown number of glibenclamide tablets by a sibling. Her blood glucose on admission was 4.7 mg/dL. She was discharged 15 days later but required anticonvulsant medication and had moderate right-sided hemiparesis (Pavone *et al.*, 1980).

NPIS cases

There were only six cases involving children with follow-up details in the NPIS cases files (Table 52). All six children remained asymptomatic.

Toxicity

A single tablet of glipizide (Quadrani *et al.*, 1996, Szlatenyi *et al.*, 1998), chlorpropamide (Quadrani *et al.*, 1996) or glibenclamide (Quadrani *et al.*, 1996) has been reported to cause hypoglycaemia in a child. Hypoglycaemia may be delayed in onset and serious neurological sequelae can result from delay in admission.

Table 52: A summary of sulphonylurea cases with follow-up reported to NPIS (L).

Drug	Cases
Chlorpropamide	Only one case with follow-up. The dose was unknown and the child (1.5 years) remained asymptomatic.
Glibenclamide (glyburide)	4 cases with follow-up. In 2 cases the dose was unknown, in the other two the ingested dose was 5 mg (1 tablet) and 45 mg (9 tablets). All 4 children remained asymptomatic.
Glibornuride	No cases with follow-up.
Glimepiride	No cases with follow-up.
Gliquidone	No cases with follow-up.
Gliclazide	No cases with follow-up.
Glipizide	No cases with follow-up.
Tolazamide	No cases with follow-up.
Tolbutamide	Only one case in a 7 year old. He ingested one 500 mg tablet and remained asymptomatic.

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Temazepam

Temazepam is a short-acting benzodiazepine available in 10 mg and 20 mg tablets.

Temazepam has been given to children as a premedicant in doses of 0.5-1 mg/kg up to a maximum of 30 mg, although it is not recommended. NPIS (L) recommends children who have ingested more than 1 mg/kg should be observed in hospital. Temazepam is more rapidly absorbed than other benzodiazepines and has a therapeutic half-life of less than 10 hours.

Clinical effects of poisoning
Clinical features of poisoning with benzodiazepines usually occur within 0.5-3 hours. The most common features of overdose are drowsiness and ataxia, with slurred speech and confusion. Drowsiness may progress to coma and comatose patients may develop hypotension and respiratory depression.

The duration of CNS depression ranges between 12-36 hours in most cases. However, this will be influenced by a number of factors including the rate and extent of distribution of the individual benzodiazepine in the CNS, the patient's tolerance, and the rate of elimination once complete distribution has taken place (Gaudreault *et al.*, 1991). Temazepam is more sedating in adults than other benzodiazepines (Buckley *et al.*, 1995)

Epidemiology
Accidental ingestion of benzodiazepines by children is common. Temazepam was one of the most frequently named solid-dose drugs in the sample of attendances at emergency departments by children under 5 years resulting in admission for one day or more, reported to HASS between 1996 and 1999. It accounted for 26 of the 452 solid-dose drugs implicated (6%) Temazepam is also one of the most frequently implicated agents involved in child ingestions reported to NPIS (L).

In adults, temazepam is the one of the most common causes of death attributable to poisoning from a single drug in the United Kingdom (Crome *et al.*, 1993), but no childhood deaths due to accidental ingestion of temazepam were reported by ONS in England and Wales between 1993-1999, nor were there any childhood deaths reported to data AAPCC between 1983-2000.

Most cases reported to the NPIS (L) exhibit only mild symptoms. Reports on the NPIS enquiry database between March 1997 and December 2001, included five cases of children under 5 years who had ingested temazepam alone in amounts ranging between 20 mg and 120 mg, and another five reports of children who had ingested an unknown quantity. Seven of these children were reported to be suffering depressed consciousness described non-specifically as "coma". One child had a respiratory arrest and there was one report of death implicating temazepam (see Table 53). Unfortunately no follow up details have been received on any of these cases. Since there was no report of an accidental death due to temazepam in the ONS data, the death was probably unrelated to ingestion of temazepam, but could possibly have been due to intentional administration.

Table 53: A summary of temazepam cases with severe clinical effects retrieved from the NPIS (L) enquiry database.

Case reference	Age (years)	Clinical effects	Dose	Time since ingestion (hours)
97/105594	2	Death.	2 tablets	1
97/128190	2	Drowsy, respiratory arrest.	unknown	3.5
01/58875	3	Tetanic convulsions, drowsy.	unknown	2

NPIS cases
There were three cases reports with estimates of dose ingested. Two had minor symptoms of drowsiness from 190 mg and 40 mg, the fourth ingested 60 mg and was unresponsive for one hour. All the children recovered.

Toxicity
A search of Poisindex®, and the published literature failed to find any record of serious toxicity or death in a child from unintentional ingestion of temazepam.

Benzodiazepines are said to be capable of marked CNS depression in relatively small doses. The NPIS cases with follow-up provide evidence that moderate toxicity could be expected from three tablets of 20 mg strength. These effects could be life threatening if the child was not brought to hospital promptly, but with prompt and adequate medical care would pose no serious risk.

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Summary of results

These assessments are based on limited data. The number of cases with some estimate of dose varied from 89 for hyoscine and 132 for Lomotil®, to less than 10 for amoxapine, atenolol, propranolol and temazepam (Table 54). Few of the fatal cases for any of the drugs assessed included dose estimates; the highest numbers available were for nifedipine, quinine and imipramine, (6, 8 and 9 respectively).

Evidence of toxicity

Death was associated with doses of less than 8 of the highest strength dose units of methadone, nifedipine, imipramine, and quinine (based on a review of 4-9 cases), and of dothiepin, amoxapine, carbamazepine, Lomotil®, dapsone, hyoscine (based on a review of only one or two cases).

For some of the drugs for which there were only one or two fatal cases with dose estimates, supporting evidence for toxicity of doses lower than 8 units was provided by the cases with moderate or severe toxicity (PSS 2 and 3). For dothiepin and Lomotil® there were 10 and 19 cases respectively of severe poisonings with dose estimates, and there were 8 cases for carbamazepine. For all these drugs severe toxicity (PSS 3) was associated with less than 8 of the highest strength dose units. There were no cases of hyoscine poisoning with severe toxicity but there were 58 cases of moderate toxicity, and at least 20 of these had ingested less than 8 units.

Evidence of lack of toxicity

No reports were found of death due to atenolol, temazepam, or sulphonylureas, and only one death reported due to propranolol. For each of these drugs there was only a small number of cases with moderate to severe toxicity, although some of these cases involved less than 8 dose units. A published case series provided evidence that propranolol and atenolol were generally of low toxicity. Although there was little evidence of moderate to severe poisoning from temazepam or sulphonylureas it was noted that effects of moderate/severe poisoning (unconsciousness, hypoglycaemia) could be life-threatening if the patient was not taken to hospital promptly.

Table 54: Number of highest strength dose units and doses associated with each grade of severity of poisoning in children under 5 years.

	Highest dose unit (mg) *a*	Cases with PSS 1 from known dose	No of dose units (col a) equivalent to highest dose associated with PSS 1	No of cases with PSS 2 or 3 from known dose	No of dose units (col a) equivalent to lowest dose associated with PSS 2	No of dose units (col a) equivalent to lowest dose associated with PSS 3	No of fatal cases from known dose	No of dose units (col a) equivalent to lowest dose associated with PSS 4
amoxapine	100	*1*	1.5	*2*	1	-	*2*	1
methadone	5	*11*	8	*7*	2	2	*4*	4
nifedipine	60	*5*	1	*7*	0.5	-	*6*	<0.5
dothiepin	75	*4*	1-10	*26*	1	1	*1*	1.6
carbamazepine	400	*7*	7.5	*10*	1.5	2	*1*	4
imipramine	25	*4*	5-20	*13*	3	20	*9*	4.8
quinine	300	*8*	6	*13*	1	6.5	*8*	5
Lomotil®	2.5	*50*	>10	*82*	1.3	3	*1*	6
propranolol	160	*4*	5	*5*	0.25	0.5	*1*	0.5
atenolol	100	*0*	?	*2*	0	0.5	*0*	-
hyoscine	0.3	*31*	>7	*58*	1.5	-	*1*	6
dapsone	100	*4*	5	*8*	1	15	*1*	50
temazepam	20	*2*	8.5	*1*	3	-	*0*	-

Variability of response

There appeared to be variability in response to many of these pharmaceuticals. For nifedipine, Lomotil®, methadone, imipramine, and hyoscine there were several reports of mild toxicity (PSS 1) at doses higher than the lowest dose associated with severe toxicity or death (PSS 3 or 4) (Table 54). Indeed for all of these drugs except hyoscine the majority of cases with mild toxicity had taken a dose higher than that associated with PSS 3 of 4 (Table 55). There were also reports, but in smaller numbers, of mild toxicity from doses associated with PSS 3 or 4 for amoxapine, dothiepin, carbamazepine, and quinine.

Table 55: Number of cases with mild toxicity (PSS 1) from doses higher than the lowest dose associated with severe poisoning or death (PSS 3 or 4)

	Number of cases with PSS 1 taking dose > lowest dose associated with PSS 3 or 4	total number of cases with PSS 1
amoxapine	1	1
methadone	10	11
Lomotil®	34	43
nifedipine	4	5
dothiepin	2	4
carbamazepine	2	7
imipramine	4	4
quinine	1	8
hyoscine	10	31
propranolol	0	4

Comparison of toxicity assessment with the epidemiological data

The overall danger from these drugs depends on how frequently they are implicated in childhood poisonings as well as their toxicity. The information gathered from HASS, the NPIS enquiry database, ONS, the AAPCC, the literature and NPIS case files is summarised in Table 56.

Table 56; Summary of information on frequency of involvement in poisoning

	HASS 1996-99 * cases admitted to hospital	NPIS enquiry database 1997-2001 ** cases with moderate/severe poisoning	Deaths England & Wales, 93-99 ***	Deaths reported to AAPCC 1983-2000	Other deaths reported in the literature
dothiepin	26	15	4		2
temazepam	26	10		4	
carbamazepine	12	7			2
hyoscine	9	1			1 (1966)
methadone	1	5	4	4	many
nifedipine				6	
imipramine	3	2			>9
quinine	4				>9
amoxapine			1	1	
Lomotil®	1			2	2
propranolol	5	1			1
dapsone					1 (1950)
atenolol					

* HASS: sample of attendances at emergency departments resulting in stay of one day or more.
** NPIS enquiry database: reports of ingestions with moderate-severe poisoning from ingestion of named drug only.
***From ONS official mortality statistics.

The drugs reviewed in detail can be categorised into the following groups:

1. Drugs which have been associated with severe toxicity in young children following ingestion of less than 8 dose units
    - those frequently implicated in childhood ingestions in the samples obtained from HASS and NPIS
    - those infrequently implicated in childhood ingestions in those samples.

2. Drugs which have not been associated with severe toxicity in young children following ingestion of less than 8 dose units

Drugs that have been associated with severe toxicity in young children following ingestion of less than 8 dose units

Those frequently implicated in the samples of childhood ingestions:

- **Dothiepin** has been associated with four recent deaths in England and Wales and was one of the solid-dose drugs most frequently reported in the sample of ingestions reported to HASS; over the last four years it has been more frequently reported to NPIS (L) as a cause of severe poisoning in children under 5 years old than any other solid-dose pharmaceutical.

- **Carbamazepine**: although there are a number of reports to HASS and NPIS of childhood ingestions, there have been no recent child deaths in England and Wales.

- **Hyoscine**: there is less evidence of severe toxicity from less than 8 dose units than for other drugs in this category, only one moderate to severe poisoning on the NPIS (L) enquiry database, and one death occurring in 1966. There were a number of reports to HASS of ingestions resulting in one day's stay or more, and large numbers of cases with moderate poisoning, reported over a number of years, in the NPIS case file. This suggests that exposures resulting in mild to moderate clinical effects occur relatively frequently, but seldom progress to severe poisoning.

Those infrequently implicated in the samples of childhood ingestions:

- **Methadone**: despite a significant number of recent deaths, exposure seems to be relatively infrequent, indicating that these infrequent exposures are highly likely to result in severe toxicity. In recent years, in the UK at least, nearly all exposures seem to have been ingestion of syrup rather than tablets, due to changes in prescribing regulations.

- **Lomotil®**: although there are no recent reports to NPIS (L) of severe poisonings, there are a relatively large number of cases on file from earlier years. Four deaths have been reported. If exposure occurs there appears to be a significant risk of moderate to severe poisoning.

- **Imipramine** and **quinine** have not caused any recent child deaths in England and Wales, but many fatal cases have been reported in the literature.

- **Nifedipine** was not associated with potentially serious exposures in the data from HASS or NPIS(L) nor has it been implicated in recent child deaths in England and Wales, but 6 deaths have been reported in the USA.

- **Dapsone** was not associated with potentially serious cases in the data from HASS or NPIS(L) but evidence from elsewhere indicates that clinical effects are very likely to result from exposure and that there is a significant risk of moderate to severe poisoning. Death is unlikely.

- **Amoxapine** poisoning is infrequently reported; the evidence of toxicity rests on two cases of moderate toxicity and two recent deaths.

Drugs that have not been associated with severe toxicity in young children following ingestion of less than 8 dose units

- **Temazepam** is one of the solid-dose drugs most frequently reported in the data from HASS and NPIS, indicating that clinical effects are likely to result from exposure, but not likely to lead to severe poisoning.

- **Propranolol** and **atenolol** were fairly frequently reported in the sample of hospital admissions from HASS, but only one case with moderate to severe effects was reported to NPIS(L) and only one isolated report of death could be found.

- **Sulphonylureas** were not implicated as a cause of potentially serious poisoning in data from HASS or NPIS(L); clinical effects are very likely to occur following ingestion, but not likely to lead to severe poisoning if given prompt medical attention.

Discussion

Medicines commonly implicated in childhood poisoning

The aim of this report has been to identify solid-dose drugs that cause severe poisoning in children. It has therefore focussed on only a small proportion of childhood ingestions. Many surveys of child poisoning have shown that children who develop severe poisoning as a result of ingesting medications are only a small minority of those who are exposed to them, and that a significant proportion of ingestions involve liquid formulations.

For example, a survey of hospital attendances at emergency departments by children under 5 years old following ingestion of medications found that only 22% of 1163 children developed symptoms and that these were severe in only two cases (Wiseman *et al.*, 1987b). Medications that were frequently reported in that survey were of low toxicity (gastrointestinal medicines, oral contraceptives, cough medicines), or were liquid formulations (e.g. paediatric liquid paracetamol, and medicines for cold and flu). The majority of children survey took medicines intended for themselves or young siblings. Compared with that survey, the sample from HASS of exposures resulting in hospital admission examined in this report, involved a much greater proportion of medicines intended for parents or elderly people, and these would be expected to be more toxic to children.

The survey by Wiseman *et al.* (1987b) also showed that a number of factors besides the packaging influenced the accessibility of a medication to young children and hence its incidence in childhood ingestions: for instance, where it was stored in the home, which member of the family it was intended for, and whether it had been obtained on prescription or over the counter. Accessibility is also dependent on prescribing habits and over-the-counter sales, which in turn are influenced by disease prevalence.

Identifying high-risk agents

There is no single source of information that can provide reliable estimates of the frequency of severe poisonings attributable to named medications. It is therefore not possible to determine why many of the potentially toxic medications that were frequently implicated in the sample of accidents resulting in admission to hospital, for example, paracetamol, nifedipine, and aspirin, did not feature among those implicated in moderate to severe poisonings reported to NPIS(L). These admissions may have been precautionary, for observation of children that might have developed serious symptoms but did not, or they may have been moderate or severe poisonings that were not reported to NPIS(L). Conversely there were a number of drugs that featured in moderate to severe poisonings reported to NPIS(L) but not in the sample from HASS, for example chlormethiazole, clozapine, and orphenadrine. Exposures to these drugs are relatively infrequent so it is possible that the HASS sample was not large enough to detect them, but another possibility is that cases were not detected because these were not correctly identified for some reason during the data collection process, perhaps because the names are less well-known.

However, even if incidence of severe poisonings is unknown, an agent that is frequently reported to NPIS as a cause of moderate poisonings and also frequently reported by HASS as resulting in more than one days stay in hospital is clearly a priority for further consideration. Data from both poisons centre enquiries and accident surveillance systems are important complementary sources of information. Poisons centres can sometimes provide more information for toxicity assessments than is available elsewhere. For five of the drugs in this study (dothiepin, imipramine, quinine, hyoscine and Lomotil®) more case data was available in NPIS(L) files than in the literature. However, because of the limitations of both sources more information should be sought from the literature and possibly by research, including laboratory confirmation of exposure when possible, to determine the risk of poisoning with pharmaceuticals, the possible reasons for frequent exposure and possible means of prevention.

Assessing toxicity using case reports from poisons centres and published literature

Assessing the toxic dose of a drug for children is difficult. There are large numbers of case reports of poisoning or suspected poisoning in young children, but small numbers of confirmed reports. From an epidemiological standpoint confirming poisoning is desirable, but from a case management perspective it is often either unnecessary or positively harmful and not justified.

Even when the drug is well established and has been available for many years, the information on dose-related effects in children that can be obtained from cases reported in the literature or to poisons centres is limited. There are uncertainties about dose in most cases of childhood ingestion because there are seldom any adult witnesses to the event:

- In very many cases the dose is totally unknown.
- When a dose has been estimated from circumstantial evidence, such as the amount of product left in the container, there is usually no proof that the entire estimated dose has been absorbed/ingested.
- The dose may be overestimated if history is incorrect, if vomiting occurred or if gastric decontamination took place in hospital.

Callers to NPIS(L) often say that they do not know the dose ingested by a child. However dose is an important factor in determining the treatment advice given by NPIS so callers are concerned to be as accurate as possible in the circumstances. When doses are reported in cases of children with moderate to severe poisoning doses, it is likely that there will be some evidence to justify it.

Published case series do not always include enough information on individual cases for the relationship of dose to effect to be identified for children under 5 years. Even detailed case reports are often inadequate. For example:

- The weight of the child may not be reported, making it was impossible to determine the dose in mg/kg.
- The numbers of tablets may be reported but not the tablet strength.
- The report may not state whether a solid or liquid formulation was ingested, although the medication was available in both formulations.

Other data were also frequently incompletely reported: for example, data on presence or absence of clinical effects, inaccurate data on time course of ingestion, delay between ingestion and onset of effects and decontamination, duration of effects and duration of hospital stay.

Many of the assessments of toxicity found differences in the effects and outcome of exposure to similar doses. This may be evidence of true variability in response across the population, the causes of which are discussed in Part 2 of this report. Alternatively the data may not reflect reality because it was not possible to base the assessments on mg/kg doses. There is a wide range in weight across this age group and different results might have been obtained if we had been able to calculate mg/kg doses in each case. Another possibility is that some of the cases that appeared to be similar had been inaccurately reported, with the result that differences in dose, clinical effects, or even the agent(s) ingested, could not be detected. The cause of unreliability in reporting exposures in this age group has already been addressed.

The limitations of the assessments presented in this report

In the second part of this report we discuss the need for expert evaluation of the toxicity of an individual drug in order to determine the type of packaging required. Does the assessment presented here represent such an expert evaluation? Although the authors are confident of their expertise in assessing case data and using it to make a judgement on toxicity, this study does not claim to have made the exhaustive search for data that ought to be attempted as a basis for decisions related to safety. Time constraints did not allow us to contact other poisons centres to request case reports, to ask manufacturers for pre- and post-marketing data or to approach authors of published reports to ask for unpublished data e.g. data on individuals included in case series.

Other methods for assessing toxicity

The drugs we studied were all well established drugs that have been available for tens of years. As a result there is a significant amount of information regarding overdose, especially in adults, but also in children. For many drugs, however, there is much less information on overdose either because they are newer drugs, or because their pattern of use makes it unlikely that children will come into contact with them frequently. Alternative information that can be used to determine the toxic dose is needed for these drugs.

Alternatives include the Minimum Intolerated Dose, i.e the dose at which more than 50% of patients suffered limiting adverse events, or the Maximum Tolerated Dose (MTD), i.e. the highest dose it is safe to administer to patients. Other information could be gathered from dose-ranging studies where increasing doses are administered to patients to determine the appropriate therapeutic dose. This usually involves administration of doses that eventually will be higher than the normal therapeutic dose, and tolerability is noted. Since these doses are given as one-off doses they are more relevant to the accidental ingestion situation than repeated doses of drugs which may cause quite different adverse effects.

For older drugs, such as the ones we studied, an MTD has never been formally defined, and it is necessary to rely on case reports to determine the toxic dose. However, for newer drugs that are potentially toxic an MTD is more likely to have been defined.

Products that cause poisoning with less than 8 dose units.

From cases reported to NPIS(L) and in the literature, it would be expected that all tricyclic antidepressants and opioids would be likely to cause severe poisoning in children in amounts that could be equivalent to less than 8 dose units of some products. Each product would need to be assessed individually, particularly for opioids that are present in many different products in varying amounts.

Information in Poisindex and NPIS(L) gives paediatric toxic doses equivalent to less than 8 of the highest dose units available in UK for many of the other drugs in the samples from HASS and the NPIS enquiry database; namely chlormethiazole, chloral hydrate, chlorpromazine, clozapine, dextropropoxyphene, codeine, flecainide and clonidine, verapamil, orphenadrine, risperidone, thioridazine, flecainide, theophylline, and chloroquine. These should be assessed using the methods recommended in the second part of this report to verify the toxicity and determine packaging requirements.

Implications of the results of this study for decisions about packaging

The dose ingested was reported in about 60% of the 110 moderate to severe poisonings in the sample from the NPIS (L) enquiry database, but the number of dose units was reported in only 39 (35%). However, in a large proportion (82%) of cases where the number of dose units was reported ingestion involved 8 dose units or less. Although it is possible that most of these cases involved ingestion of large numbers of tablets this is unlikely. It is realistic to expect that the majority of accidental ingestions in children would be of a small number of tablets because it is likely that carers would notice what was happening before a large number could be ingested. What is impossible to establish from this NPIS (L) enquiry data is the source of the tablets, i.e. whether they were taken directly from the packaging, or had been decanted into another, non-child-resistant, container either in bulk or a day's dose at a time, or simply taken from the packaging and left out in the open. Attempts to increase the resistance of packaging will not reduce poisoning incidents if tablets have been removed from their original container. Indeed some could argue that it might increase these poisonings if the resistant packaging frustrated the intended user sufficiently to encourage them to remove tablets from the original packaging at times other than when they intended to take the tablets. Studies into reclosable child-resistant packaging have demonstrated that the elderly often have difficulties opening the containers (Page, 1981; Robbins and Jahnigen,

1984), and may therefore leave them open with the contents easily accessible (Burns and Jenkinson, 1980; Myers, 1977).

There has been little research into blister packs. One study of elderly patients found that 89.9% were able to open a blister pack, compared with only 36.1% who could open a reclosable 'push-and-turn' child-resistant container (Nikolaus *et al*, 1996). With a reclosable container, if a patient found it difficult to open, the alternative is to avoid reclosing the container, thus leaving the contents easily available to both the patient and a child. However with non-reclosable containers, such as blister packs, each tablet still has to be extracted from the blister, regardless of whether the tablet will be taken at the time of extraction or at a later time. It is possible that all the tablets could be removed and placed in an open container, but people are less likely to do this than to leave the lid off a bottle, as it requires two extra steps (extracting each tablet, and finding another container).

The fact that significant toxicity has developed following ingestion of a relatively small number of tablets is of concern and supports the need for effective child-resistant packaging to prevent ingestion of amounts capable of causing severe toxicity.

Conclusions

These assessments of a limited number of drugs demonstrate that they can cause serious harm to children less than 5 years old in doses of 8 dose units or less. There is also evidence from NPIS (L) enquiry data that a significant proportion of severe poisonings from medications in this age group are caused by fewer than 8 dose units.

Our assessments of toxicity are consistent with what we expected to find, based on our previous analysis of the incidence and severity of poisonings reported to our centre, and our knowledge of existing reports from other poisons centres, from HASS and from mortality statistics.

We have demonstrated the validity of using data from an accident surveillance system, from mortality statistics and from poisons centres to assess toxicity. However the overall paucity of data highlights the need for harmonised, defined and verified data collection systems, especially for case histories from medical professionals. More observational research, including prospective, focussed, multicentre, even multinational studies, needs to be carried out by poisons centres and others to investigate the toxicity of drugs and the epidemiology of poisoning due to drugs.

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Appendix 1: Clinical effects specified in the search strategy used to retrieve cases with moderate and severe poisoning from the NPIS (L) enquiry database.

These are terms selected from the thesaurus used for clinical effecs in the NPIS(L) enquiry database

apnoea
ARDS (adult respiratory distress syndrome)
aspirated
aspiration pneumonia
asystole
atrial fibrillation
AV block
brain death
bronchospasm
bundle branch block
cardiac arrest
cardiac not otherwise specified
cardiogenic shock
cardiorespiratory arrest
coma III
coma IV
coma not otherwise specified
conduction defects
convulsions epileptiform
convulsions grand mal
convulsions not otherwise specified
convulsions petit mal
convulsions tetanic
convulsions tonic/clonic
CVA
death
DIC
ECG changes not otherwise specified
haemolysis
heart block
hepatitis
hyperpyrexia
intracerebral haemorrhage
intracranial haemorrhage
ischaemia
liver failure
multiorgan failure
myocardial infarction
myocarditis
oedema cerebral
opisthotonus
pancytopenia
paralysis
QRS prolongation
QT prolongation
respiratory arrest
shock
SIADH
status epilepticus
subarachnoid haemorrhage
subdural haemorrhage
supraventricular tachycardia
torsade de pointes
ventricular ectopics
ventricular fibrillation
ventricular tachycardia

APPENDIX 2

A standardised scale for grading the severity of poisoning allows qualitative evaluation of morbidity caused by poisoning, better identification of real risks and comparability of data. The PSS has been published in the Journal of Toxicology and Clinical Toxicology, Volume 36, 1998, pages 205 - 13.

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Instructions

Poisoning Severity Score (PSS) is a classification scheme for cases of poisoning in adults and children. This scheme should be used for the classification of acute poisonings regardless of the type and number of agents involved. However, modified schemes may eventually be required for certain poisonings and this scheme may then serve as a model.

The PSS should take into account the overall clinical course and be applied according to the most severe symptomatology (including both subjective symptoms and objective signs). Therefore it is normally a retrospective process, requiring follow-up of cases. If the grading is undertaken at any other time (e.g. on admission) this must be clearly stated when the data are presented.

The use of the score is simple. The occurrence of a particular symptom is checked against the chart and the severity grading assigned to a case is determined by the most severe symptom(s) or sign(s) observed.

Severity grading should take into account only the observed clinical symptoms and signs and it should not estimate risks or hazards on the basis of parameters such as amounts ingested or serum/plasma concentrations.

The signs and symptoms given in the scheme for each grade serve as examples to assist in grading severity.

APPENDIX 2

Treatment measures employed are not graded themselves, but the type of symptomatic and/or supportive treatment applied (e.g. assisted ventilation, inotropic support, haemodialysis for renal failure) may indirectly help in the evaluation of severity. However, preventive use of antidotes should not influence the grading, but should instead be mentioned when the data are presented.

Although the scheme is in principle intended for grading of acute stages of poisoning, if disabling sequelae and disfigurement occur, they would justify a high severity grade and should be commented on when the data are presented. If a patient's past medical history is considered to influence the severity of poisoning this should also be commented on.

Severe cases resulting in death are graded separately in the score to allow a more accurate presentation of data (although it is understood that death is not a grade of severity but an outcome).

Severity Grades

None (0): No symptoms or signs related to poisoning.

Minor (1): Mild, transient and spontaneously resolving symptoms.

Moderate (2): Pronounced or prolonged symptoms.

Severe (3): Severe or life-threatening symptoms.

Fatal (4): Death.

APPENDIX 2

ORGAN	NONE	MINOR	MODERATE	SEVERE	FATAL
GI-tract		• Vomiting, diarrhoea, pain • Irritation, 1st degree burns, minimal ulcerations in the mouth • Endoscopy: Erythema, oedema	• Pronounced or prolonged vomiting, diarrhoea, pain, ileus • 1st degree burns of critical localization or 2nd and 3rd degree burns in restricted areas • Dysphagia • Endoscopy: Ulcerative transmucosal lesions	• Massive haemorrhage, perforation • More widespread 2nd and 3rd degree burns • Severe dysphagia • Endoscopy: Ulcerative transmural lesions, circumferencial lesions, perforation	
Respiratory system		• Irritation, coughing, breathlessness, mild dyspnea, mild bronchospasm • Chest X-ray: Abnormal with minor or no symptoms	• Prolonged coughing, bronchospasm, dyspnea, stridor, hypoxemia requiring extra oxygen • Chest X-ray: Abnormal with moderate symptoms	• Manifest respiratory insufficiency (due to e.g. severe bronchospasm, airway obstruction, glottal oedema, pulmonary oedema, ARDS, pneumonitis, pneumonia, pneumothorax) • Chest X-ray: Abnormal with severe symptoms	

APPENDIX 2

ORGAN	NONE	MINOR	MODERATE	SEVERE	FATAL
Nervous system		• Drowsiness, vertigo, tinnitus, ataxia • Restlessness • Mild extrapyramidal symptoms • Mild cholinergic/anticholinergic symptoms • Paresthesia • Mild visual or auditory disturbances	• Unconciousness with appropriate response to pain • Brief apnoea, bradypnoea • Confusion, agitation, hallucinations, delirium • Infrequent, generalized or local seizures • Pronounced extrapyramidal symptoms • Pronounced cholinergic/anticholinergic symptoms • Localised paralysis not affecting vital functions • Visual and auditory disturbances	• Deep coma with inappropriate response to pain or unresponsive to pain • Respiratory depression with insufficiency • Extreme agitation • Frequent, generalised seizures, status epilepticus, opisthotonus • Generalised paralysis or paralysis affecting vital functions • Blindness, deafness	

APPENDIX 2

ORGAN	NONE	MINOR	MODERATE	SEVERE	FATAL
Cardio-Vascular system		• Isolated extrasystoles • Mild and transient hypo/hypertension	• Sinus bradycardia (HR ~40-50 in adults, 60-80 in infants and children, 80-90 in neonates) • Sinus tachycardia (HR ~140-180 in adults, 160-190 in infants and children, 160-200 in neonates) • Frequent extrasystoles, atrial fibrillation/ flutter, AV-block I-II, prolonged QRS and QTc-time, repolarization abnormalities • Myocardial ischaemia • More pronounced hypo/hypertension	• Severe sinus bradycardia (HR ~<40 in adults, <60 in infants and children, <80 in neonates) • Severe sinus tachycardia (HR ~>180 in adults, >190 in infants and children, >200 in neonates) • Life-threatening ventricular dysrythmias, AV block III, asystole • Myocardial infarction • Shock, hypertensive crisis	
Metabolic balance		• Mild acid-base disturbances (HCO3- ~15-20 or 30-40 mmol/l, pH~7.25-7.32 or 7.50-7.59) • Mild electrolyte and fluid disturbances (K+ 3.0-3.4 or 5.2-5.9 mmol/l) • Mild hypoglycaemia (~50-70 mg/dl or 2.8-3.9 mmol/l in adults) • Hyperthermia of short duration	• More pronounced acid-base disturbances (HCO3- ~10-14 or >40 mmol/l, pH ~7.15-7.24 or 7.60-7.69) • More pronounced electrolyte and fluid disturbances (K+ 2.5-2.9 or 6.0-6.9 mmol/l) • More pronounced hypoglycaemia (~30-50 mg/dl or 1.7-2.8 mmol/l in adults) • Hyperthermia of longer duration	• Severe acid-base disturbances (HCO3- ~<10 mmol/l, pH ~<7.15 or >7.7) • Severe electrolyte and fluid disturbances (K+ <2.5 or >7.0 mmol/l) • Severe hypoglycaemia (~<30 mg/dl or 1.7 mmol/l in adults) • Dangerous hypo- or hyperthermia	

APPENDIX 2

ORGAN	NONE	MINOR	MODERATE	SEVERE	FATAL
Liver		• Minimal rise in serum enzymes (ASAT, ALAT ~2-5 x normal)	• Rise in serum enzymes (ASAT, ALAT ~5-50 x normal) but no diagnostic biochemical (e.g. ammonia, clotting factors) or clinical evidence of liver dysfunction	• Rise in serum enzymes (~>50 x normal) or biochemical (e.g. ammonia, clotting factors) or clinical evidence of liver failure	
Kidney		• Minimal proteinuria/haematuria	• Massive proteinuria/haematuria Renal dysfunction (e.g. oliguria, polyuria, serum creatinine of ~200-500 µmol/l)	• Renal failure (e.g. anuria, serum creatinine of >500 µmol/l)	
Blood		• Mild haemolysis • Mild methaemoglobinaemia (metHb ~10-30%)	• Haemolysis • More pronounced methaemoglobinaemia (metHb ~30-50%) • Coagulation disturbances without bleeding • Anaemia, leucopenia, thrombocytopenia	• Massive haemolysis • Severe methaemoglobinaemia (metHb >50%) • Coagulation disturbances with bleeding • Severe anaemia, leucopenia, thrombocytopenia	
Muscular system		• Mild pain, tenderness • CPK ~250-1,500 iu/l	• Pain, rigidity, cramping and fasciculations • Rhabdomyolysis, CPK ~1,500-10,000 iu/l	• Intense pain, extreme rigidity, extensive cramping and fasciculations • Rhabdomyolysis with complications, CPK ~>10,000 iu/l • Compartment syndrome	

APPENDIX 2

ORGAN	NONE	MINOR	MODERATE	SEVERE	FATAL
Local effects on skin		• Irritation, 1st degree burns (reddening) or 2nd degree burns in <10% of body surface area	• 2nd degree burns in 10-50% of body surface (children: 10-30%) or 3rd degree burns in <2% of body surface area	• 2nd degree burns in >50% of body surface (children: >30%) or 3rd degree burns in >2% of body surface area	
Local effects on eye		• Irritation, redness, lacrimation, mild palpebral oedema	• Intense irritation, corneal abrasion • Minor (punctate) corneal ulcers	• Corneal ulcers (other than punctate), perforation • Permanent damage	
Local effects from bites and stings		• Local swelling, itching • Mild pain	• Swelling involving the whole extremity, local necrosis • Moderate pain	• Swelling involving the whole extremity and significant parts of adjacent area, more extensive necrosis • Critical localisation of swelling threatening the airways • Extreme pain	

APPENDIX 3

Data from the Home Accident Surveillance System.

Solid dose pharmaceuticals implicated in accidents involving children under 5 years old and resulting in one or more days stay in hospital: the number of reports for 414 pharmaceuticals listed by non proprietary name and classified by therapeutic use in a sample from 18 hospitals between 1996 and 1999.

There were 452 solid pharmaceuticals in the sample, of which 38 were not identified.

	No of occurrences
tricyclic antidepressant	
dothiepin	26
amitriptyline	12
imipramine	3
clomipramine	2
lofepramine	2
fluphenazine + nortriptyline	1
unspecificed tricyclic	1
total	*47*
anxiolytic	
temazepam	26
diazepam	13
lorazepam	1
lormetazepam	1
unspecified	1
total	*42*
analgesic – compound	
co-proxamol	15
co-dydramol	4
co-codamol	4
paracetamol+codeine+caffeine	2
paracetamol+phenylpropanolamine/ diphenhydramine	1
phenylpropanolamine +chlorpheniramine	1
not specified	2
total	*29*
iron	
ferrous sulphate	12
ferrous sulphate + folic acid	1
iron unspecified + folic acid	1
iron unspecified	13
total	*27*
non steroidal antiinflammatory	
ibuprofen	14
mefenamic acid	7
diclofenac	4
indomethacin	1
naproxen	1
total	*27*
analgesic – non opioid	
paracetamol	17
aspirin	7
unspecified	1
total	*25*
anticonvulsant	
carbamazepine	12
phenytoin	2
vigabatrin	1
total	*15*

APPENDIX 3

	No of occurrences
beta blocker	
atenolol	6
propranolol	5
oxprenolol	1
not stated	3
total	*15*
laxative	
phenolphthalein	11
senna	2
total	*13*
thyroxine	
thyroxine	12
liothryonine	1
total	*13*
antidiabetic	
metformin	4
glicazide	2
glibenclamide	1
glicazide +acarabose	1
unspecified	4
total	*12*
antiemetic	
hyoscine	9
prochlorperazine	2
unspecified	1
total	*12*
vitamins	
multivitamins with iron	1
multivitamin preparations	10
total	*11*
antipsychotic	
flupenthixol	5
trifluoperazine	3
chlorpromazine	1
haloperidol	1
thioridazine	1
total	*11*
calcium channel blocker	
amlodipine	4
nifedipine	5
verapamil	1
total	*10*
hypnotic	
zopiclone	2
chloral hydrate	1
zolpidem	1
unspecified "sleeping pill"	5
total	*9*
antihistamine	
chlorpeniramine	2
hydroxyzine	2
astemizole	1
prochlorperazine	1
terfenadine	1
trimeprazine	1
triprolidine + pseudoephedrine	1
total	*9*
antidepressant – SSRI	
fluoxetine	4
paroxetine	4
sertraline	1
total	*9*
ACE inhibitor	
lisinopril	5
enalapril	2

APPENDIX 3

	No of occurrences
captopril	1
total	*8*
analgesic – opioid	
codeine	3
dihyrocodeine	2
meptazinol	1
morphine	1
tramadol	1
total	*8*
analgesic unspecified	7
diuretic	
bendrofluazide	4
frusemide	1
unspecified	2
total	*7*
antibiotic	
amoxicillin	1
ampicillin	1
cephalexin	1
penicillin	1
total	*4*
antimalarial – quinine	4
antiobesity – phentermine	4
antidepressant – lithium	3
antiasthmatic	
aminophylline	1
salbutamol	1
unspecified	1
total	*3*
antidepressant unspecified	3
antianginal	
glyceryl trinitrate	1
isosorbide	1
total	*2*
antiarrhythmic	
amiodarone	1
flecainide	1
total	*2*
antihypertensive unspecified	2
antiparkinsonian	
benztropine	1
carbidopa + levodopa	1
total	*2*
H2 receptor antagonists	
cimetidine	1
ranitidine	1
total	*2*
non steroidal anti-inflammatory compound	
diclofenac + misoprostol	1
ibuprofen + codeine	1
total	*2*
other	
antimigraine – zolmitriptran	1
herbal tranquillizer	1
drug dependency treatment, lofexidine	1
unspecified contraceptive	1
CNS stimulant – caffeine	1
cardiac glycoside – digoxin	1
unspecified cardiac medication	1
bronchodilator – terbutaline	1
for bladder disorder – oxybutynin	1
antidiarrhoeal – diphenoxylate + atropine	1
antidepressant – MAOI –	1

APPENDIX 3

	No of occurrences
phenelzine	
anticoagulant – warfarin	1
anticholinergic – dicyclomine	1
anticancer – methotrexate	1
antacid – lansoprazole	1
total	*15*
Grand total	414

Source: Consumer Affairs Directorate, Department of Trade and Industry

Appendix 4: Fatal cases in children 5 years and under involving pharmaceuticals reported in the Annual Reports of the AAPCC TESS 1983-2000. Cases involving drugs of abuse, parenteral overdose/error or mixed drug ingestion are excluded.

Drug	Dose	Age/sex	Details
1983 Annual Report (Veltri et al., 1984)			
Iron	NS	16m/NS	Not stated.
Iron	NS ferrous sulphate	17m/NS	Not stated.
1984 Annual Report (Litovitz et al., 1985)			
Verapamil	NS	1 y/NS	Not stated.
Quinidine	NS	2 y/NS	Not stated.
1985 Annual Report (Litovitz et al., 1986)			
Imipramine	NK, 1 bottle of 50 mg tablets	18m/M	Convulsions and cardiac arrest during lavage 30 m post-ingestion, resuscitated. Coma, hypotension, ECG changes, anuria, deteriorated and died 27.4 h post-ingestion.
Nifedipine	NK	1 y/F	Hypotension, respiratory depression, cardiorespiratory arrest.
Iron	NK Ferrous sulphate 300mg tablets	3 y/F	Coma, then at 21 h hypotension due to GI bleeding, cardiac arrest (26 h). Died 2 days post-ingestion. Serum iron 682 mcmol/L (3h), 153 mcmol/L (8h).
1986 Annual Report (Litovitz et al., 1987)			
Digoxin	NS	4 y/NS	Not stated.
Carbamazepine	NS	2 y /NS	Not stated. Concentration 19 mg/L (PM).
Caffeine	NK diet tablets	1 y/M	Convulsions, tachycardia (200), rigidity, hyperreflexia, status epilepticus, hypotension, arrested, hypertensive, Concentrations 1.1 g/L (40h), brain death on 72h.
Iron	NK	1.5 y/NS	Concentration 4122 mcmol/L (6h), hypotension (12-16 h), bowel necrosis with perforation and peritonitis, elevated LFTs, respiratory (7d), died 14th day.
Chloroquine	1g	1 y/F	Coma (30m), cardiopulmonary arrest, resuscitated but refractory hypotension. Life support withdrawn 3rd day.
Phenytoin	6 or more capsules	3 y/M	Ataxia, tachycardia, tachypnoea, respiratory arrest (9 h), diabetes insipidus, EEG minimal activity, died on 3rd day. Concentrations 50 mg/L (1h), 47 mg/L (12h), 43 mg/L (18h), 40 mg/L (24-48h).
1987 Annual Report (Litovitz et al., 1988)			
Methadone	35 mg in 8oz of milk, drank 1.5 oz	1 y/M	Respiratory and cardiac arrest. Resuscitated but died next day after cardiac arrest. Methadone put into bottle by older sibling.
Amitriptyline	NK	17 m/M	Convulsions, coma, tachycardia, hypotension. Died on 12th hospital day. Amitriptyline and metabolites found in gastric contents.
Chloroquine	NK	2 y/F	Unresponsive, no pulse, arrhythmias 90 minutes after ingestion. Resuscitated but developed hypotension and convulsions. Life support withdrawn 24 h after presentation. Concentration 2.9 mg/L (serum 4 h before death) and 9.9 mg/L (PM blood).
Iron	up to 22g ferrous sulphate	10 m/F	Drowsy, haematemesis, coma, shock. Serum iron 786 mcmol/L and >1254 mcmol/L (no times given). Many tablets seen in gut on x-ray. Renal and hepatic failure. Died 2 days post-ingestion.
Imipramine	NS	13 m/NS	Not stated.

Appendix 5 Cases of moderate to severe poisoning associated with ingestion of pharmaceuticals reported to the NPIS(L) March 1997-December 2001 excluding multiple ingestions

	circum-stance	ages	gender	agent	type If stated	route	amount	time	agent comment	Clinical feature and comment		case comment
ACEPROMETAZINE												
	AC	1	M	ACEPROMETAZINE		ING	5 T	45 M		COMA IV PUPILS CONSTRICTED	TO PAIN	
AMITRIPTYLINE												
	AC	3	F	AMITRIPTYLINE		ING	2 T	13 H	50MG	ATAXIA CONVULSIONS NS DROWSY	? NOW	
	AC	<1	NK	AMITRIPTYLINE		ING	1 T	NK	25MG. ?FED BY SIBLING	APNOEA	ATTACK	
	AC	3	M	AMITRIPTYLINE		ING	8 T	16 H	25MG. BETWEEN THE 2 CHILDREN	BUNDLE BRANCH BLOCK CLINICAL EFFECTS OTHER	GONE THIS MORNING PROLONGED QTC 0.442MG	
	AC	1	M	AMITRIPTYLINE		ING	8 T	16 H	25MG. BETWEEN THE 2 CHILDREN	BUNDLE BRANCH BLOCK	0.432MG	
	AC	1	F	AMITRIPTYLINE		ING	120 MG	2 H		CARDIAC NS HYPOTENSION	ARRHYTHMIAS	
	AC	2	F	AMITRIPTYLINE		ING	NK	2 D		CARDIAC NS	T WAVE INVERSION	
	AC	2	M	AMITRIPTYLINE		ING	15 T	24.5 H		COMA NS DILATED PUPILS SINUS TACHYCARDIA		
AMOXAPINE*												
	AC	<1	NK	AMOXAPINE*		ING	NK T	1 H	100MG	CONVULSIONS NS		
	U	0	F	AMOXAPINE*		ING	NK T	1.5 H	100MG	CONVULSIONS NS		UNRESPONSIVE TO 10MG PR DIAZEPAM
	AC	<1	NK	AMOXAPINE*		ING	NK T	NK		EPILEPSY PRE EXISTING MYOCARDIAL INFARCTION REMARKS	STATUS EMD - NO CARDIO OUTPUT	CHILD SUBSEQUENTLY DIED
BENZODIAZEPINE NK												
	AC	3	M	BENZODIAZEPINE NK		ING	NK	NK		COMA NS RESPIRATORY NS		
BETAHISTINE												
	AC	3	M	BETAHISTINE		ING	28 T	6.5 H	8MG	ATAXIA COMA NS NYSTAGMUS VOMITING	X8	NOT KNOWN IF TAKEN ANY BUT CHILD BECAME SYPTOMATIC - COULD BE RELATED

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Appendix 5 Cases of moderate to severe poisoning associated with ingestion of pharmaceuticals reported to the NPIS(L) March 1997-December 2001 excluding multiple ingestions

	circum-stance	ages	gender	agent	type If stated	route	amount	time	agent comment	Clinical feature and comment	case comment
CARBAMAZEPINE											
	ATE	1	F	CARBAMAZEPINE		ING	250 MG	3 H		CONVULSIONS NS	IN HOSPITAL
	AC	1	M	CARBAMAZEPINE		ING	800 MG	NK		COMA NS	
	AC	2	F	CARBAMAZEPINE		ING	NK	7 H		COMA IV DROWSY RESPIRATORY NS	NOW AT 13.00 DOWN
	U	4	F	CARBAMAZEPINE		ING	NK	NK		CONVULSIONS NS DILATED PUPILS SINUS TACHYCARDIA 114	X 2 FITS - NO PAST HISTORY
	AC	1	M	CARBAMAZEPINE		ING	NK	NK		CONVULSIONS NS DROWSY	
	ATE	1	F	CARBAMAZEPINE		ING	NK	10 H	10XOD X2, 600MG X2	CONVULSIONS NS VOMITING	0,125 QUICKLY
	AC	2	F	CARBAMAZEPINE	TEGRETOL	ING	800 MG	2.5 H		COMA IV DILATED PUPILS GLASGOW COMA SCALE 11 IRRITABLE	
CHLORAL BETAINE											
	AC	3	F	CHLORAL BETAINE	WELLDORM	ING	5 T	50 H		COMA NS	WAKING UP A BIT
CHLORMETHIAZOLE											
	AC	1	M	CHLORMETHIAZOLE		ING	4 C	1.5 H		COMA III PUPILS CONSTRICTED	RESPONDING TO PAIN NOT REACTING TO LIGHT
	AC	2	NK	CHLORMETHIAZOLE	HEMINEVRIN	ING	3 C	30 H		COMA NS GLASGOW COMA SCALE ?	
	AC	1	M	CHLORMETHIAZOLE	HEMINEVRIN	ING	1 T	30 M		COMA NS	DONT BELIEVE ITS ONLY ONE TABLET
	AC	1	F	CHLORMETHIAZOLE	HEMINEVRIN	ING	6 C	1 H		COMA NS	
	AC	1	M	CHLORMETHIAZOLE	HEMINEVRIN	ING	1 T	1.5 H		ASPIRATED	?
CHLORPHENIRAMINE											
	ATE	<1	F	CHLORPHENIRAMINE	PIRITON	ING	2 MG	1.75 H		COMA NS	ACCORDING TO MUM FOR 30 MINS- FINE IN MHAE
CHLORPROMAZINE											
	AC	2	M	CHLORPROMAZINE		ING	600 MG	4 H		COMA NS HYPOTENSION PUPILS CONSTRICTED	RESP BIT LOW
	AC	1	M	CHLORPROMAZINE		ING	200 MG	2.5 H		COMA NS PUPILS SLUGGISH	
	AC	2	F	CHLORPROMAZINE		ING	NK	1.75 H	200MG ?	COMA NS PUPILS SLUGGISH SINUS TACHYCARDIA	UNRESP TO PAIN UNRESP TO LIGHT IRREGULAR BEAT

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Appendix 5 Cases of moderate to severe poisoning associated with ingestion of pharmaceuticals reported to the NPIS(L) March 1997-December 2001 excluding multiple ingestions

	circum-stance	ages	gender	agent	type if stated	route	amount	time	agent comment	Clinical feature and comment		case comment
	AC	1	M	CHLORPROMAZINE		ING	750 MG	1.5 H		COMA NS HYPOTENSION 78 PUPILS CONSTRICTED SINUS TACHYCARDIA 130 VOMITING	RESPONDING TO PAIN	
	AC	2	F	CHLORPROMAZINE		ING	NK	NK	25MG	COMA NS		
CLONIDINE												
	AC	1	M	CLONIDINE		ING	6 T	45 M		COMA NS	NOT ROUSABLE	
	AC	3	F	CLONIDINE		ING	6 T	45 M		DROWSY		
CLOZAPINE												
	AC	2	M	CLOZAPINE		ING	NK	NK		COMA NS	FLUCTUATING	
	AC	3	F	CLOZAPINE	CLOZARIL	ING	20 T	NK		COMA NS	UNROUSABLE	
	U	1	F	CLOZAPINE	CLOZARIL	ING	NK	9 M		COMA NS DROWSY	FLOPPY VERY	SUSPECT SHE MAY HAVE TAKEN THIS ONLY AFTER INVESTIGATIONS FOR INFECTION ETC....
CODEINE												
	AC	<1	M	CODEINE		ING	30 MG	3 H		BRONCHOSPASM RASH		
CODEINE PHOSPHATE												
	AC	1	M	CODEINE PHOSPHATE		ING	450 MG	4 H		COMA III		
DIAZEPAM												
	U	2	M	DIAZEPAM	VALIUM	ING	20 MG	20 H		COMA NS	BARELY ROUSABLE	
DOTHIEPIN												
	AC	3	NK	DOTHIEPIN		ING	75 MG	NK		COMA NS	INITIALLY APPARENTLY NOT NOW	
	AC	1	F	DOTHIEPIN		ING	NK T	4 H	25MG	CONVULSIONS NS DROWSY HALLUCINATIONS SINUS TACHYCARDIA		
	AC	2	M	DOTHIEPIN		ING	4 T	6 H	75MG	AGITATION CONVULSIONS NS DILATED PUPILS REMARKS SINUS TACHYCARDIA	FITTED X2 CONSCIOUS	NOT RESPONDING TO DIAZEPAM
	AC	2	M	DOTHIEPIN		ING	6 T	16 H	75MG	COMA NS CONVULSIONS NS	EARLIER EARLIER	
	AC	2	F	DOTHIEPIN		ING	2 T	45 M	75MG	COMA NS CONVULSIONS NS		
	AC	2	F	DOTHIEPIN		ING	NK	2 H	75MG			

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Appendix 5 Cases of moderate to severe poisoning associated with ingestion of pharmaceuticals reported to the NPIS(L) March 1997-December 2001 excluding multiple ingestions

	circum-stance	ages	gender	agent	type if stated	route	amount	time	agent comment	Clinical feature and comment		case comment
										CONVULSIONS NS	POST ICTAL	
	AC	3	M	DOTHIEPIN		ING	10 T	1 H	75MG	COMA NS	SEMI-CONCIOUS	
	AC	1	F	DOTHIEPIN		ING	NK	NK	75MG	CONVULSIONS NS	X 4	
	AC	2	F	DOTHIEPIN		ING	3 T	25 H	75MG	COMA NS	YESTERDAY	
										CONVULSIONS NS	YESTERDAY	
	U	1	NK	DOTHIEPIN		ING	14 T	3.5 H	75MG			3 CHILDREN- 14 TABS MISSING
										CONVULSIONS NS		
										IRRITABLE	EALIER	
										SINUS TACHYCARDIA	NOW	
	AC	1	NK	DOTHIEPIN		U	4 T	1 H		CONVULSIONS NS		
										SINUS TACHYCARDIA		
	AC	1	F	DOTHIEPIN		ING	NK	NK		CARDIAC ARREST		
	AC	1	F	DOTHIEPIN	PROTHIADEN	ING	NK	13 H	75MG	CONVULSIONS NS		
										RESPIRATORY ARREST		
	AC	4	F	DOTHIEPIN	PROTHIADEN	ING	NK T	NK	MAYBE	CONVULSIONS NS	ON PRESENTATION	
										DILATED PUPILS		
										DRY MOUTH		
										SINUS TACHYCARDIA		
DOTHIEPIN**												
	AC	1	NK	DOTHIEPIN**	PROTHIADEN	ING	1 T	1 H	75MG	CONVULSIONS NS	X3	
	AC	1	M	DOTHIEPIN**	PROTHIADEN	ING	225 MG	7 H		CONVULSIONS NS		
										VENTRICULAR TACHYCARDIA		
FERROUS DRUG SR NK												
	AC	2	NK	FERROUS DRUG SR NK		ING	NK	NK		ACIDOSIS		
										LIVER FAILURE	TRANSPLANT LASTNIGHT	
										REMARKS	SHOCKED EARLIER	
FERROUS SULPHATE												
	AC	2	M	FERROUS SULPHATE		ING	NK	6.75 H	180 IN BOTTLE NOT SR 200MG			IRON LEVEL 390MCMOL/L AT 2H
										COLOURED URINE	DARK	
										COMA NS		
										DIARRHOEA	LOTS	
										HAEMATEMESIS		
										VOMITING	12 TABLETS BACK	
FERROUS SULPHATE*												
	AC	3	F	FERROUS SULPHATE*		ING	70 T	NK		COMA IV		
	AC	3	F	FERROUS SULPHATE*		ING	NK	NK	650MG/KG	COMA NS		
FLECAINIDE												
	AC	1	NK	FLECAINIDE		ING	1 T	NK	500MG/100MG	ECG CHANGES NS	T WAVE INVERSION V1-4 III	
FLUOXETINE												
	AC	2	F	FLUOXETINE	PROZAC	ING	3 C	5.75 H	20MG	ASYMPTOMATIC	NOW	
										HYPERACTIVE	EPISODES SINCE	
										LIVER FAILURE	EPISODES SINCE	

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Appendix 5 Cases of moderate to severe poisoning associated with ingestion of pharmaceuticals reported to the NPIS(L) March 1997-December 2001 excluding multiple ingestions

	circum-stance	ages	gender	agent	type if stated	route	amount	time	agent comment	Clinical feature and comment	case comment
HALOPERIDOL											
	AC	<1	M	HALOPERIDOL		ING	NK	5.5 H		ASYMPTOMATIC CONVULSIONS NS	NOW
	AC	2	F	HALOPERIDOL		ING	15 MG	28 H		CONVULSIONS NS PYREXIA	
	AC	2	NK	HALOPERIDOL		U	NK	NK		COMA NS STIFFNESS	
HYOSCINE HYDROBROMIDE											
	AC	3	M	HYOSCINE HYDROBROMIDE		ING	7 T	8.5 H		ARRHYTHMIAS NS DROWSY ECG CHANGES NS HALLUCINATIONS HYPERTONIA SKIN NS SLURRED SPEECH	 ALL RESOLVED NOW PR INTERVAL PROLONGED ALL RESOLVED NOW ALL RESOLVED NOW NOW ALL RESOLVED NOW
IBUPROFEN											
	AC	1	F	IBUPROFEN		ING	NK	NK	4 LEFT IN BOTTLE	COMA NS CONVULSIONS NS PUPILS CONSTRICTED	
	AC	2	M	IBUPROFEN	BRUFEN	ING	NK	36 H		CONVULSIONS NS VOMITING	FEBRILE? TONIGHT AT TIME
	AC	2	F	IBUPROFEN	BRUFEN	ING	5 T	30 M	400MG	COLLAPSE CONVULSIONS NS	
IBUPROFEN*											
	AC	1	M	IBUPROFEN*		ING	20 T	8 H		ASYMPTOMATIC COMA NS	PUPIL
	AC	1	M	IBUPROFEN*		ING	20 T	NK	400MG	ACIDOSIS COMA NS	MILK FOR 10 HRS
IMIPRAMINE											
	AC	2	F	IMIPRAMINE		ING	16 T	14.5 H	25MG	CONVULSIONS NS SUPRAVENTRICULAR TACHYCARDIA	

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Appendix 5 Cases of moderate to severe poisoning associated with ingestion of pharmaceuticals reported to the NPIS(L) March 1997-December 2001 excluding multiple ingestions

	circum-stance	ages	gender	agent	type If stated	route	amount	time	agent comment	Clinical feature and comment		case comment
IMIPRAMINE*												
	AC	1	NK	IMIPRAMINE*		ING	NK	NK		AGITATION COMA NS CONVULSIONS NS HYPOTENSION PYREXIA SINUS TACHYCARDIA 250		
	AC	2	M	IMIPRAMINE*		ING	NK T	42 H		CONVULSIONS NS VENTRICULAR TACHYCARDIA		
IRON (DRUG) NK												
	AC	4	M	IRON (DRUG) NK		ING	NK	NK M		CLINICAL EFFECTS OTHER COMA NS VOMITING	FRESH BLOOD COMING UP GASTRIC TUBE LOST CONSCIOUSNESS ++	PARENTS HAVE NO IRON IN THE HOUSE. ONLY MULTIVITAMIN + IRON PREPS. SEEMS UNLIKELY THAT CHILD COULD HAVE INGESTED ENOUGH TABLET
KARVOL												
	AC	1	F	KARVOL		ING/EYI	2 DROP	2 H		APNOEA EYE NS	FOR A FEW MINUTES	
MEFENAMIC ACID												
	AC	2	M	MEFENAMIC ACID		ING	3 G	36 H		CONVULSIONS NS		
METHADONE												
	AC	1	F	METHADONE		ING	NK	NK		COMA NS COMA NS		
	AC	1	F	METHADONE		ING	NK	5 H		HALLUCINATIONS RESPIRATORY ARREST		
	AC	3	M	METHADONE		ING	35 MG	2 D		BRAIN DEATH DEATH		WAS ON IV INFUSION OF NARCAN. NARCAN STOPPED CHILD WELL - WENT TO BED 6HR LATER 5.5 - 6HR LATER NURSE DID HID OBS AND HAD RESPI
	AC	3	M	METHADONE		ING	30 MG	NK		COMA NS DROWSY	UNCONSCIOUS O/A - RESPONDED TO NALOXONE AGAIN	
	AC	1	F	METHADONE		ING	NK T	NK		ASYMPTOMATIC RESPIRATORY ARREST	NOW, AFTER NAL	
METHOCARBAMOL												
	AC	1	M	METHOCARBAMOL		ING	NK T	30 M		CONVULSIONS NS HYPOTONIA	QUERY FIT	

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	circum-stance	ages	gender	agent	type if stated	route	amount	time	agent comment	Clinical feature and comment		case comment
METHYLDOPA	U	3	F	METHYLDOPA		ING	2.5 T	1.5 H	250MG	COMA NS	EARLIER - OK NOW	
METOCLOPRAMIDE	AC	<1	F	METOCLOPRAMIDE	PRIMPERAN	ING	5 MG	2 H		CONVULSIONS NS		EPS, NOT A FIT?
OLANZAPINE	AC	<1	M	OLANZAPINE		ING	10 MG	1 H		COMA NS	'FLAT'	
OPIATE NK	AC	<1	F	OPIATE NK		U	NK	NK	BEEN WITH THEM 1 1/2 - 2HRS	COMA NS HYPOVENTILATION PUPILS CONSTRICTED	UNREPONSIVE	
	U	<1	M	OPIATE NK		ING	NK	NK	? METHADONE (MOTHER ON METHADONE)	COMA NS PUPILS CONSTRICTED	NON ROUSABLE AGAIN	
ORPHENADRINE	AC	2	M	ORPHENADRINE		ING	2 G	2 H		VENTRICULAR TACHYCARDIA		
OXYBUTYNIN	AC	1	F	OXYBUTYNIN		ING	16 T	NK		COMA NS REMARKS	SEMI CONSCIOUS FLOPPY	
PAROXETINE	AC	2	M	PAROXETINE	SEROXAT	ING	2 T	1 H	20MG	VENTRICULAR ECTOPICS BEATS		
PHENOBARBITONE	AC	2	M	PHENOBARBITONE		ING	NK	7 H		ATAXIA CONVULSIONS NS DROWSY	GETTING BETTER IN BATH	HE MAY NOT HAVE TAKEN ANYTHING SO CHECK A LEVEL TO CONFIRM
PHENTERMINE	AC	1	F	PHENTERMINE	IONAMIN	ING	4 T	1 D		HYPERACTIVE MYOCARDIAL INFARCTION	LAST NIGHT SUBDUED TODAY	
PHENYTOIN	ATE	<1	F	PHENYTOIN		ING	NK	6 D		CLINICAL EFFECTS OTHER HYPOGLYCAEMIA LIVER FAILURE	ILEUS	
PROPRANOLOL	AC	1	M	PROPRANOLOL	INDERAL LA	ING	320 MG	1.5 H		COMA NS		

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	circum-stance	ages	gender	agent	type if stated	route	amount	time	agent comment	Clinical feature and comment	case comment
RISPERIDONE											
	AC	4	M	RISPERIDONE		ING	NK	NK		ABDOMINAL PAIN	INITIAL COMPLAINT
										COMA NS	
										HYPERTENSION	
										SINUS TACHYCARDIA	
	AC	3	M	RISPERIDONE		ING	2 T	NK	2MG		
										COMA IV	NO RESPONSE TO PAIN/VERBAL
										MUSCLE SPASM	GENERALISED
										PYREXIA	AT FIRST, OK NOW
										RIGIDITY	MUSCLE
SODIUM FLUORIDE (DRUG)											
	U	2	NK	(DRUG)		ING	NK	1 H	7.8MG/KG	CARDIAC NS	SMALL PAUSE ON ECG
SODIUM VALPROATE											
	U	1	M	SODIUM VALPROATE		ING	NK	3 D			
										ACIDOSIS	
										COLLAPSE	
										HAEMATURIA	
										HEPATIC NS	
										HYPERNATRAEMIA	
										HYPOTENSION	
										PERIPHERAL VASOCONSTRICTION	
										RENAL NS	DYSFUNCTION
										RESPIRATORY ARREST	
										THROMBOCYTOPAENIA	SHOCK
SULPIRIDE											
	AC	<1	M	SULPIRIDE		ING	NK	NK		COMA NS	SEDATED
TEMAZEPAM											
	AC	4	M	TEMAZEPAM		ING	NK T	1.5 H	20MG	COMA NS	
	AC	2	F	TEMAZEPAM		ING	NK T	NK	10MG	COMA NS	
	AC	2	M	TEMAZEPAM		ING	120 MG	30 H		COMA NS	
	AC	1	M	TEMAZEPAM		ING	20 MG	NK		COMA NS	ONLY RESPONDING TO PAIN
	AC	2	M	TEMAZEPAM		ING	NK	3.5 H		DROWSY	
										RESPIRATORY ARREST	
	AC	3	M	TEMAZEPAM		ING	70 MG	1.5 H		COMA NS	
	AC	2	M	TEMAZEPAM		ING	2 T	1 H	20MG	DEATH	
	AC	3	NK	TEMAZEPAM		ING	9 T	9 H	10MG	COMA NS	NOW IN LAST HOUR
										DROWSY	EARLIER
	AC	1	M	TEMAZEPAM		ING	NK	2.5 H	20MG		WAS FLAT EARLIER BUT WOKE
										COMA NS	UP AND IS DISTROUGHT

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Appendix 5 Cases of moderate to severe poisoning associated with ingestion of pharmaceuticals reported to the NPIS(L) March 1997-December 2001 excluding multiple ingestions

	circum-stance	ages	gender	agent	type if stated	route	amount	time	agent comment	Clinical feature and comment		case comment
	AC	3	M	TEMAZEPAM		ING	NK T	2 H		CONVULSIONS TETANIC DROWSY		
THEOPHYLLINE NK												
	ATE	0	M	THEOPHYLLINE NK		ING	NK	NK	45MG TDS (60MG/KG/D)	IRRITABLE SUPRAVENTRICULAR TACHYCARDIA VOMITING	RESISTANT TO ADENOSINE	
THIORIDAZINE*												
	AC	1	F	THIORIDAZINE*		ING	150 MG	4 H		AGITATION BUNDLE BRANCH BLOCK DROWSY SINUS TACHYCARDIA VOMITING	RIGHT 220	
	AC	1	F	THIORIDAZINE*		ING	150 MG	3 H		BUNDLE BRANCH BLOCK SINUS TACHYCARDIA		
TIAGABINE												
	AC	1	F	TIAGABINE		ING	1 T	6 H	20MG	COMA NS CONVULSIONS TONIC/CLONIC	X3. RESOLVED SPONTANEOUS	
TRICYCLIC ANTIDEPRESSANT NK												
	AC	1	NK	TRICYCLIC ANTIDEPRESSANT NK		ING	NK	4 D		BRAIN DEATH		0.5MG/L LEVEL TODAY D/W DR VOLANS. >THAN 0.3MG/L THERAPEUTIC LEVEL CANNOT DECLARE BRAIN DEATH UNTIL <TOP END OF THERAPEUTIC
	AC	1	M	TRICYCLIC ANTIDEPRESSANT NK		ING	6 T	30 M	75MG	CONVULSIONS NS SINUS TACHYCARDIA		
TRIFLUOPERAZINE												
	AC	<1	M	TRIFLUOPERAZINE	STELAZINE	ING	NK	1 H		CONVULSIONS NS		

GLOSSARY

Circumstance	AC = accidental childhood ingestion ATE= accidental therapeutic erro; U = unknown
Age	Given in years
Sex	F= female; M= male; NK = not known
Agent	* after agent name shows calls about the same patient ** after agent name shows calls probably about the same patient
Route	ING = ingestion; EYE = eye
Amount	C=capsule; T= Tablet; MG = milligrams; NK = not known
Time	Time since exposure; M= minutes; H= hours; D= Days; NK = not known
Additional information	usually refers to tablet strength
clinical features and comments	NS= type not stated

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Drug	Dose	Age/sex	Details
1988 Annual Report (Litovitz et al., 1989)			
Aspirin	30 chewable tablets 80 mg (600 mg/kg)	3 y/F	Only 4.3 kg, had Blackfan Diamond disease (congenital hypoplastic anaemia) and Hirschsprung's disease. Tablets given by older sibling. Tachypnoea, acidosis, hypotension, pulmonary oedema, cardiomegaly, respiratory failure 12 days later. Concentrations 102 mg/dl (6 h), 97 mg/dl (9 h), 37 mg/dl (20 h).
Amitriptyline	NK	5 y/M	Had cerebral palsy. Found in cardiopulmonary arrest the morning after being found playing with tablets. PM concentration 1.15 mg/L (nortriptyline 0.79 mg/L). Death attributed to overdose and *Staphylococcus aureus* pneumonia.
Desipramine	about 500 mg tablets	15 m/M	Unreponsive with hypotension. Died on second hospital day. Concentration 2.56 mg/L.
Diphenhydramine	NK capsules	15 m/M	Repeated convulsions, died on 8th hospital day, no EEG activity. Concentration 9.8 mg/L (3 h).
Iron	NK 300 mg ferrous sulphate tablets	15 m/F	Within 30 minutes vomiting, lethargy, hypotension. Serum iron concentration 215 mcmol/L. Nine tablets in stomach seen on X ray after gastric lavage. Cyanosis, fixed dilated pupils, bradycardia, coagulopathy, acidosis and dysrhythmias. Died the day after admission.
Iron	NK prenatal tablets	17 m/M	Vomiting. Concentration 4480 mcmol/L (6 h haemolysed), 788 mcmol/L (12 h). Acidosis, coagulopathy, oedema, anuria, massive bowel necrosis. Died on 4th hospital day. Tablets belonged to a guest.
Iron	NK prenatal ferrous sulphate 325 mg tablets	17 m/M	Vomiting, lethargy, hypotension, hypothermia, acidosis, 40-50 tablets seen on X-ray and removed by gastric lavage. Concentration 251 mcmol/L. Improved over 24 h but developed liver damage, coma, pulmonary oedema, shock, bowel necrosis. Iron tablets found in bowel at PM.
Paracetamol	NS, adult preparation	5 y/NS	NS. Concentration 215 mcg/ml. Circumstance intentional misuse.
Verapamil	NK	4 y/M	Convulsion morning after been found with grandmother's drugs. Cardiac arrest in ambulance. Pronounced brain dead 6 hours after convulsions. PM concentration 2.02 mg/L cerebral oedema and erosive oesophagitis. Premortem toxicology screen found an unidentified phenothiazine.
Aspirin	NS	3 y/NS	PM concentration 66 mg/dl. Circumstance unknown.
1989 Annual report (Litovitz et al., 1990)			
Methadone	10 mg	5 y/F	Mother's medication. Given to 'help her stop coughing'. Found 5 hours later cyanotic, hypothermic and unresponsive. Resuscitation unsuccessful.
Carbamazepine	27 chewable tablets 100 mg, 2.7 g	2.5 y/F	Coma, respiratory depression, convulsions, arrhythmias, ileus, hypotension, arrested. Died 2 days post-ingestion. Initial concentration 59 mg/L, then 109 mg/L (6 h). PM: aspiration pneumonia, renal congestion and hepatomegaly.
Desipramine	NK	18 m/F	Convulsion, cardiac arrest, acidosis. Serum tricyclic concentration 1.38 mg/L; screen also positive for methamphetamine. Unresponsive, tachycardia, increased cranial pressure, hyperventilation. Life support withdrawn 4 days post-ingestion. Coroner confirmed despiramine overdose as cause of death.
Desipramine	12-16 50mg tablets 600-800 mg	20 m/M	Convulsion, tachycardia, no blood pressure, cardiac arrest. Concentration 1.6 mg/L (2 h).
Verapamil SR	6-10 tablets 240 mg 1.44-2.4g plus 2-4 capsules of cold preparation	4 y/M	Drowsy 4-5 hours later, then cyanosis and asystole. Unresponsive, hypothermia and no EEG activity, cardiac arrest 24 hours after admission. Verapamil concentration 0.07 mg/L, then 0.054 mg/L (13-14 h). Paracetamol 8.7 mg/L.

Drug	Dose	Age/sex	Details
	(paracetamol, chlorpheniramine, pseudoephedrine and dextromethorphan)		
Diphenhydramine	NS	5 m/NS	PM concentration 2.2 mg/L.
Diphenhydramine	NS	21 m/NS	PM concentration 1.3 mg/L.
Propoxyphene	NS	20 m/NS	Not stated
Iron	10 or more ferrous sulphate 325 mg >3.25g	15 m/M	Numerous tablets seen on x-ray. Serum iron 141 mcmol/L, 52 mcmol/L. Convulsions 10 h post-ingestion, hypernatramia (187 mmol/L) and alkalosis following sodium bicarbonate. Tablets still visible in gut, 8 removed by endoscopy. CT scan showed cerebral dehydration and haemorrhage. Serum iron 117 mcg/dl. CT scan at 48 h showed cerebral swelling with no blood flow. Died 56 hours post-ingestion.
Diphenoxylate/ atropine	13 tablets	14 m/F	Dyspnoea by 11 h and acidosis. Improving until 2 days post-ingestion then apnoea with fixed dilated pupils. CT scan showed changes consistent with cerebral infarct or cerebral oedema, hypotension, bradycardia and asystole.
1990 Annual report (Litovitz et al., 1991)			
Despiramine	5-6 100 mg tablets 500-600mg	10 m/F	Drowsy, tachycardia, arrhythmias, acidosis. Died 2.5 hours post-ingestion.
Diphenhydramine	NK 25 mg capsules	11 m/F	Convulsions, bradycardia. Life support withdrawn. Died 3 days post-ingestion.
Iron	NK ferrous sulphate	10 m/F	Refractory hypotension, respiratory distress, coagulopathy and bradycardia. Serum iron 18,930 mcg/dl.
Iron	NK ferrous sulphate	11 m/F	Lots of tablets seen on x-ray at 2 h. Serum iron 1792 mcmol/L and 2509 mcmol/L.
Iron	NK ferrous sulphate	14 m/M	Serum iron 1792 mcmol/L (2 h), 1434 mcmol/L (4 h). Acidosis, drowsy. Respiratory distress syndrome 1 week later, liver damage. Arrested 3 weeks after admission, died 53 days post-ingestion.
Iron	NK	15 m/M	Ingestion possibly 10 h before presentation. Haematemesis, coagulopathy. Tablets seen on x-ray. Serum iron 69 mcmol/L. Gastric bleeding, oliguria, jaundice, respiratory distress, hepatomegaly and encephalopathy. Cardiac failure and died 1 week after ingestion.
Iron	up to 30 325 mg tablets 1.05g	16 m/F	Hypotension. Lots of tablets retrieved by lavage, after 2nd lavage no tablets seen on x-ray. Serum iron 1523 mcmol/L (3 h). Coagulopathy, liver damage, respiratory distress, severe acidosis, refractory hypotension. Died on 4th hospital day. PM: haemorrhagic gastritis and hepatomegaly.
1991 Annual report (Litovitz et al., 1992)			
Propoxyphene	NK	19 m/M	Respiratory distress after 3.5 h, cardiopulmonary arrest. Concentration 1.3 mg/L (norpropoxyphene 6.8 mg/L). Died about 7.5 h after arrival.
Despiramine	possibly 1 x 50 mg tablet	2 y/M	Ataxia at 1 h, convulsions and cardiorespiratory arrest at 72 minutes.
Nifedipine	NK	18 m/F	Hypotension, no cardiac output, dysrhythmias. Concentration on arrival 0.59 mg/L, at PM 0.27 mg/L.
Iron	NK 325 mg tablets	9 m/F	Lethargy, Serum iron 604 mcmol/L (5 h), 187 mcmol/L (11 h), 54 mcmol/L (18 h). Small bowel obstruction and necrosis at 5 days. Respiratory distress and pneumomediastinum at 8 days. Died on 33rd hospital day.
Iron	35-40 325mg tablets 11.38-13g	1 y/M	Lethargy, vomiting, multiple tablets seen on x-ray. Serum iron 721 mcmol/L (3 h). Neurological and cardiovascular status deteriorated, anuria. Died 18 h post-ingestion.

Drug	Dose	Age/sex	Details
Iron	NK 325 mg ferrous sulphate tablets	14 m/M	Lethargy, hypothermic, acidosis. Pneumothorax and pneumomediastinum at 60 h, refractory hypotension. Serum iron 374 mcmol/L (1-2 h)
Iron	about 40 x 325 mg 13g	18 m/F	Unresponsive, hypotension, acidosis, 32 tablets seen on x ray in small intestine. Serum iron 295 mcmol/L, 37 mcmol/L. Haematuria, liver damage, coagulopathy, GI bleeding and renal failure. Died on second hospital day.
Iron	90 tablets ferrous sulphate	2 y/M	Shock, GI bleeding, acidosis, Serum iron 2509 mcmol/L, 32 mcmol/L (6 h). Multiple organ failure, died on 6th hospital day.
Iron	about 35 ferrous sulphate tablets	2 y/M	Acidosis, drowsy, bezoar seen on x-ray, aspiration pneumonia. Serum iron 1138 mcmol/L. Multiple organ failure and cardiac arrest.
Iron	30 ferrous sulphate tablets 136 mg/kg elemental iron	3 y/M	Coma, respiratory depression, acidosis, liver failure, coagulopathy, hypotension, cardiac arrest, died 29 h post-ingestions. Serum iron >1792 mcmol/L (4 h), 3721 mcmol/L (6 h). PM: GI haemorrhage, haemorrhagic pulmonary and cerebral oedema.
Iron	NK ferrous sulphate tablets	3 y/M	Lethargy, sudden onset hypotension at 15.5 h with cardiac arrest. Serum iron 68 mcmol/L (3 h), 36 mcmol/L (5.5 h).
Iron	1 bottle of prenatal vitamin and iron	17 m/M	No blood pressure, anuria, a 10 cm bezoar seen on x-ray (removed by endoscopy), shock, renal and hepatic failure and coagulopathy. Serum iron 3180 mcmol/L. Respiratory distress syndrome, fulminant liver failure. Died on 69th hospital day.
Iron	NK prenatal vitamin and iron (65 mg elemental iron)	18 m/F	Vomiting, acidosis, ascites, coagulopathy. Serum iron >179 mcmol/L (4.5 h), 41 mcmol/L. Respiratory distress syndrome and died on 5th hospital day.
1992 Annual report (Litovitz et al., 1993)			
Carbamazepine	NK tablets, her own medication	2 y/F	Irritable, drowsy,status epilepticus, pyrexia, brain death. Concentration on admission 38.8 mg/L (had been 1.8 mg/L before overdose).
Amitriptyline	NK	9 m/F	Coma, convulsions, respiratory distress, asystole, Concentration 1,800 ng/ml (3.5 h), 5,500 ng/ml (4 h, noramitripyline 0.8 mg/L), PM 10.8 mg/L amitriptyline; 1.8 mg/L. Gastric contents 253 mg amitriptyline. Mother claimed to have given 50 mg 'to get her to sleep'.
Diphenydramine	NK	3 y/F	Convulsions and tachycardia. Concentration 2.5 mg/L. Mother gave for night-time sedation. Heart block at 48 h and bradycardia, aspiration, pulmonary oedema died 5 weeks later.
Theophylline SR	NK	4 y/F	Refractory convulsions, died 6 days later. Concentration 262 mg/L, 162 mg/L.
Nifedipine	about 4 x 10 mg capsules 40mg	11 m/M	Flushed, sweating, bradycardia, cardiopulmonary arrest, hypotension, acidosis, convulsions. Died on second hospital day.
Iron	NK	1 y/M	Vomiting, cardiac arrest, GI bleeding, respiratory and cardiac arrest. Died 26 h post-ingestion. Serum iron 279 mcmol/L (30 m), 896 mcmol/L (11 h).
Iron	35 tablets 210 mg/kg elemental iron	19 m/M	Hypotension, acidosis, died 7 hours post-ingestion. Serum iron 1075 mcmol/L (1 h), 3405 mcmol/L (3 h), 1165 mcmol/L (5 h).

Drug	Dose	Age/sex	Details
Iron	30 prenatal vitamins with iron (300 mg ferrous sulphate) 9g	15 m/M	Lethargy, acidosis, GI bleeding, coagulopathy, hypotension, respiratory distress, bradycardia, asystole. Died on 6th hospital day. Serum iron 896 mcmol/L. PM: Extensive hemorrhage of gastric mucosa, iron concentration 118 mcmol/L.
Iron	NK prenatal vitamins with iron	16 m/M	Lethargy, haematemesis, acidosis. Serum iron 215 mcmol/L. Died on 3rd hospital day. PM: evidence of respiratory distress syndrome, coagulation, ascites.
Iron	50 prenatal vitamins with iron 325 mg	16.25g	Lethargy, haematemesis, 30-50 tablets seen on x-ray Serum iron 258 mcmol/L, 6 mcmol/L (24 h). Pneumomediastinum, pnemothorax, hypertension, oliguria, acidosis, bradycardia, asystole. PM: hepatomegaly, pnemonia.
Iron	90 prenatal vitamins with iron (60-64 mg)	21 m/F	Lethargy, 10-20 tablets in stomach and 30 in bowel on x-ray at 3 h, vomiting, drowsy, acidosis, bradycardia, hypotension, cardiac arrest, died 47 h post-ingestion. Serum iron 333 mcmol/L (6.5 h).
Codeine	NS	1 m/NS	PM concentration 0.34 mg/L, morphine 0.04 mg/L.
Chloral hydrate	10 ml (prescribed as 250 mg/5 ml)	3 y/F	Apnoea and asystole within 45 minutes, acidosis. Resuscitation unsuccessful. Given by mother as premedicant.
1993 Annual report (Litovitz et al., 1994)			
Amoxapine	NS	17 m/NS	Not stated.
Desipramine	NS	20 m/NS	Not stated.
Desipramine	NS	2 y /NS	PM concentration 8.0 mg/L.
Flecainide	NS	9 m/NS	Acute on chronic, PM concentration 21.3 mg/L.
Iron	NS	20 m/NS	Serum iron 194 mcmol/L.
Iron	NS	11 m/NS	Serum iron 5466 mcmol/L (6 h).
Chloral hydrate	NS	5 y/NS	Not stated.
1994 Annual report (Litovitz et al., 1995)			
Diphenhydramine	NK	16 m/M	Convulsions within 15 m, cardiopulmonary arrest.
Diphenhydramine	NS	18 m/NS	Concentration 13.7 mg/L.
Nifedipine	about 20 tablets	14 m/F	Ataxia, tachycardia, hypotension, convulsions, pulmonary oedema and bradycardia. Died within 12 hours.
Iron	1 bottle of ferrous sulphate tablets	18 m/M	Haematemesis, treatment refused by family, died on way to hospital 9 h post-ingestion.
Iron	NK	1 y/F	Lethargy, haematemesis, tachycardia, acidosis, 45 tablets seen on x-ray, 32 removed by endoscopy, hypotension, bowel obstruction. Died 66 h post-ingestion. Serum iron 174 mcmol/L.
Clozapine	NK 100 mg tablets	2 y/F	Ataxia, apnoea, aspiration, anaemia, respiratory distress, cardiac arrest.
Doxepin	NS	5 y/NS	Not stated.
Nortriptyline	NS	5 y/NS	Concentration 558 ng/ml.
Imipramine	NS	5 m/NS	Concentration 0.41 mg/L, desipramine 0.042 mg/L.
Methadone	NS	4 y/NS	Not stated.
1995 Annual report (Litovitz et al., 1996)			

Drug	Dose	Age/sex	Details
Aspirin	NK 325 mg tablets	2 y/F	Tachypnoea, vomiting, convulsions, coma, cerebral oedema and intracranial haemorrhage day 5. Concentration 109 mg/dl (6 h).
Methadone	NK elixir	19 m/M	Coma, cardiac arrest. PM concentration 0.5 mg/L. Mother and partner on methadone.
Methadone	NK	2 y/M	Bizarre movements, apnoea, dead on arrival about 12 h post-ingestion. Uncle's medication fed by sibling.
Desipramine	NK	1 y/F	Respiratory arrest, bradycardia, acidosis, died 3 h post-ingestion.
Despiramine	2-3 100 mg tablets on top of normal 100 mg dose 400 mg	3 y/M	Refractory convulsions, tachycardia, brain death 47 h post-ingestion. Concentration 1.47 mg/L (on arrival), 0.22 mg/L (antemortem). PM: cerebral oedema, bronchopneumonia.
Iron	96 ferrous sulphate tablets (549 mg/kg elemental iron)	22 m/M	Drowsy, acidosis, coagulopathy, respiratory distress, multiple organ failure. Died on 2nd hospital day. Serum iron 9 mcmol/L (on admission), 463 mcmol/L (6.5 h)
Iron	NK prenatal vitamins with iron	1 y/M	Presented 12-14 h post-ingestion. Only 1 tablet seen on x-ray. Hypotension, coma, DIC, died 11 h after arrival. Serum iron 1057 mcmol/L, 1075 mcmol/L, 1062 mcmol/L.
1996 Annual report (Litovitz et al., 1997)			
Imipramine	possibly ½ a tablet	16 m/F	Drowsy, bradycardia during charcoal administration then systole. Imipramine not detected on toxicology screen.
Morphine	NS	2 y/NS	PM concentration 0.15 mcg/ml.
Valproic acid	NS	1 y/NS	Concentration 1,296 mg/L.
Amitriptyline	NS	3 y/NS	Not stated.
Nifedipine	up to 60 x 20 SR tablets 1.26g	2 y/M	Vomiting within 3 h. Rapid deterioration.
Iron	Prenatal iron	16 m/NS	Not stated.
Iron	Prenatal iron	17 m/NS	Not stated.
1997 Annual report (Litovitz et al., 1998)			
Methadone	up to 12 ml (120 mg)	2 y/M	Cyanosis and coma within 1 h, cerebral oedema and multiple infarcts. Died 3 days post-ingestion.
Carbamazepine	33 x 200 mg tablets 6.6g	5 y/M	Coma by 4 h, lethargy, ileus, hypotension, respiratory distress and cardiac arrest. Concentration 44 mg/L (on arrival).
Iron	NK Ferrous sulphate	16 m/M	Tachypnoea, cyanosis, shock, tachycardia, tablets seen on x-ray, coagulopathy, hypotension, GI bleeding. Died the day after ingestion. Serum iron 2150 mcmol/L.
1998 Annual report (Litovitz et al., 1999)			
Propranolol SR	?80mg	2 y	Coma, convulsions, hypoglycaemia, tachycardia and cerebral oedema. Died 2.5 days later. Concentration <100 mg/L, C-peptide analysis 'inconclusive'.
Phenylbutazone	NK	2 y	Hypotension, convulsions, coagulopathy, acidosis, cardiac arrest 3 days later.

Drug	Dose	Age/sex	Details
Desipramine	1-1.25g	2 y	Apnoea and unresponsive on way to hospital. Asystolic and resuscitation unsuccessful. PM concentration 3.9 mg/L.
Doxepin	NS	3 y	Not stated.
1999 Annual report (Litovitz et al., 2000)			
Methadone	NK	5 m/F	Presented in respiratory arrest. Intentional poisoning in infant formula (concentration 21 mcg/ml). Methadone concentrations 0.3 mg/L (heart blood), 1.4 mg/kg (liver).
Clonidine	NK	23 m/F	Drowsy, agitation, severe bradycardia, unable to resuscitate. PM blood concentration 46 mcg/L.
Theophylline SR	NK	3 y/M	Presented in status epilepticus. Blood concentration 114 mg/L (post-dialysis 23 mcg/ml). Died 60 h post-presentation. PM: cerebral herniation and necrosis.
Nifedipine SR	NK	20 m/M	Grandmother's medication and may have ingested other cardiac drugs. Tablets found in throat on intubation, died shortly after arrival. Concentration 0.56 mg/L (blood), 3.99 mg/L (gastric contents).
Iron	NK	14m/M	GI bleeding, DIC, died 16 hours post-ingestion. Serum iron 2727 mcmol/L.
2000 Annual Report (Litovitz et al., 2001)			
Methadone	NK	22 m/M	Apnoea, died several days after admission. Antemortem concentration 0.1mg/L. Grandfather on methadone.
Methadone	NK	8 m/F	Found dead. PM concentration 0.23 mg/L. Both parents on methadone.
Amitriptyline	NK	2 m/F	Malnourished and dehydrated. Given 'adult doses' to make her sleep.
Diphenhydramine	62.5 mg	2 m/M	Cardiorespiratory arrest. PM concentration 1.6 mg/L (heart blood), 0.7 mg/L (vitreous humour). Given by father.

DIC: dissemination intravascular coagulation, EEG: electroencephalograph, GI gastrointestinal, SR: sustained release; m: months; y: years; h: hours; PM: post-mortem; NK: not known; NS: not stated

Guy's and St Thomas' Hospital NHS
NHS Trust

Guidelines for determining and predicting toxic doses of pharmaceuticals for children

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Contents

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1. Introduction

Part 1 of this Report identified pharmaceuticals reported to have caused severe accidental poisoning in children up to 5 years of age, using information from the UK Home Accident surveillance System (HASS), official mortality data from Office for National Statistics (ONS), information from the National Poisons Information Service (London) enquiry database [NPIS(L)] and files of case histories, and reports from the published literature. The Review also assessed toxicity of twelve selected pharmaceuticals and one class of pharmaceuticals using data from the NPIS(L) case files and the literature and found that the majority of them were reported to have caused severe poisoning in amounts fewer than 8 dose units.

The results demonstrated the validity of using data from these sources to assess toxicity, and the validity of using poison centre data for detecting severe outcomes and providing evidence of dose related toxicity. It is proposed that these sources could be used in decisions on which pharmaceuticals should be selected as priority candidates for the most effective child resistant packaging.

However, even for well-established drugs, case reports are limited in their ability to provide information on toxic doses. Also this approach may not identify all the pharmaceuticals in current use that represent such risks, because it looks only at medications actually taken by accident, and it certainly is of no use when a drug first becomes available for predicting the risk to children.

The second part of the Report looks at the best methods of predicting toxic doses in under-5 year olds. Sources of data are evaluated, and a method for using the data is proposed, with a route to be followed to ensure that data is reviewed in the right order and assessed in the correct way.

2. *Considerations*

In this next section it is important to define the facts linking medication and young children and in doing so discuss the main pharmacokinetic and pharmacodynamic features which separate this sub-group of the population from the adult population. The importance of this cannot be over emphasised since a vast majority of medications are brought to the market with little or no data in paediatrics and officially only intended for adult consumption. Thus therapeutic doses, let alone toxic doses are ill defined and often have little evidence base. It is also important to define how in the presence of few or no specific clinical studies it is often necessary to "predict" a child's dose. These methods are open to many inaccuracies, but some sort of prediction is perhaps better than none.

Along side the different drug handling of the child it is important to consider if it is possible to define the "average" child in the age group under 5 years and thus treat this small sub-set of the general population as a group despite huge variations (e.g. weight range 0.5kg – 25kg). As well as these huge variations there are other varying factors such as abnormal-for-age problems in renal or hepatic function, and genetic variations.

A short reference will be made to the potential problems of excipients, to ensure that it is always remembered that a medication is not just the perceived active drug, but is often a group of compounds or salts which may have a biological action in their own right.

2.1 Drug Handling in Neonates, Infants and Children

Prediction of the toxic dose in young children must be based on a sound understanding of the main pharmacokinetic and pharmacodynamic features that separate this sub-group of the population from the adult population. The usefulness of scaling down assumptions about toxic doses from adults to children is limited, because of the physiological differences between them and the resulting differences in drug pharmacokinetics.

The differences are most significant for children under 6 months old, which vary considerably in their renal function and metabolic processes, to the extent that we have excluded them from consideration in this guidance. A more detailed account of the main differences in paediatric pharmacokinetics is given in Appendix 1.There may also be differences in the response at the receptor site, which affect any determination of the toxic dose by extrapolation from adult data.

2.2 Paediatric Studies

Since toxic doses may have to be predicted from paediatric therapeutic data, it is important to understand how therapeutic doses are determined for young children.

Ideally every drug would have dose / plasma level charts plotted for them with therapeutic effectiveness and toxicity aligned with them. However pharmacokinetic and pharmacodynamic data are seldom available for children because most medications are officially only intended for adult consumption and have not undergone specific pre-marketing clinical studies in children. Data on therapeutic doses for children are often anecdotal case reports or very small population studies, especially for new drugs, which are usually only studied in adult populations. This makes it of poor scientific merit. Thus therapeutic doses are ill defined and often have little evidence base.[1]

Part of the reasons for this dearth of information for paediatric patients are the stringent regulations put in place in 1962 following the thalidomide tragedy that had the effect of discouraging research in paediatrics. The legislation surrounding drugs trials also currently discourages trials in children, although in recent years there has been a call for more studies in children.[2]

2.3. Estimating Paediatric Doses from Adult Data

The first approach to estimating a paediatric toxic dose is to extrapolate from an adult dose. This practice is often clinically successful for estimating a therapeutic dose. Numerous methods of predicting paediatric dosing scaling down adult doses have been developed over the years based on age, weight, height and surface area (see Appendix 2). Despite these methods becoming common practice there is little scientific evidence to back them up. These practices are generally acceptable for drugs with low toxicity and wide therapeutic ranges. For drugs with narrow therapeutic windows much more data is required from well-conducted pharmacokinetic studies and generally there is more information on these drugs.[3]

2.4 Formulation Factors

A medication includes not only the perceived active drug, but often a group of compounds or salts which may also have a biological action. Formulation factors that need to be taken into account when looking at medication consumption and assessing possible toxicity, include ingredients used to increase stability, enhance taste, or improve bioavailability, that may contribute to toxicity (See Appendix 3). Fortunately these factors are of minor importance for estimating the toxic dose of solid medications, because they have few additives. Nevertheless, it is important that additional ingredients of pharmaceutical products are easily accessible so that in the case of an accidental ingestion their presence may be taken into account.

2.5 Clinical Modifying Factors

Many factors may influence the drug handling of a child and could alter an individual's response to a given dose. These include genetic variations, such as glucose-6-phosphate dehydrogense (G-6-PD) deficiency, porphyria, differences in speed of acetylation of drugs; weight; clinical conditions such as fever, toxaemia, dehydration, oedema; or renal and hepatic insufficiency. Alongside these are the normal varying factors such as abnormal-for-age problems in renal or hepatic function and the huge variations that exist within this small sub-set of the general population (e.g. weight range 0.5kg – 25kg). However, general guidelines for assessing toxic doses must be based on the "normal" population.

2.6 Age Distribution for Accidental Poisoning

An additional justification for excluding children under 6 months is the lower incidence at this age of unintentional poisoning due to a child itself extracting medication from a container. This is confirmed by data from a survey of enquiries made to the Centre Antipoisons in Lille between 1995-1999, which found that only 2% (960) of enquiries in children under 15 years involved children under 6 months. In 76% of exposures the cause was adult mistake, therapeutic mistake, therapeutic accident, product misuse or indoor air pollution[4]. Similarly the National Poisons Information Service in Edinburgh found that between 1990-1999 only 0.5% (344) of all enquiries made to the centre involved children under 6 months, and a significant proportion of these were due to therapeutic error[5]. Child resistant packaging has a limited role in protecting this age group.

2.7 Summary

We have now established that many factors influence drug toxicity within the under 5 age group and thus to try to ensure reasonable standards when predicting toxicity we must always be cautious. However the greatest clinical variances have been shown in the under-6 month age group. In view of this and the fact that very few accidental ingestions occur in this age group, it is reasonable to restrict the assessment of medication toxicity in the under 5 year age group, to the age range 6 months to 5 years.

It is also worth noting that when reviewing a medication for toxicity, all potentially active components of the medication should be reviewed, including potentially toxic excipients.

3. *Choice of method for predicting toxic doses*

The surface area method and the weight method are the only methods currently used to predict paediatric therapeutic doses from adult doses and that therefore need to be considered as methods for predicting toxic doses.

Surface Area Method

The surface area or percentage method for estimating doses is calculated as follows:

$$\frac{\text{Surface area of child } (m^2)}{1.76m^2} \times 100 = \text{per cent of adult dose}$$

[$1.76m^2$ being the average adult surface area]

Children are often said to tolerate or require larger doses of drugs than adults based on a mg/kg basis and the percentage method helps explain this phenomenon. Body water (total and extracellular) are known to equate better with surface area than body weight[6]. It thus seems appropriate to prescribe drugs by surface area if they are distributed to the extracellular water.

Weight Method

$$\frac{\text{Adult dose (mg)}}{70kg} = \text{mg/kg dose}$$

[70kg being the average adult weight]

This method will give lower doses than the percentage method using surface areas. It is far less accurate in clinical terms and usually inappropriate for accurate therapeutic dosing. However since it gives lower and thus safer estimates of what the toxic dose may be, it is more practical and reasonably cautious to use it for extrapolation of toxic doses.

4. *Defining the toxic dose*

Part One of this report demonstrates the difficulty in determining the toxic dose of a drug in children. There is unfortunately no one source that defines for all drugs the maximum dose a child can swallow without causing serious toxicity. It is possible to identify that a drug has caused severe toxicity at a particular dose, but there are usually other cases of less severe toxicity following ingestion of the same dose. This is for a variety of reasons, many of which have been mentioned already, such as different genetics and estimation of doses ingested.

Furthermore, for new drugs about which there will be very limited (if any) experience of overdose in children or adults, it would be impossible to find data to either determine or corroborate a dose that would cause severe toxicity. It is not possible to relate a toxic dose to a therapeutic dose (e.g. to say that a toxic dose is twice the normal daily dose), as clearly that could be different for some drugs. Therefore to standardize the toxic dose a more practical value is required.

The suggested value is that of the dose below which medical intervention is not required or the No Treatment Dose (NTD) Ingestion of a dose lower than this is unlikely to result in toxicity, but toxicity would be expected at a higher dose. Whether toxicity occurs at a dose a little higher or much higher will differ between drugs, depending on the source of the data used to define this dose (the sources will be discussed in the next section). A benefit of using this as the intervention dose is that it is conservative and therefore likely to allow for most individual differences in tolerance to drugs. Importantly, for new drugs, about which there will be little other suitable information, there is likely to be a suitable proxy measure of this dose: the Maximum Tolerated Dose, determined in phase I clinical trials. In practical terms, if a child ingests the drug at the dose below which medical intervention is not required, attendance at hospital is unlikely to be necessary, reducing distress to the child and his or her family, and saving health service resources.

There may be clinical effects following ingestion of less than the dose, such as vomiting, however they would be expected to be self-limiting, easily self-managed and without sequelae. This dose will be referred to as the NTD (no treatment dose) and can be considered as the dose above which toxicity, categorised with a PSS score of 1 or above, will probably occur.

5. *Sources of information for determining the "No Treatment Dose" - below which medical intervention is not required*

Just as there is no one source of the toxic dose, there is no one source of the NTD, and it has been necessary to produce a flow chart to describe the most appropriate use of available data sources (see p10). Each of the recommended data sources is described below.

For new drugs the most suitable proxy measure is the Maximum Tolerated Dose. In the case of older medications where the Maximum Tolerated Dose is unlikely to have been determined (due to a lack of Phase 1 trials) other sources of information will need to be consulted. These are:

- Poison centre data.
- Published literature.
- Mortality data.

For some drugs suitable information may not be found within those sources, so data regarding structurally and pharmacologically similar drugs should be considered. As a last resort, the single treatment dose could be used as the dose below which medical intervention is required.

5.1 Maximum Tolerated Dose

The term Maximum Tolerated Dose (MTD) is often used in clinical trials to help define the most appropriate therapeutic doses of a new drug[7]. The MTD is the highest dose that is safe to administer to patients and defines the upper limit of the usable dose range for efficacy studies. Dose ranging schedules are applied to assess medication tolerability in Phase 1 trials, in which successive volunteers are exposed to increasing drug doses. In this way an indication of the maximum tolerated dose may be obtained. Clearly, it is important to determine whether the estimated therapeutic dose can be exceeded without mishap. If this dose is not determined, patients may be exposed to unsafe levels of medication or subtherapeutic doses of specific drugs. The upper end of the spectrum is characterised by the build-up of adverse events that may outweigh the benefits to the patient. Towards this end of the spectrum we define the minimum intolerated dose (MID), the dose at which greater than 50% of the patients in a study succumb to limiting adverse events, or a medically unacceptable adverse event. The dose below this is defined as the MTD and can be thought of as the maximum dose having an adverse event profile in the population that is acceptable, based on indication-specific prospective criteria[8].

The MTD tends to be used to describe the maximum dose one is willing to administer again to healthy subjects. For example if there was mild transient nausea in the majority of subjects at 15mg then 10mg would be the MTD. Variability in human drug response and the severity of the adverse effect are taken into account. Hence if the adverse effect is severe (eg tonic-clonic convulsion) even if it only occurs in one subject at a particular dose level, then the dose below this would be used to describe the MTD.

Failure to define the dose-limiting toxicity may lead to significant complications. However there are often separate MTDs for a healthy population versus a target population, and many factors will shift the dose-response curve dramatically such as genetic make up, or renal or hepatic differences. This means that in reality the MTD is a group of numbers rather than one unique number[7]. For the purposes of this report the most appropriate MTD is one in healthy volunteers as determined in Phase 1 trials, since most children are unlikely to have underlying medical conditions.

Pharmacodynamic markers may help in determining the top dose administered to patients in a trial, especially if the MTD is not determined by dose-limiting toxicity. Having established

adequate therapeutic effect there is usually no reason to push doses higher and thus the MTDs are not defined e.g. if the dose response curve reaches a plateau at non-toxic doses.

The MTD is a useful tool but for most drugs will only be available for adults. It will be necessary to extrapolate this dose, as described earlier, to a mg/kg dose for use in paediatrics.

MTD's are only likely to be available for fairly new medication since it is a term that is still finding its place and still being discussed in terms of more structured definitions. Despite these limitations it is a valuable source of data if it has been defined as it relates to actual study data on toxicity.

5.2 European Poisons centres

Poisons Centres (PCs) receive telephone requests for information about the clinical effects and management of inappropriate exposures to substances. Enquiries are received from hospital emergency departments, other health professionals or from members of the public. PCs function as continuous monitoring and surveillance systems and most European PCs have access to large numbers of case records collected over many years.

There are two sources of data: information about the patient and the exposure recorded at the time of the enquiry, and unpublished case reports, usually obtained from enquirers to the telephone service

Enquiry data

Poisons centre enquiries provide agent specific case reports of exposures, including dose-related clinical data, and is useful for detecting exposures to specific agents that have not been detected by other surveillance systems. To define the dose causing serious toxicity in children, assessment should be based on expert review of the validity of each case taking into account:

- The unreliability of data about doses taken unintentionally by children. Inferences about doses not causing toxicity should only be made with caution from a large number of cases, since many asymptomatic children may never have been truly exposed to the amounts reported.

- The person reporting the case. Clinical details reported by a member of the public may not be accurate, however the agent is likely to be identified accurately whoever reported the case, because PCs take some trouble to verify it at the time of the call to ensure that the caller is given appropriate information. Accurate identification may not always extend to a specific product name.

- Whether the calls from health facilities are describing patients who have not yet arrived at hospital, since these will be less reliable.

Enquiry data is not a population-based or a statistically representative sample. The usefulness of the enquiry data depends on the size of the population served by the poisons centre that has provided the data. Centres that serve a limited population may be unable to detect unusual events, such as serious poisonings in children, or be unable to provide enough cases for a valid assessment of toxic dose.

Unpublished case reports

Case reports that are detailed enough to enable a toxicological assessment to be made are a valuable source of information. The follow-up process can obtain details that would not be published in the literature or reported to any other source. Isolated case reports that would not

be of any particular value or interest to a single hospital, particularly if there were only minor clinical effects, can be of value when accumulated by a poisons centre.

US Toxic Exposure Surveillance System (TESS) data
The database includes a very large number of cases from a very large population, so there is potentially more data available on exposure to a specific agent and greater possibility of finding information than from any one poisons centre in Europe, providing the agent is available in US. Deaths submitted to TESS undergo several levels of verification and attempts to integrate clinical information and autopsy findings.

However, pharmaceuticals may be available in quite different formulations in the US compared with Europe, and indications and uses may also differ. These factors would have implications for both the reported incidence and severity of poisoning.

For a more detailed assessment of the value and limitations of poisons centre data for assessment of dose response see Appendix 4.

5.3 Published case reports

Cases reported in the medical literature may be either detailed individual case reports or a series of cases. The report may or may not have been peer reviewed. Well-documented reports are a valuable primary source of information and may be the only source, other than poisons centres, with both clinical and circumstantial information.

Dose response cannot be assessed from isolated cases of unintentional child exposure because of the unreliability of the evidence of dose, but a collection of case reports can provide useful evidence for comparison with data from poisons centres and other sources. Evidence from a case series or a collection of individual case reports is more convincing than a few isolated reports, but a case series may not present the data in a way that it useful for dose response assessment. For example the data for 0-5 year olds may not be presented separately from that for older children. Specific effects may be reported in relation to a range of doses or blood concentrations, rather than to specific doses.

Cases reported in the literature may not accurately reflect human experience, since cases of exposure that did not result in clinical effect are unlikely to be published.

For a more detailed assessment of the value and limitations of poisons centre data for assessment of dose response see Appendix 4.

5.4 Mortality statistics

In most European and other developed countries, registration of deaths is compulsory and there are national systems for collection of mortality data. In most countries, official reporting systems include all poisoning deaths, including those that might not be reported to a poisons centre e.g. deaths occurring outside hospital.

However, there are few child poisoning deaths from pharmaceuticals in Europe, and the data give no clue to the incidence of serious non-fatal poisonings, which are more frequent. The internationally agreed coding used to classify cause of death mostly covers groups of drugs and cannot be used to identify deaths due to specific pharmaceuticals. The Office of National Statistics can provide data for England and Wales that includes names of any drugs mentioned on the coroner's certificate.

Mortality statistics may indicate whether a pharmaceutical has been reported as a cause of death in children, or whether deaths have been reported from products of similar pharmacology or therapeutic class. However, even when one can be confident that mortality

statistics will have registered all deaths, the problems with identifying specific agents must be borne in mind. The doses likely to have caused death will have to be investigated using other data from poisons centres or the literature.

For a more detailed assessment of the value and limitations of mortality statistics for assessment of dose response, data see Appendix 4.

5.5 Structurally and Pharmacologically Related Drugs

Drugs often come from a specific "class", unless they are designed to be completely unique. This is a useful concept where they are structurally and pharmacologically similar (e.g. angiotensin converting enzyme inhibitors). In the absence of specific data on a drug it would be reasonable to use data from other similar drugs to estimate the MTD of the drug being examined. Thus if the MTD is known to be at least 10 times the STD (single treatment dose – see below) for the other members of the group, it would be appropriate to consider the factor the same for the drug being examined.

The importance of being both structurally and pharmacologically similar cannot be over stated, as sometimes there are sub-classes within a class. This is well demonstrated with the calcium channel blockers, which actually comprise three subclasses of different actions and toxicities. This must be taken into account.

5.6 Single Treatment Dose

In the absence of any toxicity data in either adults or paediatrics it is necessary to examine treatment doses to determine the NTD. These are best used from specific paediatric data, but in their absence may need to be extrapolated from adult data as described previously. There are often several doses quoted for a single drug and it is important to define the appropriate dose for predicting the NTD.

A single, normal treatment dose (STD) is defined as the highest single starting dose (for any indication) stated by a valued reference source. A valued reference source will normally be that of the Summary of Product Characteristics (SPC) as submitted from the manufacturer. If there is no such document, then it would be reasonable practice to use a national formulary that defines doses under peer review. For Paediatric Dosing used outside the SPC the referred to text should be *Medicines for Children*[9] or another peer-reviewed paediatric formulary[10].

Thus the STD is a normal starting dose of a drug irrespective of whether the dose thereafter would normally be titrated up or down. It does not include doses that may be given as test doses (such as those given before starting amphotericin). If a drug may be given using a higher loading dose then this is the STD. If a drug is used normally at much higher doses for a specific indication, then this is the STD e.g. metronidazole 2gram dose for Giardiasis.

6. *Guidelines for determining the No Treatment Dose*

The flow chart describes the processes required to determine the dose below which medical intervention is not required (NTD). It is recommended that the flow chart should be used by an expert body, since there are steps within it which require expert evaluation. The first step is to examine the pharmacological and, where known, toxicological actions in order to predict whether acute toxicity is possible from ingestion of an excessive quantity. There are some drugs that would not be expected to produce effects requiring medical intervention following ingestion of even large amounts. An example of this would be prednisolone, which might cause gastric upset that would be self-limiting and with adequate oral fluid intake (easily achievable at home) would not require medical intervention.

If this is the case, then a NTD does not need to be determined, as it is unlikely that toxicity (described as category PSS1 or above) would develop from ingestion of this drug.

Once it has been determined that toxicity is possible, the next step of the flow chart is to see if an MTD has been established in children. At present this is unlikely, given that few studies are carried out in children. However in the future this figure may become more available as pharmaceutical companies will need to carry out more clinical trials in children. If a paediatric MTD is available, then this should be used as the NTD.

If this is not the case, it will be necessary to find the MTD in adults, extrapolate it to a paediatric dose using the mg/kg method described in Section 3 (i.e. divide by 70, unless it is already in mg/kg), and use it as the NTD.

If an adult MTD is not available, it will be necessary to consult the various data sources detailed earlier: poison centre data, published literature, and mortality data. As in Part One, these sources can be used in combination to determine the NTD. Firstly an accepted NTD should be sought. However this may be difficult to find, for reasons already described. If necessary the various data sources should be used in combination, considering the weaknesses and strengths of the data presented, in particular the number of cases available. If sufficient data is not available regarding paediatric ingestions it would be necessary to repeat the process to determine a NTD for adults, and calculate the paediatric NTD.

In determining the NTD an expert panel should bare the following facts in mind along side the usefulness of individual data sources as described in Appendix 4. This list is not supposed to exhaustive or describe in detail the way to proceed as this would constitute describing the total mind set of the evaluating expert. It should however highlight some of the main areas of consideration when reviewing literature and highlight some of the many pitfalls that data may present.

- Have doses been estimated, either in terms of number of tablets, strength of tablets or what was likely to be absorbed? This is often hard for any second party reporting a poisoning incident to relay with accuracy.
- Is the age fully recognised or weight stated; or are terms such as toddler used with various interpretations involved? Cases stating an "Infant" could mean any child between 6 and 20kg.
- Cases without outcomes can be used, but should not be used in isolation as the sole basis of assessment.
- Data from case reports should be in line with what may be expected from previous experience (eg. If a child had taken 100 tablets, could they possibly be asymptomatic?)
- Is there laboratory confirmation to confirm ingestion? This factor may help with confirmation of the first point (above) but figures will vary greatly depending on the time after exposure.

- Is there a possibility of exposure to other toxins which may explain the suggested toxicity? Often poisoning may involve multiple substances.
- Are the side effects quantified? (eg "A racing heart"? – specified heart rate?)
- Were there reports of underlying medical conditions that may have affected medication response?
- At what stage was medical treatment initiated and would this have affected the patients response to the medication. Thus if gastric levage has occurred soon after ingestion, the report is not about the absorption of the reported ingestion.
- Was the report based on enquiry data or follow up data, as data often varies in terms of the time of the report and who is the reporter?
- Is the reporter a reliable source of information (doctor, nurse, patient, parent)?
- Is it possible to judge if the clinical effects were due to medication or treatment; as in the case of vomiting?

In the absence of any reliable case data, it would be pertinent to examine drugs of the same class, taking into consideration the pharmacological and toxicological actions of the drug and comparators. These drugs should be taken through the same processes as above.

The final process, if no other information is available, is to use the STD. Again the paediatric STD should be used if it is available or if not, then the adult STD should be used to calculate a dose suitable for paediatrics.

For established drugs it would be expected that information regarding MTDs would be limited, but that more case reports would be available for drugs that are commonly ingested by children (analgesics, anti-depressants, anti-hypertensives, hypnotics). For newer drugs the adult MTD should be available from Phase I clinical studies. The STD may need to be used for drugs that have been available for many years but which are infrequently ingested by children.

Background paper on prEN 14375: "Child-resistant non-reclosable packaging for medicinal products - Requirements and testing

June 2003

Development of the standard

The draft European standard prEN 14375 entitled "Child-resistant packaging – Requirements and testing procedures for non-reclosable packages for pharmaceutical products" was published in March 2002. It is based on child panel testing following the internationally accepted procedures. The test consists of 2 periods of 5 minutes each. At least 85 % of the children shall be unable to open a number of units in the first part of the test. A demonstration is given to those children unable to gain access to the contents of the package and test is continued for another 5 minutes. At least 80 % of the panel shall be unable to open the number of units in the full test period of 10 minutes.

It is an open and contentious issue how many units the children are allowed to open. According to the German standard DIN 55559 the children (percentages as described above) shall be unable to open more than 8 units of blister packages (and similar packages) irrespective of the size and the toxicity of the packed pharmaceuticals. By contrast, the US regulation follows a different approach (Code of Federal Regulations 16 Part 1700 to 1750, Subchapter E – Poison Prevention Packaging Act of 1870 Regulation, Revised as of January 1, 2000). A package is considered to have failed the test if the children (percentages as described above) open or gain access "to the number of individual units which constitute the amount that may produce serious personal injury or serious illness" or "to more than 8 individual units, whichever number is lower". In other words: more toxic substances require packages which are more difficult to open. A package which complies with the DIN standard is not necessarily considered as child resistant in the US as the toxic dose could be much lower than 8 units. In the extreme, almost all children in the test could gain access to a number of units corresponding to a toxic dose which could be as low as 1 unit or even below and still such a package could be designated as "child resistant" according to the DIN standard as long as less than 20 % of the children are able to access more than 8 units over the full test period.

Originally it was the intention of the CEN working group to develop a classification of child resistant packages depending on the number of units children are able to open in the test. The number of units (the test result) may range between 1 and more than 8. The lower the number, the more difficult it is to open the packages. As an example a result of 4 indicates that the test panel was unable to open 4 units (percentages as described above), but was able to open 3 units.

According to previous working drafts of the European standard manufacturers were required to select the appropriate package type according to the toxicity of the pharmaceuticals in order to prevent "serious personal injury or serious illness. Unfortunately the concept outlined above was dropped after 3 years of work. The draft European standard followed the DIN philosophy. Without going into details it can be stated that this was due to strong pressure from industry.

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ANEC commissions study

ANEC felt that the provisions of the draft European standard are insufficient. Based on a proposal by its Child Safety WG a research project was commissioned in November 2001. The contractor was the Medical Toxicology Unit, Guy's and St. Thomas' Hospital, London, UK. Dr. Franz Fiala was the ANEC project advisor and supervised the study.

The purpose of the study was to provide the necessary information in support of the implementation of European rules (regulation/standardisation) for child-resistant packages for pharmaceuticals representing a high level of protection following the US approach. The major elements of the study are:

- identification and quantification of the most important medications involved in accidental poisoning of children up to 5 years leading to severe symptoms, in particular those having a high toxicity (less than 8 units constitute a serious health hazard)
- determination of the toxicity of selected medications (dose requiring medical intervention) by using different databases with a view to identifying possible discrepancies
- investigation of the determination of a toxic dose in those cases where human empirical data are missing
- establishment of a guidance document for the selection of the appropriate type of child-resistant package in terms of the number of units which are accessible in a child panel test taking into account the size of the unit doses and their toxicity
- provision of some examples of how to apply the guidance document in practice.

Identification of relevant medications

Solid medications involved in home and leisure accidents in children under 5, were identified using information from:

- the UK Home Accident surveillance System (HASS)
- death statistics from England and Wales reported by the Office for National Statistics(ONS)
- records from the National Poisons Information Service London NPIS(L)
- reports of deaths due to poisoning published annually by the American Association of Poison Control Centres

In order to reduce the number of pharmaceuticals to a manageable number and to select the most relevant ones certain criteria were applied. Apart from mortality data only those medications were pre-selected for further consideration which led to a minimum stay of one day in a hospital and which were listed at least 3 times in the HASS data set and those which were scored moderate to severe toxicity in the NPIS(L) enquiry database.

From these lists 14 drugs were chosen for an in depth toxicity assessment.

Toxicity assessment of selected medications

Assessments of toxicity were undertaken for dothiepin, imipramine, carbamazepine, temazepam, hyoscine travel sickness tablets, atenolol, propranolol, sulphonylurea antidiabetic drugs, methadone, Lomotil®, nifedipine, quinine, dapsone and amoxapine. Case histories from the NPIS(L) database as well as reports published in the open literature were used in addition to the sources mentioned above.

The major result was that serious poisoning or death can occur after ingestion of less than 8 dose units of the highest strength tablets available. In some cases even less than one tablet can severely damage a child's health. It seems that a large proportion of moderate to severe poisonings could have resulted from ingestion of less than 8 dose units.

The numbers of dose units indicated in the tables below are calculated based on the reported dose information for cases of accidental poisoning and the highest strength tablets available in the UK.

Lowest reported fatal dose

Medication	No. of dose units
nifedipine	<1
propranolol	<1
amoxapine	1
dothiepin	1,6
carbamacepine	4
methadone	4
impramine	4,8
quinine	5
Lomotil ®	6
hyoscine	6

For example, in case of nifedipine the lowest reported dose leading to a fatal accident corresponds to less than 1 tablet of the highest strength pill of that medication available in the UK.