United States
CONSUMER PRODUCT SAFETY COMMISSION
Washington, D.C. 20207

MEMORANDUM

DATE: August 28, 2003

TO : HS

Through: Todd A. Stevenson, Secretary, OS

FROM : Martha A. Kosh, OS

SUBJECT: Petition PP 03-1, Petition for Amendment of the Child-Resistance Testing Requirements for Unit Dose Packaging

ATTACHED ARE COMMENTS ON THE CP 03-1

COMMENT	DATE	SIGNED BY	AFFILIATION
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CP 03-1-3	7/30/03	Steven Marcus, MD Executive Director	New Jersey Information & Education System
CP 03-1-4	7/30/03	Anthony Manoguerra Pharm.D, DABAT, FAACT, Director	California Poison University of California
CP 03-1-5	7/30/03	Suzanne Doyon, MD Medical Director	Maryland Poison Center University of Maryland
CP 03-1-6	8/01/03	James Mowry Director	Indiana Poison Center Indianapolis, Indiana
CP 03-1-7	8/01/03	Marc Wilenzick Senior Corporate Counsel	Pfizer Inc. 235 East 42nd Street New York, NY 10017

Petition PP 03-1, Petition for Amendment of the Child-Resistance Testing Requirements for Unit Dose Packaging

CP 03-1-8	8/04/03	Robert Geller Medical Director & Assoc. Professor Of Pediatrics	Georgia Poison Center Emory University School of Medicine
CP 03-1-9	8/07/03	Hugh Lockhart Professor & Laura Bix Asst. Professor	Michigan State Univ. 153 Packaging East Lansing, MI 48824
CP 03-1-10	7/23/03	Laurie Smaldone Sr. Vice President Global Regulatory Sciences	Bristol-Myers Squibb Pharmaceutical Research Institute P.O. Box 4000 Princeton, NJ 08543
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CP 03-1-14	8/12/03	Alexander Perritt CEO Scott Perritt President Richard Ward Vice President Consumer Product Testing	Perritt Laboratories 145 South Main St. P.O. Box 147 Hightstown, NJ 08520
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CP 03-1-17		VACANT (duplicate comment)	

Petition PP 03-1, Petition for Amendment of the Child-Resistance Testing Requirements for Unit Dose Packaging

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CP 03-1-20	Ken Kulig,MD Chairman	Patient Safety Sub-committee, American College of Medical Toxicology
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CP 03-1-25	John M. Coster,Ph.D Vice President Policy and Programs	National Association of Chain Drug Stores 413 North Lee Street P.O. Box 1417-D49 Alexandria, VA 22313
CP 03-1-26	Mark R. McMahon Chief Operating Officer	MeadWestvaco Corporation World Headquarters One High Ridge Stamford, CT 06905
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Comment
PP03-1

Office of the Secretary
Consumer Product Safety Commission
Washington, DC 20207
United States of America

ANEC2003/0301/tva

Brussels, 24 June 2003

Petition PP 03-1, Petition for Amendment of the Child-Resistance Testing Requirements for Unit Dose Packaging

Comments from ANEC

Dear Sir,

I am writing to you on behalf of ANEC, the European consumer voice in standardisation. Established in 1995, ANEC's mission is to represent and defend consumer interests in the process of European standardisation and certification. ANEC is a European consumer organization. Our members are consumer organisations in the European Union and EFTA (European Free Trade Association) countries.

ANEC is very worried about the above mentioned petition.

In Europe, we are actively fighting the approach suggested by the US Healthcare Compliance Packaging Council (HCPC). A draft European standard (prEN 14375: "Child-resistant non-reclosable packaging for medicinal products - Requirements and testing") is currently under development in the European Standardization Body CEN. According to the draft standard a test shall be considered as failure if within 10 minutes the child removes more than 8 units from a unit dose packaging. The 8 units criterion applies irrespective the dose and the toxicity of the medication. For ANEC, this approach is insufficient.

A study commissioned by ANEC (Toxicological criteria for the selection of non-reclosable child-resistant packages for pharmaceuticals, Medical Toxicology Unit, Guy's and St Thomas Hospital, London, May 2002) clearly shows that

- a small number (less than 8) of ingested tablets of some pharmaceuticals can seriously damage the health of a child
- in certain cases less than 1 pill can kill a child
- there is reason to believe that in a large proportion of moderate to severe poisonings less than 8 units could be involved

Please find enclosed for your information a copy of our study and an updated background paper.

We hope that this petition by the US Healthcare Compliance Packaging Council will not lead to a dilution of consumer protection in the United States.

Yours sincerely,

Tania Vandenberghe
Programme Manager

Encl.: - Final Report of the Study commissioned by ANEC, May 2002
- Guidelines (Part 2 of the report), May 2002
- Updated background document, June 2003

Guy's and St Thomas' Hospital NHS
NHS Trust

MEDICAL TOXICOLOGY UNIT

PART 1

Toxicological criteria for the selection of non-reclosable child-resistant packages for pharmaceuticals

28 May 2002

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This report has been commissioned by
The European Association for Consumer Participation in Standardisation.

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Abbreviations

AAPCC	American Association of Poison Control Centers
ACE	angiotensin-converting enzyme
CEN	Comité Européen de Normalisation (European Committee for Standardisation)
CNS	central nervous system
CRC	child-resistant closure
DIN	Deutsches Institut für Normung (German Institute for Standardisation)
EAPCCT	European Association of Poison Centres and Clinical Toxicologists
GCS	Glasgow coma scale
HASS	Home Accident Surveillance System (UK)
ICD	International Classification of Diseases
IPCS	International Programme on Chemical Safety
IR	immediate release
LASS	Leisure Accident Surveillance System (UK)
NHIS	National Health Interview Survey (USA)
NK	not known
NOS	not otherwise specified
NPIS (L)	National Poisons Information Service (London)
NS	not stated
ONS	Office of National Statistics (UK)
PSS	Poison Severity Score
®	registered trade name
SR	sustained release
SSRI	selective serotonin reuptake inhibitor
TESS	Toxic Exposure Surveillance System (USA)

Summary

The objective of this report is to identify medications reported to have caused severe accidental poisoning in children up to 5 years of age, and to assess their toxicity. This information has been used to validate a method developed by our research group to determine the type of child-resistant container needed for a particular pharmaceutical. The method is for consideration by the European Commission in the development of a regulation, and by European standards bodies in the development of a related standard, for non-reclosable child-resistant containers for pharmaceutical products.

Solid-dose medications involved in home and leisure accidents in children under 5, were identified using information from the UK Home Accident surveillance System (HASS). These were compared with medications associated with death or moderate to severe poisonings in children, using the following data:

- deaths in children under 5 years due to medications in England and Wales for 1993-1999 reported by the Office for National Statistics(ONS);
- records from the NPIS(L) enquiry database between March 1997 to December 2001, of children under 5 years with clinical effects consistent with moderate or severe toxicity following ingestion of pharmaceuticals;
- case histories from NPIS(L) case files, generated by following up enquiries since 1963;
- reports of deaths due to poisoning published annually by the American Association of Poison Control Centres since 1983.

Liquid preparations were excluded when possible because the objective was to determine the hazard due to solid 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. Cases histories obtained from the NPIS(L) files and published literature were scored using the Poisons Severity Score (PSS) developed by the European Association of Poison Centres and Clinical Toxicologists (EAPCCT),and compared with the epidemiological data from HASS and ONS.

Reports of death associated with doses of less than 8 of the highest strength dose units were found for methadone, nifedipine, imipramine, quinine, dothiepin, amoxapine, carbamazepine, Lomotil®, dapsone, and hyoscine. There were no reports of death due to atenolol, temazepam, or sulphonylureas, and only 1 death due to propranolol.

A variation in dose-response was noted for nifedipine, Lomotil®, methadone, imipramine, hyoscine, amoxapine, dothiepin, carbamazepine, and quinine, such that doses associated with severe toxicity or death, were in other cases associated with only mild toxicity. This may reflect true variation within the age group or may be due to some case reports containing inaccurate or inadequate data.

Of those drugs associated with severe toxicity in young children following ingestion of less than 8 dose units:

- dothiepin, carbamazepine, and hyoscine were all frequently reported in the sample of childhood poisonings from HASS; dothiepin has been associated with four recent child deaths in England and Wales.

- methadone, Lomotil®, imipramine, quinine, nifedipine, dapsone and amoxapine were all only infrequently reported in the sample of childhood poisonings from HASS. All except dapsone have been associated with at least one death in the sources reviewed in this study. Methadone has been associated with four recent child deaths in England and Wales.

Of those drugs with toxic doses greater than 8 dose units, temazepam was one of the drugs most frequently reported in the sample of accidents from HASS, and there were a number of cases involving propranolol and atenolol, but no reports of sulphonylureas as a cause of potentially serious poisoning in data from HASS or NPIS(L).

There were other products associated with cases of childhood poisoning recorded in the sample from HASS that could be toxic in less than 8 dose units, e.g. all tricyclic antidepressants, products containing large doses of opioids, chlormethiazole, chloral hydrate, chlorpromazine, clozapine, dextropropoxyphene, codeine, flecainide, clonidine, verapamil, orphenadrine, risperidone, thioridazine, theophylline, and chloroquine. It was not possible to assess all these to verify their toxicity.

Data based on a small number of cases from the NPIS enquiry database indicate that a large proportion of moderate to severe poisonings in young children could have resulted from ingestion of less than 8 dose units.

There is no single source of information on the frequency of severe poisonings attributable to named medications in the UK. Poisons centres and accident surveillance systems are important sources of information for determining the risk of poisoning with medications and priorities for action. Data should also be sought from the literature, although for five of the drugs in this study, (dothiepin, imipramine, quinine, hyoscine, and Lomotil®), there were more cases in NPIS(L) files than in the literature. More observational research based on prospective, focussed, multicentre, even multinational studies is needed to investigate the toxicity of drugs and the epidemiology of poisoning.

For medications where there is little information on effects of overdose, it might be possible to evaluate toxicity using the Minimum Intolerated Dose (the dose at which more than 50% of patients suffered limiting adverse events), or the Maximum Tolerated Dose (the highest dose it is safe to administer to patients). These may be available for newer drugs.

Introduction

The European standardisation institution, the Comité Européen de Normalisation (CEN), is currently developing a draft standard entitled 'Child-resistant packaging – Requirements and testing procedures for non-reclosable packages for pharmaceutical products'.

Criteria for designating a container as child-resistant are based on the number of units a child should be able to open. However there is disagreement on what this number should be and how it should be determined. According to the German standard DIN 55559, a specified percentage of children should be unable to open more than 8 units of blister (or similar) packs irrespective of the size and the toxicity of the packed pharmaceuticals. By contrast, the US regulation (Code of Federal Regulations 16 Part 1700 to 1750, Subchapter E – Poison Prevention Packaging Act of 1870 Regulation, Revised as of January 1, 2000) takes into account the toxicity of the substance in the container, requiring more toxic substances to be packaged in containers that are more difficult to open. Thus a pack is considered to have failed the test if a specified percentage of children 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".

Originally it was the intention of the CEN working group to develop a classification of child-resistant packs depending on the number of units children were able to open in the test, with a range of between 1 and more than 8, so that some packs would fail if, for example, 3 or 4 units could be opened by the specified percentage of the child test panel under the defined test conditions. Manufacturers would then be required to select the appropriate pack type according to the toxicity of the medication in order to prevent "serious personal injury or serious illness".

In order to apply such a standard, manufacturers and other agencies need to know the toxicity to children of a particular pharmaceutical to be able to determine which pack is appropriate and, if no data are available, to have some method of predicting risk.

The Medical Toxicology Unit has been asked by ANEC, the European Association for Consumer Participation in Standardisation, to identify medications frequently associated with accidental poisoning of children up to 5 years of age resulting in severe symptoms, in particular those having a high toxicity (less than 8 units constituting a serious health hazard); to assess the toxicity of a selection of these; and to develop a document to be presented to the European Commission giving guidance on how to determine what kind of pack type is needed for a particular pharmaceutical depending on its toxicity.

This report reviews information available on solid-dose medications implicated in accidental ingestions by children under 5 years old and identifies those most likely to cause severe poisoning in less than 8 dose units. The review was limited to solid-dose formulations because the information was needed for guidance on non-reclosable containers for solid medications. Assessments of toxicity were undertaken on a number of substances associated with moderate to severe poisoning in children following ingestion of less than 8 dose units, using published information and records of cases reported to the National Poisons Information Service (London) at the Medical Toxicology Unit.

The duration of the study was limited by the timetable for development of the European standard. At the outset it is important to acknowledge that in the two and half months available for the study it was not possible to assess exhaustively all the possible information on childhood poisonings, for example to contact other poisons centres or other centres collecting epidemiological information on childhood poisoning, or to follow up possible accidental poisonings for which the Medical Toxicology Unit Laboratory had undertaken toxicological analyses.

Poisoning in children under five years old

In 1998, in England and Wales, deaths from poisoning due to drugs and medicaments was only 2 per million in the 0-4 yr age group (Office for National Statistics, 2001). This is similar to other European countries, for example Germany, where there are between 20-40 deaths in a population of 81 million (0.25 per million).

The incidence of severe, non-fatal poisonings is unknown. Poisons centre surveys and hospital based surveys indicate that only a very small percentage children attending hospital with suspected poisoning are admitted, and that only a minority of these develop serious effects. Since numbers of attendances are high, such small percentages may nevertheless represent many hundreds of children per year, across Europe. For example, the Berlin Poisons Centre has estimated that there are about 100,000 ingestions and 500 severe non-fatal poisonings per year in small children in Germany alone (Giftnotruf, 2000).

Statistics on incidence and severity of poisoning in this age group are subject to a degree of inaccuracy because, in the majority of cases, it is difficult to know how much a child has ingested or even whether the child has swallowed anything at all. Histories from parents or carers may be unreliable, and they may under- or over-estimate the amount taken. If the child remains asymptomatic it may be impossible to decide whether or not ingestion of a non-toxic amount occurred. There may be circumstantial evidence of the amount taken if, for example, someone knows how many tablets were in the pack before the child obtained it, but even this may be inaccurate. Proof that ingestion has occurred and a reliable estimate of the approximate dose ingested can only be obtained by taking blood samples, but this is only justified in a young child if there is a risk of serious poisoning or if the information is needed for treatment.

Sources of information

There is no single source of comprehensive statistics on the occurrence of poisoning in the UK. We obtained information from the following sources.

To assess toxicity of medications

- case reports from NPIS(L)
- case reports of deaths due to poisoning published by the American Association for Poison Control Centres.

To assess incidence of poisoning in UK

- reports on accidents resulting in attendance at accident and emergency departments, from the Home Accident Surveillance System operated by the Department of Trade and Industry
- mortality statistics for England and Wales from the Office for National Statistics.

National Poisons Information Service London Centre (NPIS (L))

The National Poisons Information Service (London) receives telephone enquiries from health professionals seeking advice about the clinical effects and management of inappropriate exposures to substances. Most enquiries are received from hospital emergency departments; NPIS (L) does not provide a service to the public.

Since it began in 1963, NPIS (L) has kept records of each enquiry received and built up extensive files of detailed case histories of cases of special interest, with the specific intention of using this data to monitor epidemiology of poisoning and efficacy of treatment.

Serious childhood poisoning is rare, but NPIS (L) is in a good position to detect rare events because it monitors events in a large population of approximately 50 million and is probably informed of most of the serious cases of accidental poisoning in young children occurring in the region. The concern generated by poisoning in young children and the desire to prevent future occurrences

usually ensures that they will be publicised and reported to organisations known to be concerned with monitoring and prevention.

NPIS (L) Enquiry Database
Records generated at the time of the enquiry include the age of the patient, clinical effects, name of agent with estimated dosage, route and time since exposure, when it is available from the enquirer. Clinical details are usually reported by a clinician or nurse who has assessed the patient, not by a member of the public.

This information is entered into a computerised database to allow searching of the data. Clinical effects are entered according to a thesaurus enabling accurate searching using the approved term. Agents are identified as they were identified by the caller (e.g. Anadin® Extra). Within the database each agent has been assigned codes according to their ingredients (for Anadin® Extra this is aspirin, paracetamol and caffeine), and, in some cases, use (generally household products), using a tree structure. This means that the agent names are controlled data. This characteristic of the database allows searches of groups of similar agents (e.g. all analgesics), as well as searches of ingredients (e.g. all aspirin-containing products), or individual trade names (e.g. Anadin® Extra).

NPIS (L) began developing computer databases to hold summaries of most enquiry records and a selection of more detailed case histories, in 1983. The current database includes cases referred by telephone to the centre since 1991, a total of approximately 1.5 million enquiries. Approximately 20% of these enquiries relate to children under 5 years of age. This large number of cases gives representative information on comparative frequency of occurrence of exposure to named agents.

There are limitations to the use of the NPIS (L) database for assessing the incidence of poisoning. The case records are not a complete record of every exposure event that occurs in the region it serves, nor even of every event that results in a hospital attendance. The cases obtained from this database are likely to under-represent the number of cases of moderate or severe toxicity in the UK for several reasons:

- The data collected at the time of the telephone enquiry provide only a snapshot of the case, and consequently the database rarely includes information regarding outcome unless a call is made through the emergency telephone lines to notify NPIS (L) of a death.
- The majority of enquiries are made shortly after the patient presents to the health professional (usually the emergency department). Clinical effects that develop subsequently are not available to be recorded unless further calls about that patient are received by NPIS (L). On the other hand, if it is later discovered that the condition is unrelated to exposure, and the diagnosis is later shown to be unfounded, that information may not be reported to the NPIS (L).
- There is no requirement for health professionals to seek advice from the NPIS (L) when treating a poisoned patient. They contact poisons centres only when they need information. Although this could bias the data toward the more unusual or potentially serious poisons, it also means that other cases of moderate or severe toxicity may have occurred that were managed using previous experience or other information sources or NPIS centres.

Information received over the telephone is not validated, and it is possible that incorrect information is provided. Until recently there was only limited validation of the data input process to detect errors that had occurred during recording or input. However the information is logged during telephone conversations by fully-trained Specialists in Poisons Information, and then entered into the NPIS (L) database by dedicated data input clerks. This reduces the likelihood of human error during collection or input of the data, since both groups are experienced in dealing with this data.

To try to overcome some of these limitations, some of those cases expected to result in serious poisoning are followed up to verify the case details. In case of serious illness in a young child

some effort will have been made by the clinician in charge, and also the NPIS (L), to verify the cause.

Despite its limitations, the database can provide reasonably representative information on the medications most frequently ingested by children. Although there has been no formal study to prove it, from monitoring published case reports and surveys in medical press and mass media and comparing NPIS data with data from other UK poisons centres, we believe that childhood poisoning exposures recorded on the database are reasonably representative of the UK as a whole.

American Association of Poison Control Centers database

Toxic Exposure Surveillance System (TESS) data are compiled by the American Association of Poison Control Centers (AAPCC), using information from most of the American poison centres. Each report includes a list of all participating centres. TESS began in 1983 and the reports are published each September in volume 5 of the *American Journal of Emergency Medicine*. The reports are also available on the AAPCC website at www.aapcc.org. Since 1983 the number of participating centres, and consequently the volume of data, has grown, and the AAPCC database now contains almost 30 million records of human poisoning (Litovitz *et al.*, 2001). The reports contain brief details of all fatal cases giving age, circumstance, route and, where available, blood concentrations.

A number of studies have looked at the differences between poison centre data and data from other sources. There are discrepancies between hospital data and poison centre data (Harcelroad *et al.*, 1990), mortality statistics and poison centre data (Hoppe-Roberts *et al.*, 2000) and between medical examiners' records and poison centre data (Soslow and Woolf, 1992; Linakis and Frederick, 1993).

A recent report comparing national mortality statistics (compiled by the National Center for Health Statistics) and deaths reported to poison control centres (in TESS) concluded that the only 5% of poisoning deaths in the USA were reported in TESS (Hoppe-Roberts *et al.*, 2000). In another survey comparing TESS data and National Health Interview Survey (NHIS) data, the number of poisoning cases in children <6 years of age reported in the NHIS was only half that of the 1997 annual report TESS data (Polivka *et al.*, 2001).

Some studies have also looked at discrepancies in individual states. In a study in Massachusetts comparing poison centre records, death certificates and medical examiner's office records, 77% of deaths occurred outside hospital, and so were not present in the poison centre data. However, the poison centre was not consulted in over 47% of deaths occurring in hospitals in Massachusetts. In contrast 15% of deaths reported to the poison centre were not found in the other two sources. Concordance between all three datasets of was only 17% (Soslow and Woolf, 1992). Similarly, in a study of mortality reporting over a 4 year period in Rhode Island, 369 deaths were reported to the medical examiner and only 49 to the regional poison centre. In most cases the deaths reported to the medical examiner occurred outside hospital and poisoning was often not confirmed until post-mortem examination. Only 29% of the poisoning deaths that occurred in hospital were reported to the regional poison centre (Linakis and Frederick, 1993). In a study in Pittsburgh only 26% of patients with a potentially toxic exposure presenting to a study hospital were reported to the local poisons centre (Harcelroad *et al.*, 1990).

In summary, poisoning deaths are often not reported to a poisons centre, particularly when the incident occurred outside hospital or when poisoning is not initially suspected as a cause of death. As a result, cases of poisoning including deaths are underreported in poisons centre data in the USA and elsewhere (Butera *et al.*, 1999). However, although it is not a complete list of all deaths due to poisoning in the USA, TESS gives an indication of the relative importance of specific drugs as causes of death, the brief clinical details are valuable, the data are of good quality and the report is readily available.

UK Home Accident surveillance System (HASS)

HASS collects a representative sample of data on all home and leisure accidents that take place in the UK and result in the victim attending hospital. At any one time 18 hospitals submit information. They are selected from around the country, using a formal statistical procedure so that national estimates can be calculated. Trained clerks collect the data in the emergency department by interviewing patients or their parents/carers or by consulting the medical records. The database includes unintentional injury or suspected injury except deliberately self-inflicted/suspected suicide, attacks from other persons, sudden illnesses, incidents occurring in the home, including the garden etc, including permanent and voluntary institutions but not temporary, non-voluntary institutions, such as hotels, boarding houses.

There is no clinical information on these databases, so there is no indication of severity of injury in an individual case. If a child is admitted to hospital following suspected poisoning, this is no indication of the severity of poisoning because the length of hospital stay may be determined by factors other than the clinical condition of the patient. However, it would seem reasonable to assume that children who are not admitted to hospital did not suffer severe clinical effects.

Office for National Statistics (ONS)

ONS receives reports of all deaths due to poisoning in England and Wales and classifies them using the International Classifications of Diseases version 9. Records include names of drugs given in the Coroner's text on the record of death.

Method

Identification of medications involved in accidental poisoning leading to severe symptoms in children under 5

Information obtained from HASS on the incidence of poisoning was used to identify the medications most frequently implicated in childhood poisoning. To determine which products would be likely to cause severe symptoms, this information was compared with data from ONS, the NPIS (L) enquiry database, NPIS(L) files of case histories, and the AAPCC annual reports. Since the objective of the study was to provide information for discussions on the packaging of solid pharmaceuticals, the analysis was restricted to consideration of solid-dose pharmaceuticals.

Home Accident Surveillance System (HASS)

HASS provided information on the sample of home and leisure accidents to children aged 0-4 years old involving medicine and resulting in a hospital stay of one day or more, reported between 1996 and 1999 to 18 hospitals. Since HASS does not collect clinical information there is no way of selecting only those cases with moderate or severe poisoning. By excluding the children not admitted to hospital most of those who suffered only minor consequences following ingestion were excluded from the sample. Most records included either a product name or a type of medication e.g. sleeping pills. Cases involving liquid formulations were identified either by product name, or by information in the description of the accident, e.g. a liquid measure of amount, or description of patient drinking medicine; these were discarded from further consideration. Records of ingestion of solid-dose medications were classified and sorted by pharmaceutical name and type, using the British National Formulary classification.

The relative frequency in accidents was of interest rather than the actual number of incidents in UK, so the analysis looked at the numbers in the sample, rather than the national estimates that can be calculated from them.

Mortality data from the Office of National Statistics (ONS)

ONS was asked for information on all accidental deaths in England and Wales due to medications for children of less than 5 years, from 1993-1999 where death was classified by the following ICD9 codes:

292 (drug psychoses)
304 (drug dependence)
305.2-305.9 (nondependent abuse of drugs)
E850-E858 (accidental poisoning by drugs, medicaments and biologicals)
E980.0-E980.5 (poisoning by solid or liquid substances, undetermined whether accidentally or purposely inflicted)
E962.0 (assault by poisoning - drugs and medicaments).

American Association of Poison Control Centers fatality data

A table listing substances implicated with numbers exposed, age groups, circumstances, severity and outcome is given in each annual report. A separate table is provided listing the fatal cases by agent. Each case is listed individually with age, circumstance, route and, where available, blood concentrations. Brief case details for some of these cases are also given in an appendix to the report, usually including the formulation. Data were extracted from the annual reports for 1983-2000 for children aged 5 years and under. Since the aim was to identify solid-dose medications that could cause death from single accidental ingestion, cases were excluded if the case report indicated that there had been more than one episode of ingestion, if more than one pharmaceutical had been ingested, if a liquid formulation was involved, or if exposure was non accidental or by another route.

National Poisons Information Service (London) telephone enquiry data

A search of the database was carried out for all drug-related cases reported between March 1997 to December 2001 (1998 included July-December only) involving children aged under 5 years with clinical effects that NPIS (L) considered to be associated with moderate or severe toxicity (including death), as listed in Appendix 1. The search excluded calls that were not "emergency calls", for example, calls for information only, and calls where the clinical effects were assessed by the Specialist in Poisons Information dealing with the enquiry as unrelated to the exposure.

The results of this search were edited manually to exclude the following:

- Exposure by routes other than ingestion;
- Multi-agent exposures;
- Exposures to non-solid dosage forms, where the formulation was specified or the dose was given as volume e.g. in millilitres;
- Incidents where the medication was given to the child by an older child or adult;
- Obvious mistakes during the recording or input process e.g. exposures coded as intentional self-harm, or involving ingestion of large numbers of tablets (<1% of result of search).

The coding of clinical effects did not differentiate cases according to the degree of a clinical effect, for example, cases with 'vomiting' that is a sign of minor toxicity (PSS 1) could not be distinguished from those with 'pronounced or prolonged vomiting' that is a sign of moderate toxicity (PSS 2), nor could cases with 'mild and transient hypo/hypertension' (PSS 1) be distinguished from those with 'more pronounced hypo/hypertension' (PSS 2). Consequently some cases of moderate toxicity are likely to have been missed.

Assessment of toxicity of selected drugs

Toxicity was assessed from case reports retrieved from NPIS (L) case files, Poisindex® and the literature. Particular note was made of the clinical effects that would be expected from ingestion of up to 8 dose units, since this is the basis of the DIN standard.

Toxicity assessments were carried out for a limited number of drugs for which there were a reasonable number of case reports with reliable data on dose ingested, and which were either:

- implicated at least three times in the sample of incidents obtained from HASS thus indicating that suspected ingestion is more than an isolated occurrence, and that the products represented some degree of risk; or
- were implicated as a cause of serious poisoning in NPIS (L) or as a cause of death in data from AAPCC or ONS.

Poison Severity Score (PSS)

In order to standardise the severity of poisoning from the different sources the Poisons Severity Score (PSS) was applied to individual cases. This scheme was proposed by the European Association of Poison Centres and Clinical Toxicologists (EAPCCT) and developed with the International Programme on Chemical Safety (IPCS) and the European Commission. The severity of poisoning of individual cases is graded as follows:

- 0 none — No symptoms or signs related to poisoning
- 1 minor — Mild transient, and spontaneously resolving symptoms
- 2 moderate — Pronounced or prolonged symptoms
- 3 severe — Severe or life-threatening symptoms
- 4 fatal — Death

The score is intended as an overall evaluation of a case (Persson *et al.*, 1998) and lists more detailed criteria than the scheme used by the AAPCC to assign severity scores for case evaluation. Within each body system (e.g. gastrointestinal tract, respiratory, nervous and cardiovascular system) or parameter (e.g. metabolic balance) specific signs and symptoms are assigned to each grade. For example, methaemoglobinaemia of 10-30% is mild (1), 30-50% is moderate (2) and over 50% is severe (3). See Appendix 2.

Results

Identification of medications involved in accidental poisoning leading to severe symptoms in children under 5

Home Accident Surveillance System (HASS)

During the 4 year period 1996 to 1999, in the sample from 18 emergency departments, 1001 medicines were implicated in accidents involving children under 5 years old and resulting in one or more days stay. This included 452 solid medications. Those most frequently reported are listed in Table 1. These are not national estimates; they indicate only the relative frequency of involvement in accidents. The most frequently implicated medications were iron preparations, temazepam, dothiepin, paracetamol, co-proxamol (paracetamol and dextropropoxyphene), ibuprofen, diazepam, amitriptyline, thyroxine, carbamazepine, vitamin preparations and hyoscine travel sickness tablets.

Table 1: HASS data. The most frequently reported solid-dose medications in accidents involving children under 5 years old resulting in hospital admission, from a sample of accidents reported to 18 hospitals between 1996 and 1999.

Pharmaceutical	Number of occurrences
ferrous sulphate or iron unspecified	27
temazepam	26
dothiepin	26
paracetamol	17
co-proxamol	15
ibuprofen	14
diazepam	13
laxatives unspecified	13
amitriptyline	12
thyroxine	12
carbamazepine	12
vitamin preparations	11
hyoscine travel sickness medications	9
aspirin	7
analgesic unspecified	7
mefenamic acid	7
atenolol	6
propranolol	5
nifedipine	5
lisinopril	5
"sleeping pill"	5

Pharmaceutical	Number of occurrences
flupenthixol	5
quinine	4
paroxetine	4
metformin	4
fluoxetine	4
diclofenac	4
co-codamol	4
bendrofluazide	4
antidiabetic unspecified	4
amlodipine	4
phentermine	4
co-dydramol	4
trifluperazine	3
prochlorperazine	3
lithium	3
imipramine	3
codeine	3
beta blocker unspecified	3
antidepressant unspecified	3
zopiclone	2

Brand names were reported for only a third of the medications named. The brands most frequently reported in incidents resulting in one or more days stay are listed in Table 2. There were two medications reported more frequently under one brand name than another. Brufen® was reported 7 times, whereas Nurofen® was only reported once. This may reflect the common use of Brufen® as a generic name for ibuprofen in the UK. The hyoscine preparation for travel sickness, was reported 7 times as Joyrides® but only once as Kwells®. The NPIS(London) has not noticed a tendency to use trade names generically in this case, and it is more likely that this represents a real difference in frequency of the two brands in accidents.

Table 2: HASS data. The products most frequently reported in accidents involving ingestion of solid-dose medications children under 5 years old resulting in admission to hospital, from a sample of accidents reported to 18 hospitals between 1996 and 1999.

Brand name	Generic name	Number of occurrences
Prothiaden	dothiepin	14
Tegretol	carbamazepine	9
Brufen	ibuprofen	7
Joyrides	hyoscine	7
Prozac	fluoxetine	4
Valium	diazepam	4
Adalat	nifedipine	4
Duromine	phentermine	4
Distalgesic	co-proxamol	3
Fluanxol	flupenthixol	3
Seroxat	paroxetine	3
Stelazine	trifluperazine	3
Voltarol	diclofenac	3
Ponstan	mefenamic acid	3

When the medications were classified according to therapeutic use the classes most commonly implicated in accidents were tricyclic antidepressants, anxiolytics, analgesics, and iron (Table 3).

Table 3: HASS data. The classes of solid-dose medications most frequently implicated in accidents involving ingestion by children under 5 years old resulting in admission to hospital, from sample of accidents from 18 hospitals between 1996 and 1999.

Therapeutic class	No. of reports
tricyclic antidepressant	47
anxiolytic	42
analgesic – compound	29
iron preparations	27
non steroidal anti-inflammatory	27
analgesic – non opioid	25
anticonvulsant	15
beta blocker	15
laxative	13
thyroxine	13
antidiabetic	12
antiemetic	12
vitamins	11
antipsychotic	11
calcium channel blocker	10
antidepressant – SSRI	9
antihistamine	9
hypnotic	9
ACE inhibitor	8
analgesic – opioid	8
analgesic unspecified	7
diuretic	7
antibiotic	4
antimalarial	4
antiobesity	4
antidepressant (lithium)	3
antiasthmatic	3
antidepressant unspecified	3
antianginal	2
antiarrhythmic	2
antihypertensive unspecified	2
H2 receptor antagonists	2

Appendix 3 shows how the individual medications were classified. Some medications have more than one indication but it was not possible to distinguish the indication for which a pharmaceutical involved in accidents had been prescribed. Anticonvulsants were high on the list only because of the relatively large number of accidents involving carbamazepine, which has more than one indication. The intended user of the product was reported for 139 accidents. The majority of solid-dose products involved in accidents resulting in a stay in hospital were intended for adults, particularly grandparents (40% of the products for which the user was stated).

Table 4 lists the pack type involved in 114 of the accidents (25%). Most of the containers were bottles (63%) rather than strips or blisters (23%). Child-resistant bottles were said to be involved more often than non-child-resistant bottles, but this may reflect the fact that people were more likely report that child-resistant containers were involved in accidents than non-child-resistant ones, and does not necessarily show that child-resistant closures were more frequently implicated in accidents.

12% of solid medications were not in a container when found by the child, but were, for example, on the floor or a work surface.

Table 4: HASS data. Information about containers reported for 130 solid-dose medications implicated in accidents involving children under 5 years old from a sample reported to 18 hospitals between 1996 and 1999.

Packaging/container type	Number of occurrences
Bottle NOS	55
Bottle with a child-resistant closure	12
Bottle without a child-resistant closure	2
Bottle flip top	1
Bottle broken	2
Blister	19
Strip	7
Box/packet/pill box	16
Product not in a container when found by child (on floor, etc)	16
no information reported	317
Total	452

Mortality data from the Office of National Statistics (ONS)
There were 13 deaths due to drugs in children under 5 years of age reported to the ONS over the period 1993 to 1999 (see Table 5). Methadone and dothiepin were each involved in 4 deaths, and iron in two deaths. Sodium nitroprusside is not available as an oral preparation so this was presumably an intravenous overdose or an adverse reaction. The formulation could not be ascertained from the statistics so it is uncertain whether the methadone was liquid or solid.

Table 5: Drugs implicated in accidental deaths in children under 5 years of age in England and Wales, between 1993-1999 (Source: Office of National Statistics).

Drug	*No of fatalities*
Methadone	4
Dothiepin	4
Iron	2
Amoxapine	1
Paracetamol	1
Sodium nitroprusside (Nipride®)	1

American Association of Poison Control Centers fatality data
Over the 18 year period 1983-2000 the AAPCC annual reports listed a total of 31 drugs involved in 117 deaths in children 5 years or under due to single accidental ingestion of one drug, excluding cases known to have involved liquid formulations. The drugs are listed in Table 6, and details of the cases are summarised in Appendix 4.

Iron was involved in 34% of cases and was by far the most common cause of death. The next most common drug was desipramine at 9.5%. Even when added together the tricyclic antidepressants (desipramine, amitriptyline, imipramine, nortriptyline and amoxapine) made up only 18% of cases.

Dose was stated in 31% of these cases. Iron was usually ingested in large doses of 30 or more tablets, but most other drugs had been ingested in smaller quantities.

Table 6: Drugs involved in deaths due to accidental ingestion in children up to 5 years, listed in the Annual Reports of the AAPCC TESS 1983-2000, excluding cases involving more than one agent or repeated ingestions, and most cases involving liquid formulations.

Drug	Total number of deaths	Percentage
Iron	40	34.2
Desipramine	11	9.5
Methadone	9	7.8
Diphenhydramine	7	6.0
Nifedipine	6	5.2
Carbamazepine	4	3.4
Amitriptyline	4	3.4
Imipramine	4	3.4
Verapamil	3	2.6
Aspirin	3	2.5
Theophylline	2	1.7
Propoxyphene	2	1.7
Doxepin	2	1.7
Chloroquine	2	1.7
Chloral hydrate	2	1.7
Valproic acid	1	0.9
Quinidine	1	0.9
Propranolol	1	0.9
Phenytoin	1	0.9
Phenylbutazone	1	0.9
Paracetamol	1	0.9
Nortriptyline	1	0.9
Morphine	1	0.9
Flecainide	1	0.9
Diphenoxylate/atropine	1	0.9
Digoxin	1	0.9
Codeine	1	0.9
Clozapine	1	0.9
Clonidine	1	0.9
Caffeine	1	0.9
Amoxapine	1	0.9
Total	**117**	**100.4**

NPIS (London) enquiry database

The search of the NPIS enquiry database retrieved 110 cases with moderate or severe poisoning due to accidental ingestion of one solid-dose pharmaceutical agent by children under 5 years old. There were 40 different medications reported and 7 cases where the exact pharmaceutical was not known, including 2 each of unknown ferrous salts, tricyclic antidepressant and opiate, plus one unknown benzodiazepine. In 6 cases there was more than one enquiry about the patient, each recording moderate or severe clinical effects. All enquiries are detailed in Appendix 5.

One quarter of the cases (25%) involved a tricyclic antidepressant (dothiepin, amitriptyline, imipramine, amoxapine and unknown), 11% involved a benzodiazepine (temazepam, diazepam and unknown) and 8% an opiate (methadone, codeine, unknown). The most common agent was dothiepin, followed by temazepam, amitriptyline and carbamazepine. The number of cases for each pharmaceutical is shown in Table 7.

Table 7: Solid-dose medications involved in cases of moderate and severe toxicity from accidental ingestion of one agent by children under 5 years old, recorded on the NPIS (L) enquiry database between March 1997- December 2001.

Agent	Number of cases
Dothiepin	15
Temazepam	10
Amitriptyline	7
Carbamazepine	7
Chlormethiazole	5
Chlorpromazine	5
Methadone	5
Ibuprofen	4
Ferrous salts	4
Clozapine	3
Haloperidol	3
Clonidine	2
Codeine/Codeine phosphate	2
Imipramine	2
Opiate NK	2
Risperidone	2
Tricyclic antidepressant NK	2
Acepromctazine	1
Amoxapine	1
Benzodiazepine NK	1
Betahistine	1
Chloral betaine	1
Chlorpheniramine	1
Diazepam	1

Agent	Number of cases
Flecainide	1
Fluoxetine	1
Hyoscine hydrobromide	1
Karvol	1
Mefenamic Acid	1
Methocarbamol	1
Methyldopa	1
Metoclopramide	1
Olanzapine	1
Orphenadrine	1
Oxybutynin	1
Paroxetine	1
Phenobarbitone	1
Phentermine	1
Phenytoin	1
Propranolol	1
Sodium fluoride	1
Sodium valproate	1
Sulpiride	1
Theophylline	1
Thioridazine	1
Tiagibine	1
Trifluoperazine	1
Total	**110**

In 97 cases the exposures were reported to be accidental childhood ingestions, 5 were as a result of accidental therapeutic errors, and in 9 cases the circumstances were unknown. In 13 cases the child was less than 1 year of age, in 41 cases the child was 1 year old, in 32 cases 2 years old, in 18 cases 3 years old and in 5 cases was 4. One case was recorded as being 1 year in one call and 2 years in another. 54 children were male, 43 were female and gender was unknown in 13 cases.

There were 39 cases where the number of tablets ingested was estimated, and this ranged from 1 to a maximum of 28. The median was 5, and 82% of these cases involved ingestion of 8 tablets or fewer.

Summary of information on medications causing poisoning in children

The data on poisoning by solid-dose medications in children under 5 years old, obtained from all these sources (the HASS survey of home accidents resulting in hospital admission for one day or more; the reports to the NPIS enquiry database of cases of moderate/severe poisoning; the mortality data for England and Wales from ONS; and the fatality data reported by the AAPCC in the USA) was compared.

The medications most frequently implicated in home accidents resulting in hospital admission and also most frequently reported to NPIS as causes of moderate/severe poisoning were iron preparations, dothiepin, amitriptyline, carbamazepine, temazepam, ibuprofen. All except the last two had been implicated in deaths either in the UK or the USA and are known to be toxic, but no deaths were reported due to temazepam or ibuprofen and they were not expected to cause severe toxicity.

The medications implicated three times or more in the sample of moderate/severe poisonings from the NPIS enquiry database but infrequently implicated in accidents resulting in hospital admission were methadone, chlormethiazole, chlorpromazine, clozapine and haloperidol. Methadone was also a significant cause of recent deaths in the UK and the USA and was known to be toxic. One death due to clozapine had been reported in the USA.

Medications frequently implicated in accidents resulting in hospital admission but reported less than three times in the sample of moderate/severe poisonings from the NPIS enquiry database, included those associated with fatalities (paracetamol, co-proxamol, aspirin, propranolol, nifedipine, and mefenamic acid), and those not associated with fatalities (atenolol, diazepam, hyoscine, lisinopril, thyroxine, laxatives, and vitamin preparations).

Since HASS does not include clinical data it is not possible to determine whether children were admitted to hospital because they exhibited signs of moderate or severe poisoning, or whether they remained well and were admitted only as a precaution because of the possibility of toxic effects.

The most notable differences between the samples of mortality data from the USA and England and Wales were that desipramine and diphenhydramine were a problem in the USA but not in England and Wales, and that dothiepin was a problem in England and Wales but not the USA.

Assessment of toxicity of selected drugs

Some drugs were chosen for assessment on the basis of the results of the information obtained on childhood ingestions presented above. From the list of products most frequently implicated in childhood ingestions dothiepin, carbamazepine, hyoscine travel sickness tablets and temazepam were chosen for assessment.

Others were chosen because they were known to have caused severe poisoning or deaths in children, although less frequently implicated as a cause poisoning resulting in admission: atenolol, propranolol, sulphonylurea antidiabetic drugs, methadone, Lomotil®, nifedipine, quinine, dapsone and amoxapine.

Iron preparations were not chosen for assessment although frequently implicated in childhood ingestions, because it is well established that most cases of severe poisoning or death result from ingestion of considerably more than 8 tablets. Similarly, the toxicity of aspirin and paracetamol is also well established. Ibuprofen was not chosen because it has been monitored intensively since it first became available without prescription in the early 1980s. (Volans and Fitzpatrick, 1999). From that work it has been concluded that although accidental ingestion of the solid-dose formulation in children is frequent, serious cases are extremely rare and compared with aspirin and paracetamol ibuprofen overdose in children is considerably less hazardous.

Dothiepin (dosulepin)

Dothiepin is a tricyclic antidepressant indicated for use in depression especially where sedation is required. It is available as 75 mg tablets and 25 mg capsules.

Dothiepin is not recommended for children under 12 years of age and NPIS (L) recommends observation in hospital for any quantity of dothiepin ingested by a child less than 6 years old. Toxicity is mainly due to anticholinergic (atropine-like) effects and a quinidine-like effect on the myocardium.

Clinical effects in poisoning
Peripheral effects commonly include sinus tachycardia, hot dry skin, dry mouth, dilated pupils and urinary retention. ECG features include prolongation of the PR and QRS intervals and in very severe poisoning the ECG may be bizarre. Metabolic acidosis and hypokalaemia can occur. Central effects commonly include ataxia and drowsiness which may lead to deep coma, respiratory depression and convulsions. Increased tone and hyperreflexia may be present with extensor plantar reflexes. In deep coma all reflexes may be abolished. Hypotension may occur.

Epidemiology
In England and Wales, dothiepin was responsible for four of the 13 unintentional deaths from ingestion of drugs by children under 5 years reported to the ONS between 1993 and 1999. Dothiepin is not used in the USA and does not feature at all in the AAPCC figures.

In the HASS sample of attendances by children under 5 at 18 emergency departments between 1996 and 1999, dothiepin was one of the most frequently implicated solid-dose drugs resulting in a stay of one day or more in hospital; it accounted for 26 of the 452 agents reported (6%).

There were 15 cases with features of moderate or severe poisoning reported in the NPIS (L) enquiry database between March 1997 and December 2001 due to ingestion of dothiepin alone by children aged less than 5 years. The dose ingested was estimated in nine cases and varied from 75 mg to 1.05 g. Seven children had central nervous system depression, 12 had convulsions and one suffered a cardiac arrest.

Cases in the literature
A 1.5 year old child (10 kg) who ingested 900 mg dothiepin 1.5 hours before admission experienced convulsions, metabolic acidosis, tachycardia and other cardiac abnormalities and required ventilation (Bloodworth *et al.*, 1994). In another case a dose of 975 mg of dothiepin caused severe poisoning in an 11 month old, 9.7 kg child (Hodes, 1994).

NPIS cases
There were 41 cases of dothiepin ingestion by children in the NPIS (L) case files where the dose ingested was estimated or known. One was fatal. The dose ingested ranged from 60 mg to a possible maximum of 1200 mg, and the dose ranges for each level of PSS are shown in Table 8. A further two deaths were reported where tablet strength was not known, but where the number of tablets ingested was estimated to be seven in one case and 40 in the other.

Table 8: Severity of poisoning in cases of dothiepin ingestion by 0-5 year old children reported to NPIS (L) with follow up details available including estimated dose ingested.

Severity of poisoning	Range of dothiepin dose (mg)	No of patients	Mean age (months)	Sex m/f	Number of tablets dose range equivalent to	
					25 mg tablet	75 mg tablet
0	60-900	10	26	4/5	2.4-36	0.8-12
1	75-750	4	18	3/1	3-30	1-10
2	75-750	16	34 (15 cases)	7/9	3-30	1-10
3	75-1200	10	24	5/5	3-48	1-16
4	125	1	60	1/0	5	1.67

The toxicity of dothiepin appears to be variable (Table 9). A four year old boy who had taken an estimated 125 mg of dothiepin had a cardiorespiratory arrest on the way to hospital. Although resuscitated and ventilated, he was pronounced brain dead 92 hours after admission (NPIS (L) case report number 81/31397). However two of the four cases with PSS 1 had taken more than this amount.

Table 9: Comparison of dose ingested with symptom severity in cases of dothiepin ingestion by children under 5 years old reported to NPIS (L).

Maximum Dose (mg)	Poison severity score					Totals
	0	1	2	3	4	
60	1					1
75	1	1	2			4
100	1					1
112.5	1					1
125		1			1	2
75-150			1	1		2
150	1		2	1		4
225	2	1	1	3		7
250	1					1
150-300			1			1
300			2			2
375	1		1			2
225-450				1		1
300-450			1			1
450			2			2
150-525				1		1
500-625			1			1
675			1			1
75-750		1				1
750			1			1
900	1					1
975				1		1
1050				1		1
450-1200				1		1
Totals	**10**	**4**	**16**	**10**	**1**	**41**

Toxicity

The only dose associated with fatality was 125 mg, equivalent to 1.6 of the 75 mg tablets. The minimum dose associated with moderate or severe non fatal poisoning, from 26 cases, was 75 mg, equivalent to one of the higher strength tablets.

References

Bloodworth L Wilson A, Collins P, Rainford DJ. 1984 Severe dothiepin intoxication - a report of two cases. *Postgrad Med J* 60:442-444.

Hodes D. 1984 Sodium bicarbonate and hyperventilation in treating an infant with severe overdose of tricyclic antidepressant. *Br Med J* 288(6433):1800-1801.

Imipramine

Imipramine is a tricyclic antidepressant indicated for use in depression and to treat nocturnal enuresis in children. It is available as 10 mg and 25 mg tablets and syrup containing 25 mg/5 ml. NPIS (L) recommends observation in hospital for any quantity of imipramine ingested by a child less than 6 years old.

Toxicity is mainly due to anticholinergic (atropine-like) effects at autonomic nerve endings and in the brain. There is also a quinidine-like effect on the myocardium. It is particularly toxic to children because they are more susceptible than adults to its cardiotoxic effects.

Clinical effects in poisoning
Peripheral effects commonly include sinus tachycardia, hot dry skin, dry mouth, dilated pupils and urinary retention. ECG features include prolongation of the PR and QRS intervals and in very severe poisoning the ECG may be bizarre. Metabolic acidosis and hypokalaemia can occur. Central effects commonly include ataxia and drowsiness which may lead to deep coma, respiratory depression and convulsions. Increased tone and hyperreflexia may be present with extensor plantar reflexes. In deep coma all reflexes may be abolished. Hypotension may occur.

Epidemiology
The AAPCC reported four deaths from imipramine between 1983-2000. The dose was unknown in all cases. There were no reports in the data from ONS of unintentional deaths from ingestion of imipramine by children under 5 years in England and Wales between 1993-1999.

In the HASS sample of attendances by children under 5 years at 18 emergency departments between 1996 and 1999, imipramine was implicated in three incidents resulting in a stay of one day or more in hospital.

Two of the children under 5 years with features of serious poisoning reported in the NPIS enquiry database between March 1997 and December 2001 had ingested imipramine alone. The dose was known in only one case and was 16 tablets. Both these children developed convulsions and arrhythmias.

Cases in the literature
There are several cases of imipramine poisoning in the older literature (Table 10). The more recent papers discussing tricyclic antidepressant poisoning are mostly case series with no individual case reports on specific drugs.

Table 10: Summary of imipramine cases reported in the literature.

Severity of poisoning	Age	Dose	Clinical effects	Reference
3	1.5 y	15-20 x 25 mg tablets	Coma, convulsion, hypotension, respiratory distress and ECG changes.	Alajem and Albagli, 1962
3	19 m	50 x 25 mg	Coma, convulsions, ECG changes, and hypotension.	Arneson, 1961
3	3 y	200 mg	Convulsion, cardiac arrest.	Brown *et al.*, 1971
3	nk 4.3kg	70 mg/kg	Coma, convulsions, hypotension, arrhythmias.	Brown *et al.*, 1971
3	22 m	20 x 25 mg	Opisthotonus, convulsions, respiratory depression.	Garrison and Moffitt, 1962
3	3y 8m 13.6kg	18 x 25 mg	Coma, convulsions, ventricular tachycardia.	Southall and Kilpatrick, 1974
4	11m 10 kg	10-15 x25 mg	Convulsions, coma, cyanosis, respiratory depression, severe acidosis, arrhythmias, death at 42 h.	Fouron and Chicoine, 1971

NPIS cases

Childhood ingestions of imipramine have been occasionally reported to NPIS (L). Follow up information was available for 39 cases, of which 14 were fatal. There were 31 cases where the dose ingested was estimated or known; this ranged from 25 mg to a possible maximum of 1250 mg, and the dose ranges for each level of PSS are shown in Table 11. Another five deaths were reported where tablet strength was not known, but where the number of tablets ingested was estimated to be 20-60.

Table 11: Severity of poisoning in cases of imipramine ingestion by 0-5 year old children reported to NPIS (L) with follow up details available including estimated dose ingested.

Severity of poisoning	Range of imipramine dose (mg)	No of patients	Mean age (months)	Sex m/f	Number of tablets dose range equivalent to	
					10 mg tablet	25 mg tablet
0	25-375	5	26	4/1	2.5-37.5	1-15
1	125-500	4	24	4/0	12.5-50	5-20
2	75-1000	9	29	6/3	7.5-100	3-40
3	500-900	4	26	1/3	50-90	20-45
4	120-1250	9	22	6/3	12-125	4.8-50

Ingestion of more than 500 mg appears to be associated with definite toxicity, but deaths were reported following ingestion of less than this (Table 12).

Table 12: Comparison of dose ingested with symptom severity in cases of imipramine ingestion by children under 5 years old reported to NPIS (L).

Maximum Dose	*Poison severity score*					Totals
mg	0	1	2	3	4	
25	1					1
30	1					1
<60	1					1
75			1			1
120					1	1
125					1	1
150	1		1			2
150-175					1	1
200		1	1			2
300		1				1
375	1		1			2
380			1			1
400			1			1
125-500		1				1
250-500		1				1
500				1	1	2
625				1		1
600-650				1		1
675			1			1
750			1		3	4
900				1		1
<1000			1			1
750-1000					1	1
1250					1	1
Totals	5	4	9	4	9	31

Toxicity

A childhood fatality from a dose as low as 15 mg/kg, equivalent to 6 x 25 mg tablets in a 10 kg child, was reported by Koren, (1993), but the source of this information was not specified. From a review of 9 fatal cases in children reported to the NPIS (L) and one report in the literature (Fouron and Chicoine, 1971) the lowest dose implicated in death was 120 mg, equivalent to 4.8 x 25 mg tablets, taken by a one year old child (Table 12). A dose equivalent to three dose units was associated with

moderate toxicity (PSS 2). Eight of the nine cases with PSS 2 and all four of the cases with only mild toxicity (PSS 1) had taken a dose greater than the lowest dose associated with death.

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Amoxapine

Amoxapine is a dibenzoxazepine tricyclic antidepressant with actions and uses similar to those of amitriptyline. Amoxapine is available as 50 mg and 100 mg tablets (150 mg tablets have recently been withdrawn). It is one of the less sedating tricyclics with mild antimuscarinic effects; it also inhibits the reuptake of dopamine. NPIS (L) recommends observation in hospital following ingestion of any quantity of amoxapine in a child.

Clinical effects of poisoning

Intoxication with amoxapine can result in respiratory depression, hypotension, prolonged seizures, coma, hyperthermia, rhabdomyolysis and renal failure. Cardiac dysrhythmias and conduction delays are not a prominent feature of overdose, but have been reported, usually in patients with severe neurological toxicity. Anticholinergic effects are not prominent. Neuroleptic malignant syndrome has been reported after overdose and therapeutic doses.

Epidemiology

In 1993, the AAPCC reported the death of a 17 month old following ingestion of an unknown amount of amoxapine (Litovitz *et al.*, 1994). In England and Wales, between 1993 and 1999, the ONS records include one child under 5 years who died after ingesting amoxapine. The NPIS enquiry database between March 1997 and December 2001 included one a report of a child under 5 years with severe poisoning from ingestion of amoxapine alone, who subsequently died. It was not possible to obtain coroner's records or a case history, but NPIS (L) had received several enquiries about this case while the child was being treated in hospital, and the dose recorded on the NPIS (L) enquiry record was 100 mg.

No incidents of amoxapine ingestion were reported in the sample from HASS of attendances at 18 emergency departments between 1996 and 1999 by under 5 year olds resulting in a hospital stay of one day or more.

Case reports in the literature

Two cases, one of them fatal, are reported in the literature (Table 13). The child who died was a 15 month old male infant (10 kg) who ingested an estimated 250 mg (5 x 50 mg tablets) of amoxapine and had a serum concentration as 0.896 mg/L (therapeutic 0.1 mg/L), with 0.07 mg/L of 8-hydroxyamoxapine (therapeutic 0.5 mg/L). There was no cardiovascular toxicity. The author commented that the fatal outcome was possibly due to the 8 hour delay in controlling seizures which were refractory to phenobarbital, diazepam, phenytoin, naloxone, physostigmine and paraldehyde, rather than to toxicity of the drug itself (Shepard, 1983).

Table 13: Summary of amoxapine cases involving children under 5 years reported in the literature.

Severity of poisoning	Age	Dose (no. of tablets)	Dose (mg)	Clinical effects	Outcome	Reference
2	3 years	2	200	Drowsy, tachycardia.	Recovered.	Litovitz and Troutman, 1983
4	15 months (10 kg)	5 x 50 mg	250	Convulsions, hyperthermia.	Died 144 h after ingestion.	Shepard, 1983

NPIS cases

There were only three follow-up case reports on NPIS files. The tablet dose was estimated to be one or two tablets, but in one case the tablet size was not recorded. The patients suffered only minor to moderate clinical effects. These three cases and the report retrieved from the NPIS enquiry database of the child who died are summarised in Table 14.

Table 14: Summary of amoxapine cases reported to NPIS (L) with follow up.

Severity of poisoning	Age	Dose (No. of tablets)	Dose (mg)	Dose (mg/kg)	Clinical effects	Outcome
1	2y	1	150	12	Drowsy.	Recovered.
2	2y	2	100	8.3	Bradycardia.	Recovered.
2	9m	2	unknown	unknown	Hypotension.	Recovered.
4	1y	unknown	100	unknown	Convulsions less than 1 h after ingestion.	Died (data from time of call only).

Toxicity

The two fatal cases were both reportedly due to ingestion of amounts equivalent to less than 8 tablets: one from five 50 mg tablets ingested by a 15 month old child, the other from 100 mg ingested by a one year old, equivalent to 2.5 and one respectively of the 100 mg tablets. The lowest dose in the three cases with mild to moderate toxicity was 100 mg, equivalent to one dose unit.

References

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Carbamazepine

Carbamazepine is an iminostilbene anticonvulsant that is related chemically to the tricyclic antidepressants. It is available as 100, 200, 400 mg tablets and 200, 400 mg modified release tablets (plus a liquid formulation and suppositories).

Its licensed indications in the UK include partial and secondary generalised tonic-clonic seizures, some primary generalised seizures, trigeminal neuralgia and prophylaxis of bipolar disorder when unresponsive to lithium. It is also used as an adjunctive therapy in depression and other psychiatric disorders, and for diabetes insipidus. In children up to the age of 12 years therapy is started at 5 mg/kg once daily or 2.5 mg/kg twice daily, increased by 2.5-5 mg/kg every 3-7 days to achieve the maintenance dose, typically 5-10 mg/kg (RCPCH, 1999). NPIS (L) recommends observation in hospital for ingestion of >20 mg/kg by a child.

Carbamazepine causes central nervous system (CNS) depression and at high doses can be proconvulsant. It has anticholinergic properties, depressing gut motility, and this combined with its sedative properties can lead to apparent recovery of consciousness followed by a relapse into coma. This pattern may be repeated, and has been referred to as a cyclic coma. Cardiovascular toxicity (dysrhythmias and heart block) can occur, particularly in patients with underlying cardiovascular disease (Durelli et al., 1989), but is not common in children.

Clinical effects of poisoning
A therapeutic concentration of carbamazepine is 25-50 mcmol/l (6-12 mcg/ml) (Macnab *et al.*, 1993). Toxic effects include gastric irritation (nausea and vomiting), nystagmus, diplopia, ataxia and headache. The anticholinergic effects reported include dilated pupils, urinary retention, tachycardia and depression of gut motility. The most important effect in overdose is CNS depression, with drowsiness progressing to a coma, which may be cyclical, and respiratory depression. Convulsions frequently occur, and can lead to aspiration of stomach contents if not brought under control (Denning *et al.*, 1985).

Carbamazepine in overdose has been reported to cause cardiovascular effects including hypotension, AV block and bradycardia, but these are not common (Apfelbaum *et al.*, 1995). There have also been reports of extrapyramidal symptoms following overdose. Hyponatraemia and both hyperthermia and hypothermia and have occasionally been reported (Macnab *et al.*, 1993).

Epidemiology
No deaths of children under 5 years due to carbamazepine were reported in the ONS data for England and Wales from 1993-1999, but there were four fatal cases of carbamazepine poisoning reported in the AAPCC data (Table 15).

Table 15: Summary of fatal cases of carbamazepine poisoning reported in the AAPCC data.

Age/sex	Amount	Clinical effects reported	Reference
2 y /NS	NS	Not stated. Concentration 19 mg/L (post-mortem).	Litovitz *et al.*, 1987
2.5 y/F	27 chewable tablets 100 mg, 2.7 g	Coma, respiratory depression, convulsions, arrhythmias, ileus, hypotension, arrested. Died 2 days post-ingestion. Initial concentration 59 mg/L, then 109 mg/L (6 h). Post-mortem: aspiration pneumonia, renal congestion and hepatomegaly.	Litovitz *et al.*, 1990
2 y/F	NK tablets, her own medication	Irritable, drowsy, status epilepticus, pyrexia, brain death. Concentration on admission 38.8 mg/L (had been 1.8 mg/L before overdose).	Litovitz *et al.*, 1993
5 y/M	33 x 200 mg tablets 6.6g	Coma by 4 h, lethargy, ileus, hypotension, respiratory distress and cardiac arrest. Concentration 44 mg/L (on arrival).	Litovitz *et al.*, 1998

In the HASS data carbamazepine was one of the more frequently reported solid drugs implicated in a sample of exposures in children aged up to 5 years from 18 hospitals between 1996 to 1999 resulting

in a stay of one day or more, accounting for 12 of a total 452 solid drugs reported. In all 12 cases, carbamazepine tablets were ingested by children aged from 1 to 3 years (mean age 2 years). Three cases included two days in hospital, and 9 cases one day in hospital. The dose ingested was estimated in four cases: 1 x 200 mg, 3 x 200 mg, 1-2 tablets of unknown strength, and 3 tablets of unknown strength.

There were seven reports in the NPIS enquiry database from March 1997-December 2001 of children under 5 years with moderate or severe clinical effects due to ingestion of carbamazepine as the only agent ingested. Convulsions were reported in four cases, drowsiness in one, coma in three and respiratory depression in one. Amounts ingested were unknown in three cases of accidental ingestion. The remainder involved two accidental ingestions of 800 mg, ingestion of 250 mg (therapeutic error), and another therapeutic error of two doses of 600 mg (10 times the patient's dose). The children were aged from 1-4 years, and all but two were female.

Tibballs (1992) reported that 82 children (1-17 years) were admitted to hospital over a 10 year period for carbamazepine toxicity, out of a total of 3186 (2.6%) children with poisoning. Of the four deaths from poisoning, two were from carbamazepine. Of the 82 carbamazepine cases, 45 (55%) patients had a Glasgow coma scale (GCS) of 9-15, 27 (33%) a GCS of 5-8 (including two with convulsions), and 10 (12%) had a GCS of 3 or 4. Of the latter group, 6 had seizures and 8 required mechanical ventilation for respiratory failure.

Cases in the literature

Product information

The lowest known lethal dose reported in a child is 1.6 grams, ingested by a 3 year old girl who died of aspiration pneumonia (Product Information Tegretol® XR, 2000). Ingestion of 10 grams of carbamazepine by a 6-year-old male resulted in coma and respiratory depression (Tech Info, 1968). Full recovery was noted within 24 hours. Ingestion of 400 mg of carbamazepine by a 22 month old male resulted in drowsiness, which resolved after gastric lavage was performed (Tech Info, 1968).

Case reports - dose ingested known or estimated

There are 6 cases in the literature of severe or fatal carbamazepine toxicity in children aged under 6 years where the dose ingested was known or estimated (Table 16). These cases are presented as case reports (Sullivan, 1981; Deng *et al.*, 1986; Chatterjee *et al.*, 1992; Schuerer *et al.*, 2000) or individual cases from a case series (Tibballs, 1992); the remaining cases are detailed in the next section. All cases resulted in severe toxicity, including one death from ingestion of eight 200 mg tablets (Chatterjee *et al.*, 1992). In all cases the dose ingested could have been reached by ingestion of fewer than 8 tablets of the 400 mg strength carbamazepine, and in all but one case by ingestion of 8 or fewer 200 mg tablets, as shown in Table 17.

Table 16: Clinical effects from ingestion of carbamazepine in children aged under 6 years reported in the literature.

Effect	800 mg	1200 mg	1300 mg	1600 mg	2000 mg	Total
Number of patients	2	1	1	1	1	6
Ataxia					1	1
Nystagmus					1	1
Lethargy					1	1
Dystonic reaction			1			1
Bradycardia	1				1	2
Acidosis				1		1
Seizures		1	1	1	1	4
Coma	2	1	1	1	1	6
Respiratory failure			1			1
Hepatomegaly				1		1

Table 17: Severity of poisoning related to number of tablets ingested in cases of carbamazepine ingestion by children under 6 years old reported in the literature.

Severity of poisoning	Range of carbamazepine dose (mg)	No of patients	Mean age (months)	Sex m/f/NK	Number of tablets dose range equivalent to			Outcome
					100mg	200mg	400mg	
3	800-2000	5	27	1/1/3	8-20	4-10	2-5	Recovery
4	1600	1	36	0/1/0	16	8*	4	Death (toxic hepatitis)

* this was the reported ingestion

Cases in the literature case reports: dose ingested not known

Two case series of carbamazepine toxicity in children give specific information about some individual patients where the dose ingested was not known (Tibballs, 1992) or not reported (Macnab *et al.*, 1993). Tibballs (1992) conducted a study over 10 years of all children aged 1-17 years admitted to hospital with carbamazepine poisoning, comprising 82 patients. Macnab *et al.* (1993) collected similar data over a 4 year period for 16 children aged between 16 months and 16 years with elevated serum carbamazepine concentrations. Accidental poisoning occurred in seven cases, all children were under 38 months. Three of these resulted in serious toxicity (including a death three weeks post-ingestion of multi-organ failure), three in mild toxicity, and one child remained asymptomatic.

Tibballs (1992) presented data for the 10 children with severe toxicity, of whom five were aged under 6 years and the dose ingested was unknown. The data in Macnab *et al.* (1993) included 10 children aged under 6 years. Clinical effects in these children are summarised in Table 18.

Table 18: Summary of clinical effects for case reports where the dose ingested was not known or not reported, from the literature.

Parameter	**Tibballs 1992 n=5**	**Macnab et al 1993 n=10**	
Mean age, months (range)	40 (24-60)	34 (18-60)	
Median carbamazepine level, mcmol/l (range)	Peak: 280 (145-343)	On admission: 103 (62-244)	
Clinical effects			**Total**
Asymptomatic	0	1	1
Ataxia	-	3	3
Nystagmus	-	1	1
Drowsy	-	4	4
Slurred speech	-	1	1
Bradycardia	1	-	1
Hypotension	5	-	5
AV block	1	-	1
Seizures	4	1	5
Coma	5	3	8
Respiratory failure	5	3	8
Ileus	1	-	1
Pulmonary Oedema	1	-	1
Death	1 (septicaemia)	1 (multi-organ failure)	2

Literature reports: case series

Several case series of carbamazepine toxicity that focus on clinical effects and carbamazepine level, rather than dose ingested, have been reported in the literature (Bridge *et al.*, 1994; Stremski *et al.*, 1995, Lifshitz *et al.*, 2000), although another review included some limited information about doses (Tibballs, 1992; summarised above). Some of these include both younger and older children (Tibballs, 1992; Bridge *et al.*, 1994; Stremski *et al.*, 1995), and therefore include intentional as well as accidental exposures. Cases of chronic toxicity (Bridge *et al.*, 1994) or toxicity from drug interactions (Tibballs 1992) were also included by some. These case series' include all paediatric cases of

carbamazepine ingestion (Lifshitz *et al.*, 2000; Tibballs, 1992) or toxicity defined by a particular serum level (Bridge *et al.*, 1994; Stremski *et al.*, 1995) or attending the hospital over a particular time period. In all case series, cases involving ingestion of drugs other than carbamazepine (except in the case of drug interactions) were excluded.

Bridge *et al.* (1994) retrospectively examined case notes for 30 children aged 1-18 years who had carbamazepine concentrations greater than 9 mg/l (38 mcmol/l), and no other drug ingestion. The cases were divided into acute (18), acute on chronic (7) and chronic (5, not considered further) ingestions, and included 17 accidental childhood ingestions (plus 2 accidental therapeutic errors). The mean age of all 30 was reported as 6.0 ±5.5 years, and the group included 15 males and 15 females. Peak levels were highest in the acute on chronic group (30.3±7.7 mg/l, 127±32 mcmol/l), which was significantly higher than the acute group (22.3±9.4 mg/l, 93.7±39 mcmol/l; $p<0.0025$). Peak levels were significantly higher in patients with seizures, coma or requiring ventilatory support than those without these effects ($p<0.01$).

Stremski *et al.* (1995) evaluated children presenting with a detectable serum carbamazepine concentration over an 18 month period, and divided the 77 children into those with a peak level of 12 mcg/ml (50 mcmol/l) or less (16 children, of which 9 were 6 years and younger), and those with higher levels (61 children, of which 42 were 6 years and younger). 58% were boys. Patients who developed coma, dystonic reactions or apnoea had significantly higher mean peak serum concentrations ($p=0.0002$, <0.0001, 0.008 respectively) than those who did not.

Lifshitz *et al.* (2000) reviewed medical records of children who were admitted to the paediatric department over a 6 year period for accidental acute ingestion of carbamazepine belonging to a family member. Of the 14 children aged 2-5 years (mean 3.8 years) 65% were male. No serious toxicity developed.

In Tibballs' (1992) 10 year review of 82 children aged 1-17 years admitted to hospital with carbamazepine poisoning, it was determined that the carbamazepine level was related to the depth of coma ($p<0.001$), the occurrence of convulsions ($p=0.002$), the requirement for mechanical ventilation ($p<0.001$) and the occurrence of hypotension ($p<0.001$). Vomiting, ataxia and CNS depression were reported commonly in these case series, as shown in Table 19. Seizures were not uncommon.

Table 19: Summary of clinical effects reported in literature case series.

Group	Bridge et al (1994)	Bridge et al (1994)	Stremski et al (1995)	Stremski et al (1995)	Lifshitz (2000)	Tibballs (1992)
	Acute	Acute on chronic	Peak level <12mcg/ml (50mcmol/l)	Peak level >12mcg/ml (50mcmol/l)	n/a	n/a
Number of patients	18 (15 up to 5 years)	5 (2 up to 5 years)	16	61	14	82
Mean cbz level (range if given)	22.3±9.4 mg/l 93.7±39 mcmol/l	30.3±7.7mg/l, 127±32mcmol/l	7.0±4.4mcg/ml (2-12)	25.4±8.4 mcg/ml (15-44.8)	25±4.64 mcg/ml (8-32 mcg/ml)	17.5mcg/ml (8.9-30.7), 73 mcmol/l (37-128)
Clinical effects						
Vomiting	5 (28%)	3 (43%)	4 (25%)	22 (36%)	-	8 (10%)
Ataxia	10 (56%)	2 (29%)	1 (6%)	29 (47%)	4 (29%)	24 (29%)
Nystagmus	2 (11%)	1 (14%)	0	19 (31%)	12 (86%)	17 (21%)
Lethargy	16 (89%)	7 (100%)	0	37 (60%)	-	-
Drowsy	-	-	-	-	10 (71%)	36 (44%)
Hallucinations	-	-	-	-	-	Occasionally
Dystonic reaction	-	-	0	7 (11%)	0	3 (4%)
Tachycardia	-	-	-	-	2 (14%)	Frequently

Group	Bridge et al (1994)	Bridge et al (1994)	Stremski et al (1995)	Stremski et al (1995)	Lifshitz (2000)	Tibballs (1992)
	Acute	Acute on chronic	Peak level <12mcg/ml (50mcmol/l)	Peak level >12mcg/ml (50mcmol/l)	n/a	n/a
Hypotension	1 (6%)	2 (29%)	-	-	-	7 (9%)
Arrhythmias	2 (11%)	1 (15%)	-	-	0	-
Seizures	3 (17%)	2 (29%)	0	7 (11%)	0	8 (10%)
Coma	5 (28%)	2 (29%)	0	13 (21%)	0	37 (45%)
Ventilatory support needed	4 (22%)	2 (29%)	-	-	-	8 (10%)
Apnoea	-	-	0	6 (10%)	-	-
Death	0	0	0	0	0	2 (Septicaemia; left ventricular failure)
Nystagmus & drowsiness	-	-	-	-	8 (57%)	-
Nystagmus & ataxia	-	-	-	-	4 (29%)	-
Drowsiness & tachycardia	-	-	-	-	2 (14%)	-

Notes: - indicates that this clinical effect was not mentioned in the paper.

NPIS (L) follow-up case data

In children aged under 5 years for which follow-up data was received, there were 17 cases where the dose ingested was known or estimated. The range was 300-4800 mg, median dose 600 mg. The number of tablets ingested was reported in four cases, as one 400 mg, two 200 mg, four 100 mg, and three 200 mg tablets respectively. The maximum ingested dose of 4800 mg could have been as many as 48 x 100 mg tablets or as few as 12 x 400 mg tablets; in every other case the total dose ingested could have been fewer than 8 tablets. Clinical effects from these cases are reported in Table 20. Although there are few cases, there appears to be a dose-response relationship, as shown in Table 21.

Table 20: The frequency of clinical effects in cases of carbamazepine ingestion by children under 5 years old reported to NPIS (L).

Clinical effect	Number of cases
asymptomatic	5
drowsy	7
vomiting	5
coma	3
convulsions	3
respiratory depression/cyanosis	2
ataxia	2

Clinical effect	Number of cases
dizziness	1
restless	1
urinary retention	1
opisthotonus	1
hypotension	1
bradycardia	1

In most of the reported cases the number of tablets ingested is unknown, and only the total dose ingested has been reported. Table 22 demonstrates that the reports of at least moderate toxicity could have occurred from ingestion of fewer than 8 unit doses.

Table 21: Comparison of dose ingested with symptom severity in cases of carbamazepine ingestion by children under 5 years old reported to NPIS (L).

Estimated dose	Poison severity score					Totals
	0	1	2	3	4	
300 mg	1					1
400 mg	3	2				5
600 mg	1	1	1			3
1300 mg		1				1
1400 mg		1				1
2000 mg		1		2		3
2800 mg			1			1
3000 mg		1				1
4800 mg				1		1
Totals	5	7	2	3	0	17

Table 22: Severity of poisoning in cases of carbamazepine ingestion by children under 5 years old reported to NPIS (L) related to number of tablets ingested.

Severity of poisoning	Range of carbamazepine dose (mg)	No of patients	Mean age (months)	Sex m/f	Number of tablets dose range equivalent to		
					100mg tablet	200mg tablet	400mg tablet
0	300-600	5	24	0/5	3-6	1.5-3	<1-1.5
1	400-3000	7	25	4/3	4-30	2-15	1-7.5
2	600, 2800	2	18, 60	1/1	6-28	3, 14	1.5-7
3	2000-4800	3	24, 24, 48	1/2	20-48	10-24	5-12

Toxicity

In the cases reviewed here the only fatal case providing an estimate of the dose involved ingestion of eight 200 mg tablets (Chatterjee *et al.*, 1992), equivalent to four of the highest dose 400 mg tablets, although ingestion of more than this amount has been survived (up to 4.8 g, equivalent to 12 x 400 mg tablets in one case). Nevertheless the lowest dose resulting in severe toxicity (PSS 3) from 7 cases reported in both the literature and NPIS (L) case data was 800 mg (equivalent to two 400 mg tablets).

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Methadone

Methadone is an opioid analgesic that is dispensed to opiate addicts and is the opioid analgesic most commonly dispensed for this purpose.

In the UK, methadone is dispensed to addicts either as 5 mg tablets, as an oral liquid 1 mg/ml, available as a syrup or a sugar free liquid, or as ampoules for injection. In the UK, methadone is usually dispensed in brown amber bottles with child-resistant closures. Tablets of 10 mg and 40 mg tablets are available in some countries.

It is given to patients to take home and this accounts for the frequency of ingestion by young children. It has no recommended indications for use in children. NPIS (L) recommends observation in hospital for any quantity ingested by a child.

Clinical effects of poisoning
Opioid drugs act on various receptors that are distributed in distinct patterns throughout the brain, spinal cord and gastrointestinal tract. Opioids may act on these receptors as full or partial agonists or antagonists. There is great individual variation in sensitivity to opioids and in overdose they can cause severe effects, particularly respiratory depression.

Clinical effects of overdose include nausea, vomiting, drowsiness, decreased gut motility, urinary retention, constipation, bradycardia, convulsions and coma. Hypotension occurs occasionally. Respiratory depression is common and may lead to cyanosis and respiratory arrest. Hypoxia due to respiratory depression is the most frequent cause of death in fatal opioid intoxications. In severe cases non-cardiogenic pulmonary oedema and cardiovascular collapse may occur. Methadone has a long half-life, and the effects from poisoning may be prolonged for 24 to 48 hours, and may recur after a single dose of the opioid antagonist, naloxone, which has a short half-life.

Opioids usually produce pinpoint pupils, but they may be dilated if the patient has hypoxia, respiratory depression, hypotension or bradycardia.

Epidemiology
The epidemiology of child poisoning with methadone is different to the other drugs reviewed in this report because of the combination of a several factors:

- There are a significant number of severe poisonings and deaths.
- Case reports indicate that there are a significant number of intentional poisonings where the drug was given to a child by an adult, although harm may not have been intended. Some such cases involved children under 6 months old.
- Case reports indicate that it has been a common practice to dilute the liquid formulation in juice, that is then mistaken for juice drinks by children and caregivers.
- Poisoning has been reported following contamination of antibiotics with methadone when diluted in community pharmacies (Roland et al., 1984; Gayle et al., 1991; Lalkin et al., 1999).

Cases of ingestion of liquid have been included in this review if an estimate of dose was given, because they provide additional data on toxicity. For the same reason, cases that were clearly not accidental poisoning have also been included if an estimate of dose was given, and it is possible that other non-accidental cases that were not identified as such, have been included here.

In England and Wales, between 1993-99, methadone was reported as the cause of 4 out of 13 childhood deaths due to accidental poisoning by drugs in the mortality statistics from ONS, and between 1983-2000 it was the third most frequent cause of childhood deaths reported to the AAPCC, causing 9 deaths (8% of total). Details of these are shown in Table 23.

Table 23: Summary of the fatal methadone cases with details reported in the AAPCC annual reports.

Age/sex	Amount	Clinical effects reported	Reference
1 y/M	35 mg in 8oz of milk, drank 1.5 oz = 6.6 mg	Respiratory and cardiac arrest. Resuscitated but died next day after cardiac arrest. Methadone put into bottle by older sibling.	Litovitz *et al.*, 1988
5 y/F	10 mg	Mother's medication. Given to 'help her stop coughing'. Found 5 hours later cyanotic, hypothermic and unresponsive. Resuscitation unsuccessful.	Litovitz *et al.*, 1990
19 m/M	unknown (as syrup)	Coma, cardiac arrest. PM concentration 0.5 mg/L. Mother and partner on methadone.	Litovitz *et al.*, 1996
2 y/M	unknown	Bizarre movements, apnoea, dead on arrival about 12 h post-ingestion. Uncle's medication fed by sibling.	Litovitz *et al.*, 1996
2 y/M	up to 12 ml (120 mg)	Cyanosis and coma within 1 h, cerebral oedema and multiple infarcts. Died 3 days post-ingestion.	Litovitz *et al.*, 1998
5 m	unknown	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).	Litovitz *et al.*, 2000
22 m/NS	unknown	Apnoea, died several days after admission. Antemortem concentration 0.1mg/L. Grandfather on methadone.	Litovitz *et al.*, 2001
8 m/NS	unknown	Found dead. PM concentration 0.23 mg/L. Both parents on methadone.	Litovitz *et al.*, 2001

The sample from HASS of attendances by children under 5 years at 18 hospital emergency departments between 1996-1999 resulting in a stay of one day or more contained two reports of ingestion of methadone syrup, but no reports of ingestion of methadone tablets.

There were five reports of children under 5 years with moderate to severe clinical effects from ingestion of methadone alone in the NPIS enquiry database from March 1997 to December 2001. The formulation ingested was only recorded in one case, which involved an unknown amount of tablets. A 3 year old died after ingestion of an estimated 35 mg. Two children were reported to be comatose, and two to have had respiratory arrest, but the outcome was unknown in these four cases, although at the time of the call two children were responding to naloxone.

A survey of children presenting to Merseyside hospitals between 1989-93 (Binchy *et al.*, 1994) found 44 episodes of accidental ingestion of methadone syrup by children up to 7 years old; 2 died, 10 had respiratory depression, 2 had convulsions, and 17 were asymptomatic. The number of accidental methadone ingestions doubled between 1990-92 and this was associated with an increase in the number of patients at the Liverpool Drug Dependency Unit.

This epidemiological data indicates that childhood methadone ingestion is a significant problem in the UK, in both its frequency and severity. In recent years most ingestions have involved the syrup rather than tablets. This reflects the low proportion of prescriptions for tablets compared with the syrup following UK government recommendations, in 1996, that methadone tablets should no longer be prescribed for the treatment of drug misuse because of the practice of crushing and injecting tablets. A review of a 1 in 4 sample of community pharmacies, one year before and one year after the recommendations, found that the proportion of prescriptions in tablet form was reduced from 12.1% to 9.5%, but the annual number of prescriptions for methadone tablets still increased because the number of opiate addicts presenting for treatment increased by 20% per annum (Strang and Sheridan, 1998).

Childhood methadone ingestion is also a problem in Germany. Calls to the Berlin Poisons Centre about young children with serious symptoms due methadone ingestion increased from 4 in 1997 to 17 in 1999. The increase followed implementation of regulations that allowed addicts to take home seven

daily doses of 30-50 mg per day, but numbers have begun to fall again following stricter regulation of dispensing in child-resistant packaging and introduction of a central register of methadone prescriptions (Giftnotruf, Berlin, 2000, and personal communication, M Brockstedt, 2002).

Cases in the literature

A series of cases reported in 1973 (Aronow *et al.*, 1973) included 17 cases of ingestion of methadone tablets by children. The 15 cases for which a dose was reported are listed in Table 24. Four children had moderately severe poisoning, but none were reported to have died.

Table 24 Cases of accidental ingestion of methadone, with information on dose ingested. From Aronow et al, 1973, with Poison Severity Score scored added.

PSS	Age (months)	weight (kg)	Tablet size (mg)	No. of tab-lets	Total dose (mg)	dose (mg/kg)	urine test +ve *	Details	Therapy	Case No.
1	24	11.9	40	0.25	10	0.84	y	drowsy, miosis	nalorphine	36
1	11	9.4	40	0.25	10	1.06		drowsy , miosis	nalorphine	33
1	32	15	10	2	20	1.33	y	pupils reacting to light, drowsy, miosis	nalorphine	20
1	14	10.4	10	1.5	15	1.44		pupils reacting to light, drowsy		28
1	33	13	10	2	20	1.54		vomiting, drowsy, miosis	nalorphine	24
1	27	11.6	40	0.5	20	1.72		pupils reacting to light, vomiting, miosis	ipecac	38
1	18	11.3	10	2	20	1.77	y	pupils reacting to light, drowsy	nalorphine	35
1	24	12.6	10	2.5	25	1.98	y	vomiting, drowsy, pupils reacting to light, miosis	ipecac	40
1	23	11	10	4	40	3.64		drowsy, miosis	ipecac, lavage, nalorphine	23
1	29	not known	10	2	20	not known		pupils reacting to light, drowsy, miosis	ipecac	21
1	21	not known	10	0.5	5	not known		pupils reacting to light, drowsy	ipecac, nalorphine	34
2	11	9.3	10	1	10	1.08		coma, miosis	nalorphine	19
2	16	11	40	1	40	3.64		coma, miosis	nalorphine	37
2	27	13.6	10	5	50	3.68	y	dilated pupils, coma, apnoea	lavage, nalorphine	25
2	18	10.9	10	6	60	5.50	y	coma, miosis	lavage, nalorphine	32

* analysis of urine confirmatory for methadone.

Another seven case reports that include an estimate of dose ingested were found in the literature (Table 25). Two children who ingested 40 mg tablets both died (DiMaio and DiMaio,1973). Three children ingested liquid, including one child who survived severe poisoning (Sesso & Rodzvilla, 1975) and two who died (Li et al., 2000; Lorenzo, 1995). There were two reports of non-fatal poisoning from ingestion of measured doses of methadone-contaminated antibiotic.

Table 25 Cases of methadone poisoning reported in the literature with estimates of dose ingested.

PSS	Age months	Product ingested	Dose (mg)	Methadone concentration (mg/l)	Clinical effects	Reference
2	54	contaminated antibiotic	24	0.23 at 5 h after ingestion	Pre-existing respiratory infection. Coma, pinpoint pupils, tachycardia, tachypnoea.	Lalkin et al., 1999
3	7	liquid	10-13	n/a	Coma, respiratory depression, tachycardia, apnoea	Sesso & Rodzvilla, 1975
3	14	contaminated antibiotic	12	n/a	Drowsy, small pupils, respiratory distress, tachycardia, mild aspiration pneumonia	Gayle et al, 1991
4	48	liquid in juice	40	n/a	Dead on arrival	Li et al., 2000, case 1
4	4	2 x 40 mg tablets	80	n/a	Pre-existing epilepsy. Convulsions, constricted pupils, coma, vomiting, respiratory arrest, bradycardia. Died.	DiMaio, 1973, case 2
4	15	half a 40mg tablet	20	n/a	Died 2 h after admission. PM: pulmonary oedema, early bronchopneumonia.	DiMaio, 1973, case 3
4	48	liquid in juice	40	0.5	Dead on arrival	Lorenzo 1995, case 1.

Moderately severe poisoning was reported from doses ranging from 10-60 mg (Table 26). Respiratory depression was reported following a dose of 12 mg in a 14 month old child (Gayle *et al*, 1991), and deaths were reported from doses of 20-80 mg. However, other children survived doses up to 40 mg with only minor symptoms (Table 27).

Table 26: The dose range associated with each grade of severity of poisoning in the cases of methadone ingestion by children under 5 years summarised in Tables 24 and 25.

Poison Severity Score	Dose range (mg)	No of patients	Mean age (range)	No. of tablets equivalent to dose range		
				5 mg tablets	10 mg tablets	40 mg tablets
1	5-40 median 20	11	23. (11-33)	1-8	0.5-4	<0.5-1
2	10-60 median 40	5	25 (11-54)	2-12	1-6	<0.5-1.5
3	10-13	2	10.5 (7-14)	2-3	1-1.5	<0.5
4	20-80 median 40	4	29 (4-48)	4-16	2-8	0.5-2

Table 27: The association of poison severity score with dose in the cases of methadone ingestion by children under 5 years summarised in Tables 24 and 25.

Dose (mg)	*Poison Severity Score*				Total
	1	2	3	4	
5	1				1
10	2	1			3
10-13			1		1
12			1		1
15	1				1
20	5			1	6
24		1			1
25	1				1
40	1	1		2	4
50		1			1
60		1			1
80				1	1
Total	11	5	2	4	22

Toxicity

There were only seven cases with moderate to severe poisoning (PSS 2 and 3) and four fatal cases providing an estimate of the dose ingested. The doses associated with moderately severe poisoning ranged from 10-60 mg: doses equivalent to 2-12 tablets of 5 mg strength available in UK, or 1-6 tablets of 10 mg strength. The lowest dose associated with death was 20 mg (four of the 5 mg tablets or two of the 10 mg tablets), Response to these doses was variable. Ten out of 11 cases with mild toxicity (PSS 1) had taken more than the lowest dose associated with death.

A limited study of post-mortem toxicological examinations of five childhood deaths (Milroy and Forest, 2000), supported the opinion that only small amounts of methadone can cause death in a child, and provided evidence that small amounts of methadone could contribute to death by causing a prolonged period of unconsciousness that then leads to inhalational pneumonia, which is a common finding in methadone deaths. This study found an overlap between clinical therapeutic concentrations and those recorded in some fatalities, although it was recognised that post-mortem blood concentrations should be interpreted with care.

Besides variability of response, circumstances of ingestion also influence outcome. If children are taken to hospital promptly, life-threatening symptoms can be treated with the opioid antagonist, naloxone, and a rapid, full recovery would be expected, but there have been cases where considerable delay in taking a child to hospital has resulted in their death (Binchy *et al.*, 1994; Litovitz *et al.*, 1996). Delays may occur because caregivers underestimate the serious toxicity of methadone for children, or because they are afraid to report ingestion of an illegally obtained drug, or are afraid of being accused of child abuse or neglect. These are important factors that need to be taken into consideration when assessing the need for child-resistant packaging. It is also of note that in a study of the storage of methadone in the home, Calman *et al.*, (1996) considered only 43 of 87 patients were storing it safely.

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Nifedipine

Nifedipine is a calcium antagonist (calcium channel blocker) used primarily for treatment of supraventricular tachycardia, angina and hypertension.

It is available for oral administration as 5 mg and 10 mg immediate-release capsules, modified-release tablets of 10 mg and 20 mg, and long-acting tablets of 20 mg, 30 mg and 60 mg. The dose of nifedipine for children is 250-500 mcg/kg to a maximum 3 mg/kg/day. Modified-release tablets can be given 10-20 mg twice a day and slow-release tablets once a day. In children, NPIS (L) recommends observation in hospital for ingestion of 2 mg/kg or more (derived from Belson *et al.*, 1998).

Serum concentrations from therapeutic doses range from 25-100 mcg/L. A concentration of 590 mcg/L one hour post-ingestion in a toddler is consistent with ingestion of a single 10 mg capsule (Pearigen, 1993).

Nifedipine blocks the influx of calcium into various cells, primarily vascular, cardiac, and smooth muscle tissue, causing vasodilatation, with reduced peripheral resistance, blood pressure, and afterload, increased coronary blood flow, and a reflex increase in heart rate. It has little or no effect on cardiac conduction and no antiarrhythmic activity in therapeutic doses.

Clinical effects of poisoning
The major effects of overdose are hypotension and dysrhythmias, which are usually seen within 1 to 5 hours. Other possible effects include CNS depression, syncope, non-cardiogenic pulmonary oedema, hyperglycemia and reduced bowel motility. Symptoms may be delayed and prolonged following ingestion of sustained-release dosage forms. Hypotension can persist for longer than 24 hours despite treatment. Cardiac rhythm disturbances have been noted to persist for up to 7 days. Gastric concretions from sustained-release dosage forms have been found at autopsy.

Epidemiology
There were five reports of nifedipine ingestion out of a total 452 solid-dose drugs implicated in 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. There were no reports of childhood death due to nifedipine in England and Wales between 1996 and 1999, but nifedipine ranked as one of the most frequent causes of death in children in the AAPCC reports, with six deaths reported between 1983 and 2000.
There were no children under 5 years with features of moderate or severe poisoning due to ingestion of nifedipine alone recorded on the NPIS enquiry database between March 1997 and December 2001.

Cases in the literature
Two case series have been published. In a series of 85 children (mean age 3 years 2 months), with a mean ingested dose of 2 tablets of Adalat®, or 20 mg Adalat® Retard, only 2 children were symptomatic: these were aged 3 and 2 years and ingested 20 mg Adalat® Retard each, and had only vasodilation and facial flushing lasting 2 hours (Droy *et al.*, 1990).

In a retrospective series of cases involving 109 children reported to a regional poisons centre between January 1990 and December 1995, only four had minor symptoms and two had moderate effects. The lowest toxic dose was 2.7 mg/kg of a sustained release preparation (one 30 mg tablet). Thirty-two patients ingested ≥2.7 mg/kg of nifedipine SR without development of symptoms. There were no major effects or deaths (Belson *et al.*, 2000).

Eight cases were reported in the literature, including 2 deaths (Riggs *et al.*, 1987; Ramoska *et al.*, 1990; Wells *et al.*, 1990; Lee *et al.*, 2000). Table 28 lists the clinical effects reported in these cases and in the case series and the 5 fatal cases reported by the AAPCC not subsequently published elsewhere (Litovitz *et al.*, 1985, 1992, 1994, 1996 and 1999).

Table 28: Clinical effects associated with nifedipine ingestions by children of 5 years and under reported in the literature.

Clinical effects	Immediate release	slow release	total
No of patients	*8*	*7*	
Hypotension	3	6	9
Lethargy	3	2	5
Tachycardia	1	2	3
Cardiac arrest	3		3
Convulsions	3		3
Acidosis	2	1	3
Bradycardia	1	1	2
Hyperglycaemia	1	1	2
Vomiting	1	1	2
Respiratory depression	1		1

There was considerable overlap between doses associated with asymptomatic cases and those associated with severe poisoning or death (Table 29), although it is possible that some asymptomatic children never actually ingested the tablets.

Table 29: Severity of poisoning in cases of nifedipine ingestion by children of 5 years and under, from reports in the literature that include estimates of dose ingested.

	Immediate release				Slow release			
Severity of poisoning	Range of dose (mg)	No of patients	Mean age (months)	Equivalent no. of 20 mg tablets for dose range	Range of dose (mg)	No of patients	Mean age (months)	Equivalent no. of 60 mg tablets for dose range
0	10-110	4	24	0.5-5.5				
1	30	1	18	1.51				
2	200	1	12	10	30-480 median 45	4	21	0.5-8.0
4	40-800	2	12.5	2-40	10-1200 median 120	3	20	<0.5-20

NPIS cases

The NPIS case files contained 16 cases reports, all with an estimate of dose ingested. Half of the children ingested a slow release preparation. One child died, six suffered minor or moderate poisoning, and nine remained asymptomatic. Table 30 lists the clinical effects in the six cases that survived; no details of clinical effects prior to death were available for the child who died.

Table 30: Clinical effects associated with nifedipine ingestions by children of 5 years and under reported to NPIS (L).

Clinical effects	Immediate release	Slow release	Total
no of cases	*4*	*2*	*6*
Hypotension	2		2
Tachycardia	2		2
Possible reflex hypertension	1	1	2
Bradycardia		1	1

As with cases reported in the literature there was overlap in doses ingested without symptoms and those that caused moderate or severe poisoning (Table 31).

Table 31 Severity of poisoning in cases of nifedipine ingestion by children of 5 years and under, from reports to the NPIS that include estimates of dose ingested.

	Immediate release				Slow release			
Severity of poisoning	Range of dose (mg)	No of patients	Mean age (months)	Equivalent no. of 20 mg tablets for dose range	Range of dose (mg)	No of patients	Mean age (months)	Equivalent no of 60 mg tablets for dose range
0	10-180	4	23.5	0.5-9	20-200	5	32	0.3-1.5
1	5-60	3	44	0.25-3	20	1	24	0.3
2	40-60	1	36	2-3	30	1	24	0.5
4					120	1	36	2

Toxicity

A total of 35 cases, including nine fatal cases and seven cases of moderately severe poisoning were available for review. Information on dose ingested was available for 31 cases of which 18 were symptomatic (Table 32). The range of doses associated with each grade of poisoning is wide and with so few cases in each category it is difficult to judge the accuracy of the dose reported. The lowest of the six fatal doses reported in the literature is 10 mg for a sustained release preparation ingested by a 14 month old (Lee, 2000), equivalent to one tablet of 10 mg strength, and 40 mg for an immediate release preparation ingested by an 11 month old (Litovitz *et al.*, 1992). Four out of the five cases with mild toxicity (PSS 1) had taken more than these lowest fatal doses.

Table 32: Summary of cases reports that include estimates of dose ingested in the literature and to the NPIS: the lowest dose and dose range associated with each grade of poisoning severity.

Preparation ingested	Number of patients	Non toxic dose range (PSS 0) (mg)	Number symptomatic	Lowest dose and range causing PSS of 2 (mg)	Lowest fatal dose and range (mg)
SR	15	20-200	10	30 30-480	10 10-1,200
IR	16	10-180	8	40 40-200	40 40-800

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Quinine

Quinine is an alkaloid obtained from the *Cinchona* tree, and is the laevorotatory stereoisomer of quinidine. It is used in the treatment of falciparum malaria and in the treatment of nocturnal leg cramps, particularly in the elderly.

Solid-dose preparations are available in the following strengths:

Quinine dihydrochloride: 300 mg tablets
Quinine hydrochloride: 300 mg tablets
Quinine sulphate: 125 mg, 200 mg, 300 mg tablets

All these salts contain equivalent amounts of quinine base. Quinine bisulphate, 300 mg tablets are also available, however the amount of quinine in this salt is equivalent to just over 200 mg of the above salts. The paediatric dose for oral treatment of malaria is 10 mg/kg every 8 hours for 7-10 days. NPIS (L) recommends observation in hospital for ingestion of more than 15 mg/kg by a child.

Quinine is rapidly absorbed. The therapeutic half-life varies, depending on age and clinical status, and may be prolonged in overdose. After oral dosing, the peak serum concentration is reached in 1-3 hours, with a half-life of approximately 12 hours (Gratton Smith *et al.*, 1987). Serum quinine concentrations do not correlate well with clinical toxicity, but concentrations greater than 10 mg/L (26.5 mg/L) less than 10 hours after ingestion and greater than 15 mg/L more than 10 hours after ingestion are likely to be associated with significant toxicity (Boland *et al.*, 1985).

In overdose, quinine has a quinidine-like effect on the myocardium although it is less potent. It also acts as a membrane-stabilizing agent and may have alpha-adrenergic blocking activities; in addition quinine has a toxic effect on the retina that can result in blindness.

Clinical effects of poisoning

Mild intoxication causes nausea, vomiting and diarrhoea. Tinnitus and deafness with dizziness and headache are also common and may occur very rapidly after an overdose. Initially the skin may appear hot and flushed, and there may be sweating; however this may be followed by hypothermia. Tachycardia, hypokalaemia and tachypnoea may occur. Severe cases develop respiratory depression and cyanosis, hypotension, coma and convulsions, with ECG changes and ventricular dysrhythmias that may be fatal. Rarely anuria, acute tubular necrosis and renal failure have also been reported.

Toxic effects on the retina may be delayed for 12 to 24 hours, and include dilated pupils, which may become unreactive, blurred vision and loss of colour vision. In severe cases there may also be restriction of the visual field or blindness. All these effects may resolve over 24 hours or persist for several weeks, but blindness or restriction of the visual field may be permanent. Fixed dilated pupils are reported frequently in children following quinine overdose (Grattan-Smith *et al.*, 1987; Hla *et al.*, 1987).

Epidemiology

There were no reports of children under 5 years dying as a result of accidental quinine ingestion in England and Wales between 1996 and 1999, nor were there any such reports to the AAPCC between 1983 and 2000. There were four reports of quinine ingestion out of a total 452 solid-dose drugs implicated in 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. Reports to the NPIS enquiry database between March 1997 and December 2001 did not contain any cases of children under 5 years with features of moderate or severe poisoning due to ingestion of quinine alone.

A survey carried out by NPIS London between 1983 and March 1986, also found that quinine poisoning in children was seldom reported to the service (Hla et al, 1987). However, although cases of children with quinine poisoning represented less than 0.05% of total enquiries (Table 33), information obtained at the time of the enquiry or later by follow up, indicated that over 50% of these were symptomatic, 14% suffered convulsions, and three died. Thus although exposure is not very common the proportion of children with serious poisoning is likely to be high.

Table 33: Enquiries concerning ingestion of quinine by children under 5 years to NPIS(London) 1983-1986.

Year	Yearly total enquiries to NPIS (London)	Number of quinine cases in children <5 years
1983	35,157	7
1984	42,221	10
1985	48,178	26
1986 (5 months only)	18,998	8
Total	144,534	51

Cases in the literature

Eleven case reports were found of poisoning from unintentional quinine ingestion in under 5 year olds (Conway, 1967; Burrows et al, 1972; Garrod & Judson, 1981; Parker, 1984; Bateman *et al.*, 1985; Gratton Smith *et al.*, 1987). Eight children developed severe symptoms, five of whom died (Table 34). Toxic serum concentrations of quinine were reported in all but one of the fatal cases. Cardiac arrhythmias and irreversible visual damage were reported from ingestion of 1.5 g in one case. An estimated dose was reported in seven cases (Table 35).

Table 34: A summary of the quinine cases reported in the literature.

Severity of poisoning	Age (months)	Dose (g)	Clinical effects	Serum concentration	outcome	reference
4	20	7	Twitching, seizure, coma, apnoea, hypotonia, unreactive dilated pupils, arreflexia, bradycardia, profound hypotension.	52 mg/l 6 h after ingestion	Died 12 hr after ingestion	Gratton smith *et al., 1987*
4	16	Un-known	Vomiting, choreoathetoid movements, dilated pupils, blindness, ventricular tachycardia, apnoea, cardio-respiratory arrest, severe hypoxic encephalopathy. Airway obstruction may have precipitated dysrhythmia.	53 mg/l 1 h after onset of symptoms	Severe brain damage and blindness.	Gratton smith *et al., 1987*
4	24	7.2	Convulsions, deep coma, depressed respiration, dilated pupils, profound hypotension, ventricular tachycardia 150 p min, circulatory arrest x 3.	83 mcmol/l (26.8 mg/l) 2h after ingestion	Died 7 h after ingestion.	Garrod & Judson, 1981
4	19	10	Within 1 h: pale, clammy, drowsy, vomiting. depressed respiration, convulsions, profound hypotension, bradycardia 40 per min, apnoea, unreactive dilated pupils, anuria, ventricular paroxysmal tachycardia, hypothermia.		Died 16 h after ingestion	Conway, 1967
4	24	1.5	Irreversible visual damage, cardiac arrythmia.	20.4 mg/l, 2.5 h after ingestion	Died	Bateman *et al., 1985*
3	36	5.4	Coma, severe visual loss, "considerable complications".	400 mg/l	Complete recovery	Parker, 1984
3	17	4.5-9.0	Drowsiness within 2 h. After 4 days bilateral unreactive, dilated pupils, complete blindness.	73 mg/l 2 h after ingestion	Vision remained impaired.	Gratton smith *et al., 1987*
3	18	Un-known	At 3 h, drowsy, twitching. fitting, coma, dilated unreactive pupils, arreflexia. After 24h, deafness and blindness.	490 mg/l 4 h after ingestion,	Recovered after 5 days	Burrows *et al.*, 1972
2	16	Un-known	Amaurosis	32.5 mg/l	Recovery after 6 weeks	Moore *et al.*, 1992
2	24	2.1	Within 2 h: drowsy, with prolonged QT interval	33.5 mg/l at 2h after ingestion	Recovered	Gratton smith *et al., 1987*
1	14	Un-known	Drowsy, vomiting, ataxia, hypotonia, twitching.	42 mg/l at 5 h after ingestion	Recovered	Gratton smith *et al., 1987*

Table 35 Severity of poisoning in cases of quinine ingestion by children of 5 years and under from reports in the literature that include estimates of dose ingested

Severity of poisoning	Range of dose (g)	No of patients	Mean age (months)	Equivalent no. of tablets for dose range	
				125 mg tablets	300 mg tablets
2	2.1	1	24	16.8	7
3	4.5-9	2	17.5	36-72	15-30
4	1.5-10	4	21	12-80	5-33.3

NPIS cases

There were 47 case reports for children of 5 years and under in the NPIS files, including four cases of severe poisoning and four deaths. Some of these cases have been published by Hla *et al.* (1987). An estimated dose was reported in 38 cases, with serum concentrations for 11 of the 14 cases with a PSS of 2 or more, but for only two of the cases that were asymptomatic or had only minor clinical effects. The lowest dose associated with moderately severe poisoning was 0.3 g and the lowest dose associated with death was 4.5 g (Table 36).

Table 36: Severity of poisoning in cases of quinine ingestion by 0-5 year old children reported to NPIS (L) with follow up details available.

Severity of poisoning	Range of dose (g)	No of patients	Mean age (months)	Equivalent no. of tablets for dose range	
				125 mg tablets	300 mg tablets
0	0.1-3.2	16	23	<1-25.5	0.3-10.5
1	0.1-1.8	8	26.5	<1-14.5	0.3-6
2	0.3-5.4	7	32	2.2-43	1-18
3	2-6	3	20	16-48	6.5-20
4	4.5-12	4	16.5	36-96	15-40

Vomiting and convulsions were the most frequently reported effects (Table 37). The lowest dose associated with convulsions was 0.3 gand the lowest dose associated with coma and blindness was 2g.

Table 37: The frequency of clinical effects in 29 cases of quinine ingestion by children under 5 years old reported to NPIS (L).

Clinical effects	*Poison Severity score*				
	1 (12 cases)	*2* (9 cases)	*3* (4 cases)	*4* (4 cases)	*Total*
Vomiting	8	6	2	1	17
Convulsions		3	4	4	11
Tachycardia	1	5	1		7
Drowsiness	3	2		1	6
Arrhythmias			3	2	5
Dilated unreactive pupils		3	1		4
Respiratory/cardiac arrest				3	3
Coma		1	1	1	3
Blindness			3		3
Oliguria/anuria			1	1	2
Pale optic discs		2			2
Tremors/twitching		1		2	3
Deafness			1		1
Hypotonia		1			1
Hypotension		1			1
Hypothermia		1			1

Toxicity

In the 29 symptomatic cases reviewed here, moderate poisoning (PSS 2) was reported with amounts of 300 mg (equivalent to 1 of the higher dose tablets) and the lowest fatal dose was 1.5 g, equivalent to five 300 mg tablets (Bateman *et al.*, 1985). There were 9 cases that had apparently ingested more than this lowest fatal dose and survived moderate or severe poisoning (PSS 2 or 3) (Table 38). It is of note that there are reports of children ingesting 30-40 tablets, an unusually large number, possibly due to attractiveness of the sugar coating. The rapid onset of severe cardiac effects and convulsions occurring within 2-3 hours of ingestion increases the risk of life threatening episodes occurring before admission to hospital, with fatal consequences.

Table 38: A comparison of dose taken and poison severity score for the quinine cases reported to NPIS (L) and in the literature.

Dose	No of 300 mg	*Poisoning severity score*					
g	tablets	0	1	2	3	4	Total
0.1	0.3	1	1				2
0.15	0.5	2					2
0.3	1	3	1	2			6
0.4	1.5	1					1
0.6	2	2	1				3
0.9	3	1		1			2
<0.9	<3		3				3
1.2	4			1			1
1.5	5	1	1			1	3
1.8	6	1	1	1			3
2	6.5				1		1
2.1	7			1			1
2.4	8			1			1
<2.7	<9	1					1
<3	<10	1					1
3	10	1					1
3.2	10.5	1					1
<4.5	<15				1	2	3
4.5-9	15-30				1		1
4.5-5.4	15-18					1	1
5.4	18			1	1		2
6	20				1		1
7	23					1	1
7.2	24					1	1
10	30					1	1
12	40					1	1
Totals		**16**	**8**	**8**	**5**	**8**	**45**

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Lomotil®

Lomotil® (co-phenotrope) is available as tablets and liquid. One tablet, or 5 ml of syrup, contains diphenoxylate hydrochloride 2.5 mg and atropine sulphate 25 mcg.

The main use of Lomotil® in children is for the control of diarrhoea as an adjunctive therapy to appropriate rehydration. The therapeutic dose in children aged 4-8 years is one tablet or 5 ml three times daily; it is not recommended in children under 4 years old. Lomotil® is used widely in the Third World, elsewhere it has generally been superseded by other antidiarrhoeal drugs such as loperamide. NPIS (L) recommends children should be observed in hospital after ingestion of any amount in excess of the therapeutic dose.

Diphenoxylate is an opioid that reduces intestinal motility. The subtherapeutic dose of atropine is present to reduce the abuse potential of this formulation. Diphenoxylate is metabolised to diphenoxylate acid (difenoxin) and hydroxydiphenoxylic acid. Diphenoxylic acid is the major metabolite and is about five times more active than diphenoxylate.

Lomotil® is particularly dangerous in overdose because of the delay in onset of effects. Several children have died following overdose with this product (Ginsberg and Angle, 1969; Rumack and Temple, 1974; Wasserman *et al.*, 1975; Curtis and Goel, 1979; McCarron *et al.*, 1991). Young children appear to be more susceptible to the toxic effects of Lomotil® than adults and older children. Rumack and Temple (1974) mention eight adults who took 15-30 tablets without CNS or respiratory depression, only one patient had anticholinergic effects. The reason for this apparent difference in toxicity is unclear.

Clinical effects of poisoning
The effects of Lomotil® overdose characteristically occur in two stages and may be due to either atropine or diphenoxylate or to both. Treatment includes administration of the opioid antagonist, naloxone.

Atropine effects include dry mouth, hallucinations, flushing, tachycardia, dilated pupils, pyrexia, drowsiness and urinary retention. The effects of diphenoxylate may be sudden in onset and result in constricted pupils, reduced bowel sounds and coma. Respiratory depression may be delayed for up to twenty-four hours or longer. It is characterised by periods of apnoea and respiratory failure and is the main cause of death following Lomotil® overdose.

Epidemiology
The AAPCC data included two fatal cases of Lomotil® poisoning. One involved the liquid formulation and was excluded from the analyses. A 2 year old boy was given 8-16 drops every 4 hours for 2 days. He developed dyspnoea, lethargy and respiratory depression. He did not respond to naloxone and developed pulmonary oedema and cardiac arrest and died on the second hospital day (Litovitz *et al.*, 2001). In the only case involving tablets a 14 month old child died two days after ingestion of 13 tablets of Lomotil® (Litovitz *et al.*, 1990).

No deaths in children under 5 years due to accidental poisoning from Lomotil® were reported in the ONS data for England and Wales from 1993-1999.

In the HASS data there was only one case involving Lomotil®, out of a total of 452 solid drug ingestions by children aged up to 5 years, in a sample from 18 hospital emergency department for 1996-1999 where length of stay was one day or more.

There were no reports in the NPIS enquiry database from March 1997-December 2001 involving children under 5 years with moderate or severe clinical effects due to ingestion of Lomotil® alone.

Cases in the literature

Case summaries in the literature

A comparison of severity of poisoning with dose ingested for a series of 43 ingestions by children, reported by Curtis and Goel, (1979) is presented in Table 39. The lowest fatal dose in this series was 0.77 mg/kg of diphenoxylate.

Table 39: A summary of the Lomotil® cases reported in Curtis and Goel, 1979.

Severity of poisoning	Range of diphenoxylate dose (mg/kg)	No of patients	Mean age (years)	Average body weight for child of mean age	Number of tablets dose range equivalent to in child of average body weight	Outcome
Mild	0.62-5.8	7	2.25	12.5 kg	3.1-29	Recovered
Moderate	0.25-8.4	32	2.5	13 kg	1.3-43.7	Recovered
Severe	0.77-10	4	1.7	11.4 kg	3.5-45.64	1 Died 3 Recovered

Case reports in literature

Cases from the literature are summarised in Table 40 (Henderson and Psaila, 1969; Snyder *et al.*, 1973; Rumack and Temple, 1974; Smith and Chambers, 1978;). Only those cases where the dose was known or estimated were included. In some reports it is not clear whether the preparation was a tablet or liquid.

Table 40: A comparison of dose taken and poison severity score for the Lomotil® cases reported in the literature.

Number of tablets	Poison severity score					
	0	1	2	3	4	*Totals*
6			1	1		2
8-15				5		5
14				1		1
18				1		1
22				1		1
25				1		1
33				1		1
40				1		1
94				1		1
Totals			1	13		14

NPIS cases

NPIS case files contained follow-up information on 124 cases of ingestion by children aged 5 years or under with an estimate of dose ingested. When dose was reported as a range, the ingested dose was estimated from the lowest dose in symptomatic cases. The quantity of Lomotil® ingested ranged from 1 to 100 tablets. However, of the two children who were reported to have ingested 100 tablets, one was asymptomatic and the other was comatose with flushing and pyrexia. Both recovered and it is likely that neither of them had ingested that number of tablets. Ignoring these two cases the number of tablets ingested is between 1 and 37 tablets (that is 2.5-92.5 mg diphenoxylate and 25-925 mcg atropine).

Clinical effects were reported for 80 of these 124 children. They are summarised in Table 41. A comparison of dose taken and poison severity score is presented in Table 42.

Table 41: The frequency of clinical effects following Lomotil® overdose reported to NPIS (L).

Clinical effect	Number of reports	Frequency (%)
drowsiness	45	56
flushing	24	30
respiratory depression/cyanosis	22	27
constricted pupils	18	22
vomiting	13	16.
tachycardia	11	14
coma	7	9
ataxia	6	7
thirst/dry mouth	5	6
pyrexia	3	4
lethargy	3	4
hypotonia	3	4
hallucinations	3	4
urinary retention	2	1
irritable	2	1
hyperactivity	2	1
abdominal pain	2	1
dilated pupils	1	1
bradycardia	1	1

Table 42: A comparison of dose taken and poison severity score for the Lomotil® cases reported to NPIS (L).

Number of tablets	Poison severity score					
	0	1	2	3	4	Totals
1	1					**1**
2	3	1				**4**
3	5	2	3	1		**11**
4	5	2		1		**8**
5	6	4		1		**11**
6	4	1	4		1	**10**
7	2					**2**
8	2	3				**5**
9	1	1				**2**
10	5	10	6			**21**
>10	10	19	17	3		**49**
Totals	**44**	**43**	**30**	**6**	**1**	**124**

Toxicity

It is clear from the literature (Henderson and Psaila, 1969; Rumack and Temple, 1974; Curtis and Goel 1979) and the NPIS (L) case summaries that 8 doses or less can cause severe toxicity including fatalities. There were 82 cases giving estimates of dose ingested with PSS 2 or 3. The lowest dose associated with PSS 2 in the literature was equivalent to 1.3 tablets and in cases reported to the NPIS (L) was 3 tablets.

There were few reports of death and only three with estimates of dose ingested. The lowest published fatal dose of diphenoxylate is 1 mg/kg (Ginsberg and Angle, 1969) from a dose of 42 ml of syrup over 24 hours. This is equivalent to 6 tablets in a 15 kg child. However, 34 of 43 cases with mild poisoning

had taken doses greater than the lowest dose associated with death, so it seems the amount ingested does not correspond well with symptom severity.

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Dapsone

Dapsone is a sulphone antibiotic which is active against a wide range of bacteria, available in 50 mg and 100 mg tablets.

It is used as part of multi-drug regimens in the treatment of all forms of leprosy. Dapsone is used as an alternative to co-trimoxazole for the treatment and prophylaxis of *Pneumocystis carinii* pneumonia and in combination with pyrimethamine for the prophylaxis of malaria. It is widely used in AIDS patients and for skin conditions such as dermatitis herpetiformis. The therapeutic dose for children is 1-2 mg/kg/day up to 200 mg. NPIS (L) recommends observation in hospital for ingestion of more than 10 mg/kg by a child.

Clinical effects of poisoning

Dapsone is almost completely absorbed from the gastrointestinal tract with peak plasma concentrations occurring from 2 to 8 hours after a dose. Clinical features can appear from a few minutes to 24 hours following ingestion. Methaemoglobinaemia, haemolysis, and central nervous system stimulation are the most common manifestations. Other features of poisoning include nausea, vomiting, severe abdominal pain, cold sweating and blue-grey cyanosis from methaemoglobinaemia, hallucinations, dizziness, agitation and confusion, and in severe cases coma, tachycardia, hypotension and acidosis.

Methaemoglobinaemia and haemolytic anaemia have been reported following therapeutic dosing and after overdose. Methaemoglobin concentrations correlate with severity of intoxication. The Poison Severity Score categorises methaemoglobin concentrations of 10-30% as mild intoxication, 30-50% as moderate toxicity and over 50% as severe intoxication. Poisindex® gives the following correlation of methaemoglobin concentration and clinical effects:

- 15-20% Clinical cyanosis and chocolate-brown blood becoming evident, patient usually asymptomatic.
- 20-45% Headache, lethargy, dizziness, fatigue, syncope, dyspnoea.
- 45-55% Increasing CNS depression.
- 55-70% Coma, seizures, arrhythmias, shock.
- >70% High incidence of mortality.

Dapsone concentrations up to 10 x therapeutic concentration (1 mcg/ml) are consistent with mild toxicity, 10-21 mcg/ml with moderate toxicity and over 21 mcg/ml with severe toxicity (Carazza *et al.*, 2000).

Epidemiology

Ingestion of dapsone is infrequent in the UK. There were no cases of childhood ingestion in the sample of attendances at 18 emergency departments resulting in admission for one day or more, reported to HASS between 1996 and 1999. Dapsone was not reported as a cause of childhood death by the AAPCC between 1983-2000, nor by the ONS for England and Wales between 1993-1999. There were no cases of young children with features of moderate or severe poisoning due to ingestion of dapsone alone reported on the NPIS enquiry database between March 1997 and December 2001. However, reports of intoxication are more frequent in countries where leprosy is a significant disease. The range of therapeutic indications is increasing and now includes malaria prophylaxis, rheumatoid arthritis, and *Pnuemocystis carinii* pneumonia in AIDS patients, so its availability in the UK may increase, increasing the risk of poisoning.

Case reports in the literature

Two case series have been reported. A series obtained by San Paulo Poisons Control Centre Laboratory from a retrospective evaluation between January 1985 and December 1995 included 147 patients less than 5 years old (Carazza *et al.*, 2000). The median amount ingested was 4 x 100 mg tablets. All children developed cyanosis and 84 (57%) were said to have moderate to severe

intoxication. Mean and median dapsone concentrations and methaemoglobin concentrations were consistent with moderately severe poisoning (Table 43).

Table 43: The methaemoglobin and dapsone concentrations in the series of 147 patients less than 5 years old (Carazza *et al.*, 2000)

Parameter	Methaemoglobin concentration (%) (n=147) ± SE	Dapsone concentration (mg/L) (n=15)
mean	31.6 ± 0.88	15.7 ± 2.96
median	31.2	10.2
range	5.1-58.0	5.5-39.2

Bucharetchi *et al.* (1999) looked at a series of 17 children admitted to a hospital in Brazil between January 1988 and December 1996, with acute exposure to dapsone complicated by a methaemoglobin concentration greater than 20%. The children were aged 1-13 years, median age 3 years, and the dose ranged from 100 mg to 1200 mg (median 350 mg). Methaemoglobin ranged between 23.5%-49.7% (median 37.8%). All developed cyanosis, 11 cases were reported with tachycardia and vomiting, and 8 cases with tachypnoea.

Ten reports of poisoning were found in the literature: 8 from dapsone, one from Deltaprim® (dapsone and pyrimethamine) and one from a veterinary ointment called Udolac® (Table 44). The patient who ingested ointment died (Davies, 1950), five patients developed severe poisoning (Stanfield, 1963; Murthy, 1980; Linakis *et al.*, 1989; Hansen *et al.*, 1994; Macdonald *et al.*, 1997). and four had only minor clinical effects (Gomber *et al.*, 1994; Reigart *et al.*, 1983; Nayak *et al.*, 1989).

Table 44 Summary of cases of childhood poisoning from dapsone reported in the literature.

PSS	Age (months)	Dose (mg)	Clinical effects	Concentrations of methaemoglobin and serum dapsone	Treatment	Reference
1	30	170	Irritable, restless, central cyanosis, poor respiration	24% at 24 h post exposure	Gastric lavage methylene blue iv	Gomber et al., 1994
1	18	100	Cyanosis	27% at 20 h post exposure	Methylene blue iv, serial doses charcoal	Reigart et al., 1983
1	24	Not known	Cyanosis, irritable,		Methylene blue iv	Nyak et al., 1989
2	48	Not known	Vomiting, choreiform movements, cerebellar signs, metabolic acidosis	20.4%	Gastric lavage, ascorbic acid iv	Gomber et al., 1994
2	24	100-200	Vomiting, tachycardia, cyanosis	17.5%	Methylene blue iv, exchange transfusion	Stanfield, 1963
2	36	600 Deltaprim	Vomiting, cyanosis	44% at 2.5 h post exposure	Charcoal serial doses, methylene blue	Macdonald, 1997
2	42		Cyanosis, agitation,	44.7%, dapsone 3.9 mcg/ml	Charcoal serial doses, methylene blue, ascorbic acid	Linakis, 1989
2	16	Not known	Cyanosis, pallor, sweating, tachycardia, tachypnoea,	25% at 22h post exposure; dapsone 14 mcg/ml at 9h	Gastric lavage, charcoal serial doses	Hansen, 1994
2	60	100	Allergic skin rash, odd movements of hands and feet, hyperexcitability, restlessness, hallucinations, tachycardia		Chlorpromazine, diphenhydramine	Murthy 1980
4	22	5,000 as Udolac cream	Cyanosis, vomiting, restlessness. Died 55 hours after ingestion		Gastric lavage, phenobarbitone, paraldehyde	Davies, 1950

NPIS cases

The NPIS case files contained 12 cases, which were reported between 1973 and 1996. Clinical effects were reported that were consistent with minor toxicity in four patients, and with moderate toxicity in seven patients. while one patient was assessed as having severe toxicity on the basis of the methaemoglobin concentration. There were no deaths.

Toxicity

Severe poisoning is rare in the UK, but in countries where dapsone is more frequently prescribed, moderate to severe poisoning is more frequent in young children, 84 cases were reported in 10 years by Carraza *et al.*, (2000). The authors of that series looked at methods for determining severity of intoxication and concluded that dose was not particularly useful in determining severity of poisoning. A total 186 cases of poisoning in under 5 year olds were retrieved from the literature and the NPIS files, but dose was reported in only 13 cases (Table 45).

Table 45 Comparison of the dose, methaemoglobin concentration and dapsone concentrations for all cases reported in the literature and to the NPIS.

Parameter	Case reports from NPIS and literature				From Bucharetchi *et al.*, 1999	From Carazza *et al.*, 2000
Poison severity score	1	2	3	4	unknown, but no fatalities	unknown, but no fatalities
No. cases per class	7	13	1	1	17	147
Age	18-36 months mean 27	16-60 months mean 34	42 months	22 months	1y-13y median 3 y	less than 5 y exact ages not stated
Dose (mg)	100-500 median 260 (4 cases)	100-3200 median 550 (7 cases)	1500	5000	100-1200 median 350	median 400
Methaemoglobin concentration %	4-27 median 23.5 (4 cases)	18-45 median 38.5 (10 cases)	52	-	23.5-49.7 median 37.8	5.1-58 median 31.2
Dapsone serum concentration		3.9-73 median 14 (3 cases)			*not measured*	5.5-39.2 median 10.2 (15 cases)

Many cases were reported with moderate to severe poisoning. There was evidence that less than 8 dose units can cause moderate to severe poisoning: four cases with moderate poisoning (PSS 2) from doses ranging from 1-6 tablets, and two series of cases where mean dose ingested was 350 mg and 400 mg respectively and more than half the patients in each series developed moderate to severe poisoning. The lowest dose associated with moderate to severe poisoning was reported as 100-200 mg (Stanfield, 1963) (Table 46). The lowest dose associated with cyanosis was 100 mg (Gomber *et al.*, 1994). The only death, reported in 1950, resulted from ingestion of an amount said to be equivalent to 50 tablets. The highest survived dose with only moderate toxicity was equivalent to 32 tablets.

Table 46 Dose compared with severity of poisoning and methaemoglobin concentration.

Dose mg	Poison Severity Score				Methaemoglobin
	1	2	3	4	conc %
100	1				27
170	1				24
100-200		1			17.5
350	1				4
400		1			*not available*
500	1	1			31 and 23 respectively
600		1			44
1,000		2			*not available*
1,500			1		52
3,200		1			42
5,000				1	*not available*

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Hyoscine hydrobromide

Hyoscine hydrobromide is one of the principal drugs used for the control and prevention of motion sickness. It is available in the UK without prescription in tablets containing hyoscine hydrobromide, 0.15 mg or 0.3 mg. There are three over-the-counter preparations currently available in UK, Kwells® (0.3 mg), Junior Kwells® (0.15 mg) and Joyrides® (0.15 mg).

The therapeutic dose for children 3-7 years is 0.075-0.15 mg every 6 hours, to a maximum 0.225-0.45 mg in 24 hours. It is not recommended for children under 3 years of age. NPIS (L) recommends observation in hospital for children afteringestion of more than 0.3 mg.

Hyoscine is an antimuscarinic agent with central and peripheral actions. Its central action differs from that of atropine in that it depresses the cerebral cortex, especially the motor areas, and produces drowsiness.

Clinical effects of poisoning
Clinical effects of hyoscine hydrobromide toxicity are anticholinergic with dilated pupils, flushed, hot dry skin, slurred speech, ataxia, disorientation, tachycardia, restlessness, pyrexia, delirium, hallucinations, excitement and hyperactivity. There may also be drowsiness, confusion, agitation and shaking. In severe cases there may be convulsions, coma, respiratory depression and rarely, arrhythmias (usually with pre-existing cardiac disease). Clinical effects may be delayed in onset and prolonged because gut motility is decreased with anticholinergic poisoning. Effects usually resolve over 12-24 hours.

Epidemiology
Hyoscine travel sickness tablets accounted for 7 out of a total 452 solid–dose medications implicated in ingestions by children under 5 years attending 18 emergency departments, resulting in admission for one day or more, reported to HASS between 1996 and 1999. It was notable that hyoscine preparations were more often reported by their trade name rather than by their generic name or a description such as "travel sickness pills", and that there were seven reports of incidents involving Joyrides® but only one report implicating Kwells®. Although it is not possible to know whether this is a significant difference, it is of note that the packaging of Joyrides® might seem more attractive to children than the packaging of Kwells®.

No childhood deaths due to hyoscine were reported in England and Wales between 1993-1999 by the ONS, or reported in the US by the AAPCC from 1983-2000.

Childhood ingestions of preparations for prevention of travel sickness have been frequently reported to NPIS since the service began in the late 1960s. One of the children under 5 years with features of moderate or severe poisoning reported on the NPIS enquiry database between March 1997 and December 2001 had ingested seven tablets of hyoscine hydrobromide and was drowsy with hallucinations and arrhythmias.

Cases in the literature
Only one case report of childhood poisoning from this cause was found in the literature. A 10 year old boy developed confusion, hyperactivity, restlessness, hallucinations and short-term memory loss following ingestion of 2.4 mg (8 x 0.3 mg hyoscine tablets) from a blister pack. Hyoscine was found in the urine (Ayub *et al.*, 1997).

NPIS cases
NPIS case files contained 108 cases reports, mostly reported before 1985, including 96 cases with an indication of dose ingested. The dose range was 0.15-7.2 mg. Sixty-five children were reported to have had marked anticholinergic effects (Table 47). The outcome was uneventful in all except one child who died in 1966.

Table 47: The frequency of clinical effects in 65 cases of hyoscine ingestion in children under 5 years, reported to NPIS (L).

Clinical effects	*Number of cases*
dilated pupils	59
hallucinations	37
tachycardia	31
agitation/delerium	16
confusion	15
pyrexia	13
convulsions	3
coma	2
hypothermia	1
bradycardia	1

Case report

A 2.5 year old boy ingested 1.8 mg of hyoscine hydrobromide (6 tablets of Kwells®) and was given a gastric lavage about 4 hours later. About 6 hours post-ingestion he developed excitement, delirium and dilated pupils. This was followed by pyrexia, convulsions, coma, vasomotor collapse and respiratory depression. He was given paraldehyde, antibiotics and treated supportively with IV fluids and artificial respiration for three days but died on the fourth day. The post-mortem revealed acute tracheobronchitis (NPIS (London) case report number 66/1244).

Toxicity

90 symptomatic cases with estimates of dose ingested were available for review. Marked anticholinergic effects, (PSS 2), have been reported from doses equivalent to less than 2 tablets (Table 48). Apart from one death from 6 tablets in 1966, no severe poisonings were reported. However, the data shows variability in the response, since 20 of the cases with mild toxicity had taken a dose equal to or greater than 0.45 mg, which was the lowest dose associated with moderate toxicity (PSS 2). This supports the advice on Poisindex® that toxicity is not predictable from the dose ingested.

Table 48: Comparison of symptoms severity with estimated dose for cases reported to NPIS (L).

Dose ingested mg		**Equivalent no. of tablets**		**Poison severity score** *Number of patients in each class*					
		0.15 mg	**0.30 mg**	**0**	**1**	**2**	**3**	**4**	**Totals**
Taking lowest dose when a range is quoted	0.15-0.45	1-3	0.5-1.5	2	4	1	-	-	7
	0.6-0.9	4-6	2-3	2	7	7	-	-	16
	1.05-1.8	7-12	3.5-6	1	12	17	-	1	31
	>2.1	>14	>7	-	8	33	-	-	41
	Totals			**5**	**31**	**58**	**0**	**1**	**95**
Taking highest dose when a range is quoted	0.15-0.45	1-3	0.5-1.5		1				1
	0.6-0.9	4-6	2-3	4	10	5			19
	1.05-1.8	7-12	3.5-6	1	12	17		1	31
	>2.1	>14	>7		8	36			44
	Totals			**5**	**31**	**58**	**0**	**1**	**95**

Reference

Ayub N, Donaldson D, Bedford D, Alloway R, Ryalls M. 1997 Lessons to be learned: a case study approach. Hyperactivity and confusion in the presentation of hyoscine overdose. *J R Soc Health* 117(4):242-244.

Beta blockers

Beta blockers are indicated for hypertension, angina, heart failure, thyrotoxicosis, prophylaxis of migraine and the relief of some forms of anxiety. Atenolol is available as tablets 25 mg, 50 mg, 100 mg; capsules 50 mg and syrup 25 mg/5 ml. Propranolol is available as tablets 10 mg, 40 mg, 80 mg, 160 mg; modified release capsules 80 mg, 160 mg; and oral solution 5 mg/5 ml, 10 mg/5 ml 40 mg/5 ml, 50 mg/5 ml, and 80 mg/5 ml.

Propranolol can be given to children in oral doses of 10-20 mg 2-3 times a day for migraine prophylaxis; atenolol can be given in doses of 1-2 mg/kg once a day to a maximum 8 mg/kg per day for hypertension (an unlicensed use). Toxic doses for beta blockers are not well established in children. NPIS (L) recommends observation in hospital for ingestion of more than 2 mg/kg of atenolol by children, and for more than 1 mg/kg of propranolol (or more than the total daily dose, whichever is larger).

Beta blockers act by blocking the β-adrenergic receptors. These receptors have been classified as β_1 and β_2 receptors, and are differently distributed. β_1 receptors in the heart control heart rate and contractility, and conduction velocity; those in the kidney control plasma renin release. Consequently β_1 receptors regulate heart rate and blood pressure. β_2 receptors are present in smooth muscle including bronchial and vascular smooth muscle. β_2 receptors in the liver control glycogenolysis and gluconeogenesis.

Clinical effects of poisoning
In overdose the most important effects are on the heart. Bradycardia, hypotension, pulmonary oedema, syncope and cardiogenic shock may develop. Conduction abnormalities such as first or second degree AV block may occur and, rarely, arrhythmias.

Lipid soluble beta blockers (e.g. propranolol) are more likely to cross the blood brain barrier causing drowsiness, confusion, seizures, hallucinations, dilated pupils and in severe cases coma. Neurological signs such as coma or absence of pupil reactivity are unreliable prognostic indicators during resuscitation.

Bronchospasm may occur and, occasionally, CNS-mediated respiratory depression. The concept of cardioselectivity is much less applicable in the overdose situation and systemic effects of beta-blockade include bronchospasm and cyanosis, particularly in those with pre-existing airways disease. Hypoglycaemia and hypocalcaemia are rare.

Epidemiology
The AAPCC annual reports include one death from propranolol in a 2 year old child, following ingestion of a possible dose of 80 mg, however, the case may have been a non accidental injury (Litovitz *et al.*, 1999). There were no reports of childhood death in England and Wales between 1993 and 1999.

There were six cases involving atenolol and five involving propranolol out of a total of 452 solid drugs in the HASS sample of children aged up to 5 years attending 18 hospital emergency departments between 1996-1999 and subsequently admitted for one day or more.

No children under 5 years were reported on the NPIS enquiry database between March 1997 and December 2001 with moderate or severe poisoning due to ingestion of atenolol. There was one case involving sustained-release propranolol. A one year old child was comatose 1.5 hours after ingestion of 320 mg. No further details were available.

Cases in the literature

Few cases of ingestion of atentolol or propranolol are reported in the literature. Two siblings, a boy of 23 months and a girl of 3 years, shared 150 mg of propranolol (15 x 10 mg or less than 160 mg) between them, which resulted in bradycardia and hypoglycaemia (Hesse and Pedersen, 1973).

In a series of beta blocker ingestions by children less than 7 years old, symptoms were reported in only two of 103 children who had ingested atenolol, two of 72 children who had ingested immediate release propranolol and one of 22 children who had ingested modified release propranolol (Belson *et al.*, 2001). Of these, two children had lethargy and three developed bradycardia; hypotension was also reported in 2 cases. The cases are summarised in Table 49.

Table 49: A summary of the symptomatic cases involving atenolol or propranolol reported in Belson *et al.*, (2001).

IR = immediate release; SR = sustained release/modified release

Drug	Age	Dose	Dose mg/kg	*Clinical features*	PSS
atenolol	5 y	2 x 50 mg	5.3 mg/kg	Bradycardia (38), 12.5 h observation.	3
atenolol	2 y	2 x 50 mg	6.7 mg/kg	Bradycardia (50s), 11 h observation	3
propranolol IR	19 m	3 or more? 20 mg	5 mg/kg	Lethargy	1
propranolol IR	3 y	2 x 40 mg	5.1 mg/kg	Bradycardia (58) and hypotension, 12 h observation	3
propranolol SR	22 m	1 x 120 mg	12 mg/kg	Lethargy, hypotension, 22 h observation	2

NPIS (L) cases

Childhood ingestions of beta blockers have been occasionally reported to NPIS. Follow up information was available for 11 cases for atenolol and 22 cases for propranolol; the majority of these were asymptomatic.

A summary of the propranolol cases with follow up are listed in Table 50. Of 22 cases only six children were symptomatic. Of 11 cases of atenolol ingestion only one child was symptomatic with flushing after ingesting 200 mg.

Table 50 A summary of NPIS (L) cases involving propranolol.

Poison Severity Score	Number of patients	Age (y)	Dose (mg)
0	16	0.75-2.5 mean 1.8	10-400 median 80 15 cases
1	3	0.8-2.2 mean 1.3	30-800 median 40 3 cases
2	3	2-3 mean 2.3	40-400 median 40 3 cases

Toxicity

There were only nine symptomatic cases for propranolol and two symptomatic cases for atenolol with estimated dose available for assessment. These included one death, from 80 mg propranolol (equivalent to half of the highest strength dose unit). For each drug the lowest dose associated with PSS 3 was equivalent to less than one dose unit for both drugs: 100 mg for atenolol and 80 mg for propranolol (Table 51).

Table 51 Dose compared with Poison Severity score for cases of propranolol ingestion by children reported to NPIS (L) and in Benson *et al.*, 2001.

Dose (mg)	No of patients with each grade of Poisons severity score				
	1	2	3	4	total
20	1				1
30	1				1
40	1	2			3
80			1		1
120 SR		1			1
400		1			1
800	1				1
Total	**4**	**4**	**1**		**9**

Belson *et al.* (2001) suggest that ingestion of a quantity twice the normal recommended dose or more for atenolol or propranolol resulted in toxicity. However, the severe poisoning from atenolol reported in this case series following ingestion of 5.3 mg/kg and 6.7 mg/kg is less than the maximum therapeutic dose of atenolol (8 mg/kg), and for a 10 kg child would be only one or less of the higher strength tablets. Belson *et al.* (2001) concluded from their review of 378 children under 7 years exposed to beta blockers that most unintentional paediatric exposures to these drugs are clinically insignificant.

References

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Litovitz TL, Klein-Schwartz W, Caravati EM, Youniss J, Crouch B, Lee S. 1999 1998 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 17 (5):435-488.