COT DEATH

MUST BABIES STILL DIE?

A review of research into sudden infant death syndrome

Barry A. Richardson

November 1991

A report funded by **TOMY**

COT DEATH
MUST BABIES STILL DIE?

A review of research into sudden infant death syndrome

Barry A Richardson

Director

Penarth Research International Lirnited

PO Box 142, St Peter Port, Guernsey, Channel Islands

November 1991

The preparation of this report and the literature review on which it was based were funded by a grant from

Tomy UK Limited

The research on cot mattress biodeterioration and toxic gas generation described in Appendix 2 was funded by

Penarth Research International Limited

and the persons involved who provided their services f ree of charge

COT DEATH
MUST BABIES STILL DIE?

A review of research into sudden infant death syndrome

CONTENTS

PREFACE

There are many reasons why persons become involved in cot death research. Some are prompted by experience of a cot death in their own family, whilst others are attracted by the challenge of a problem that has remained unexplained for many years despite extensive research. There are also those who recognise that cot death is an emotive subject attracting special consideration in the allocation of Government and voluntary funding.

I became involved in cot death research when I accidentally identified a possible cause. I have been in practice since 1965 as a consulting and research scientist specialising in deterioration of materials, preservation systems and associated health problems. In September 1988 my company Penarth Research International Limited was asked to investigate deterioration of PVC fabric used in marquees and awnings. The damage was caused by fungi which were degrading the plasticiser in the PVC, causing grey and pink staining as well as progressive development of brittleness. The Austrian manufacturer suggested that the problem could be avoided by increasing the concentration of the arsenical preservative OBPA in the fabric but I warned that this could be dangerous as fungal development in the presence of an arsenic compound can result in the generation of toxic arsine gas. Peter Mitchell of Mitchell Marquees Limited, one of the companies involved, did not believe these warnings and contacted the suppliers of OBPA who assured him that it was entirely safe and even approved for use in PVC for cot mattress coverings and nappy pants. He telephoned early the following morning, describing these 'approved' uses and wondering whether arsine generation might be the cause of cot death, and he was rather surprised when I agreed that it was a possibility; I could even suggest the fungus that was most likely to be involved, a common domestic species that had similarly caused deaths in infants and illnesses in adults in the 19 century.

I exposed samples of new PVC cot mattress coverings to this fungus but it did not spread across the samples as 1 had expected, although it was clearly attracted to the PVC as it spread rapidly around the edge of each sample. I then noticed that the fungus was changing from the normal fluffy form to a slime where it was in contact with the PVC, and 1 also noticed that the PVC became distorted, suggesting that the fungus was degrading the plasticiser. However, I did not detect arsine generation, and analysis indicated that the samples did not contain OBPA, yet my assistant Sue Kelly reported that she suffered headache, the first sign of poisoning, when she was working with the cultures. I suggested to our chemical consultant Tim Cox that arsenic might be present at very low concentrations which he had been unable to detect, and he pointed out that it was not easy to detect traces of arsenic in the presence of the related elements phosphorus and antimony; phosphorus plasticisers and antimony trioxide are used in PVC fabric when fire resistance is required. This comment prompted the thought that the fungus might convert phosphorus and antimony compounds into the similar toxic gases phosphine and stibine. I could not find any reference in the scientific literature to generation of these gases but we soon detected them when samples of PVC mattress coverings were exposed to the fungus.

Peter Mitchell continued to be interested in the project and asked the coroners in England and Wales to assist by providing mattresses from cot death incidents. I was surprised to find that PVC coverings from all these mattresses were naturally infected by the fungus that I had suspected, particularly in the area affected by the warmth and perspiration of the baby. The fungal infection caused the progressive development of brittleness which indicated plasticiser deterioration, and in all cases phosphine and stibine generation were detected when phosphorus and antimony were present in the PVC fabric; traces of arsine were sometimes detected, apparently originating from arsenical impurities in the antimony trioxide, and in one case heavy arsine generation occurred from a mattress issued to a service family which contained OBPA preservative. PVC mattress coverings were sometimes coloured pink, oft en in the shape of a sleeping baby. We also found that the fungus was present on other mattress covering materials such as cotton and polyester, and particularly on the foam which is covered only by netting in modern vented mattresses; the fungal growth was concentrated where it was encouraged by perspiration,

dribble and vomit, and phosphine was generated from foam containing phosphate fire retardants, as well as stibine from a few samples of foam containing antimony trioxide. However, we also tested used cot mattress materials from homes which had not suffered cot deaths and we found that they were similarly infected and similarly generating phosphine, arsine or stibine, depending on the composition of the mattress materials. Most babies were therefore exposed to phosphine, arsine or stibine generation, and whether they were unaffected or suffered irritation, illness or death depended on various contributory factors, particularly the face down sleeping position and overwrapping as described in this report.

It was not my Intention to become directly involved in cot death research. Various cot death researchers and organizations, including the Department of Health, were therefore informed privately of the implications of our research in the hope that they would arrange for post mortem investigations to check whether cot death victims had been poisoned by the toxic gases that I had identified. By May 1989 our work had progressed to a sufficient extent for me to submit preliminary papers to the medical journals in the hope that cot death researchers and pathologists would take our findings into account in their own work, but local radio and newspaper reporters were beginning to investigate the mysterious disappearance of mattresses for our investigations, and it was not long before they contacted me. I explained that we might have accidently discovered a cause of cot death but I asked them to delay any reports until the medical profession had been informed in one of the journals, but it soon became apparent that my embargo would not be observed.

On Monday, 5 June 1989 I was working in Jersey and, when I flew back to Guernsey and returned to our laboratory, I was surprised to find a man waiting for me; he was a television cameraman and explained that he had been asked to take pictures of our laboratory and our cot death work in preparation for a television interview. He was rather dismayed when I said that I had not agreed to give any Interviews, but at that moment the telephone rang; it was his producer requesting an interview the following morning as the news services were carrying reports that I had discovered the cause of cot death! 1 was woken several times that night by reporters and, when I arrived at my office early the following morning, the telephone was already ringing continuously, and within a skort time the office was filling with newspaper and radio reporters, as well as television teams.

I decided to use this media interest to publicise my recommendations that the cot death risk could be significantly reduced by providing a new mattress for every new baby, or covering an old mattress with polythene to isolate the baby from the mattress materials. I know that parents responded as sales of new cot mattresses increased by about 15% and cot death rates started to fall; by the last quarter of 1989 the rate for England and Wales had reduced to 2.27 per 1,000 live births, representing a fall of 15% compared with the average of 2.68 for the last quarters in 1986-88, and in the last quarter of 1990 the rate dropped to 1.54, a fall of 43%.

The media interest prompted a series of questions in Parliament and on 9 March 1990 Sir Donald Acheson, Chief Medical Officer at that time at the Department of Health, announced the appointment of an Expert Group to investigate my hypothesis, although he added that he did not believe that mattresses were involved in cot death and that there was no need for parents to take any special precautions. Meanwhile I had decided to investigate whether cot death victims might have died through poisoning by the gases that I had identified. I obtained blood samples from several cot death victims that I could relate to mattress samples, and analysis by the Trace Element Unit at the University of Surrey established that the blood antimony content was exceptionally high when the victims had died on mattresses containing antimony and apparently generating an antimony gas, establishing the link between mattress biodeterioration and poisoning. The group report, published on 12 June 1991, disclosed that the Laboratory of the Government Chemist had been instructed to investigate our experimental work with the assistance of the International Mycololgical Laboratory, but they did not repeat our experiments but

tried to improve them, destroying the simplicity and sensitivity of our methods in the process so that their results were inconsistent; they often failed to detect arsine gas when it was expected, and they detected an antimony gas which they did not expect! The group ignored our blood tests and reported instead that there was no evidence that cot death victims had been poisoned by the gases as they did not show one of the symptoms of poisoning that are described in the toxicological literature; the group did not consider the fundamental biochemistry of poisoning by these gases or the possibility that babies are particularly sensitive, perhaps dying from a poisoning action that is not particularly apparent in adults before the development of the symptoms commonly associated with adult poisoning. The group reported the reduction in the cot death rate in 1989 but did not relate it to the mattress precautions that I had recommended. The group concluded that my hypothesis was unproven due to lack of independent supporting data' but they adopted most of my recommendations for changes in mattress composition, and also adopted the recommendation from my first report to the Department of Health in May 1989 that there should be further studies on the fungi and other micro-organisms that develop on mattress materials, although in announcing the appointment of a new group to make these studies the source of the recommendation was not acknowledged.

The appointment of the group in March 1990 had prompted publication by the Lancet of a letter from me summarising our findings and explaining my hypothesis, and on 4 July 1990 I presented an account of my work to a conference in Buxton arranged by the British Society for Allergy and Environmental Medicine and the American Academy of Environmental Medicine. It was an important occasion as we had just completed some further research which explained the exceptionally high cot death rates in certain parts of Australia and New Zealand. There were several Australiens present at the conference when I first announced these findings, and it was not long before I was receiving telephone calls from Australia and requests to explain my findings in radio interviews.

Following the Buxton conference I was invited to submit a paper for publication in the journal Clinical Ecology. Some of the persons who had heard my presentation at Buxton also recognised that the development of the fungal infection in cots was partly caused by moisture relationships and I was invited to address the British Society for Allergy and Environmental Medicine on this subject at their winter meeting in November 1990, a presentation that prompted publication of a further paper on humidity in buildings, micro-organisms and toxic gas generation in the journal Complementary Medical Research in June 1991 which included a brief account of the role of humidity and temperature in cot death. Meanwhile the Lancet had prompted debate on whether my hypothesis might be correct and published my reply in which I was able to report our blood analyses and our research on the situation in Australia and New Zealand.

By July 1991 it seemed that all necessary fundamental work had been completed on my hypothesis. I already knew that the use of new or covered mattresses by parents in response to my recommendations had saved many hundreds of lives in the British Isles alone, but the risk could only be completely avoided by entirely eliminating phosphorus, arsenic arid antimony from mattress materials. At this stage I was approached by Tomy UK Limited who are suppliers of toys and nursery items, and offered sponsorship for the next stage of my cot death research, but I did not consider that further experimental research was necessary; the main requirement was to collate and present existing information. This report is the result, hopefully written in a form that is interesting to the general public but which also includes sufficient technical information to make it useful to the medical profession and cot death researchers.

The Tomy sponsorship was particularly welco Our cot death project had cost about £100,000 over almost 3 years and it had been funded almost entirely by myself and my company, causing us severe financial problems. We only survived by working evenings and weekends so that we could also maintain a reasonable level of our normal work, but I was encour aged and assisted by a number of collaborators,

including Peter Mitchell who was responsible for collecting the cot mattresses for test, my assistant Sue Kelly who was responsible for the mycological work, Tim Cox who was our chemical consultant, Denis Allsopp of the International Mycological Institute who supplied the original fungus sample which enabled us to establish our hypothesis, John Watt who advised an poisoning biochemistry and physiology, and Neil Ward of the Trace Element Unit at the University of Surrey who was responsible for the blood analyses. This entire project has been remarkable because it originated by accident and has relied entirely on the voluntary efforts of those who have been involved. Their reward for their dedication to the project is in the many hundreds of lives that have already been saved through our Joint efforts and the many thousands that will be saved in the future if we can permanently avoid cot death by eliminating phosphorus, arsenic and antimony compounds from mattress materials; we have identified the main cause of cot death through scientific research but the remedy is a matter of medical, governmental and financial politics.

Barry A Richardson November 1991

1. COT DEATH; A MODERN TRAGEDY

A cot death is one of the most dreadful events that a family may encounter. The death of an infant is a tragedy but cot death is also sudden, unexpected and unexplained. Parents wonder whether their lack of care may have caused the death, and there is always suspicion, usually completely unjustified, that accidental or deliberate smothering may have been involved; there have been reports by medical researchers as recently as 1989 suggesting that smothering is the cause of most cot deaths! Parents lose confidence in themselves and in each other and become depressed, prompting marital problems. Other children in the family become seriously affected; there are almost always older children in the family as cot deaths are rare amongst first children.

A steady increase in unexplained infant deaths was first noticed in about 1952, prompting Barrett to propose in 1954 that 'unexpected deaths in sleeping quarters of apparently healthy infants' should be described as cot death, although the term crib death is preferred in north America. The cot death rates increased steadily, despite intensifying research, and in 1969 Beckwith proposed that 'the sudden death of any infant or young child which is unexpected by history, and in which a thorough post-mortem examination fails to demonstrate an adequate cause of death' should be described as sudden infant death syndrome (SIDS). This description was adopted as code 798.0 in the International Classification of Diseases, and this new item soon appeared in the mortality statistics of affected countries, demonstrating immediately that SIDS is a serious problem in some countries but unknown in others. Cot death rates continued to increase steadily, and it was considered for some years that this was due to increasing recognition and that there was a corresponding reduction in other causes of death. This suggestion was apparently confirmed by the observation that the total mortality rate for SIDS and respiratory diseases in England and Wales remained almost constant for many years but it is now recognised that this was a coincidence and that the reduction in deaths from respiratory diseases actually resulted from the introduction of improved antibiotics; this same reduction is seen, for example, in Japan where SIDS is not a problem and does not even appear in the statistics (see Appendix 3, figure 1).

The cause of SIDS could not be identified despite intensive investigative research, although epidemiological studies have been more successful recently, particularly in identifying contributory factors. The failure to identify a single cause prompted the suggestion that SIDS might be due to many different causes, but the evidence of consistency in the features of SIDS actually suggests either a single cause or a single combination of causes but with many contributory factors. The SIDS rate in west Europe, north America and most other western-style countries is about 2 to 4 per 1,000 live births, but SIDS is not recognised at all in many countries including Japan, Russia, China, Thailand, India and parts of Africa. Rates are intermediate in Hong Kong, and amongst infants of African and Asian origin in England and Wales; it has been suggested that these are communities that suff er from overcrowding which may reduce the SIDS rates by applying a continuing stimulus to infants. The rates in Australia and New Zealand are relatively low amongst caucasians but very high amongst aborigines, suggesting an ethnic relationship such as a dietary factor, although recent research indicates a geographical relationship.

It is often suggested that cot deaths are not new and that they have simply attracted more attention in recent years. It is true that unexplained and unexpected infant deaths are mentioned even in the Bible, and the rates recorded in London were very high at times during the 18 and 19 centuries, but the cot death problem with which we are concerned today represents the high rates that are now encountered in some western countries compared with the low rates that were encountered prior to 1950 in the same countries or which are encountered today in other countries where cot death is not a problem. In England and Wales, for example, there were 1,542 cot deaths annually in 1986-88, representing a rate of 2.3 deaths per 1,000 live births, but annual deaths must be reduced to below 80, a rate of 0.12, in order to return to the situation before 1950 or to approach the insignificant numbers of unexplained deaths that are encountered in Japan. These figures clearly illustrate the magnitude of the cot death tragedy; in England

and Wales one baby in 435 dies from this cause, and this death rate is at least 20 times higher than it should be. Various precautions have been suggested since 1985 and some of these have achieved significant reductions in the cot death rates. For example, it was recommended in the Netherlands in 1987 that the prone or face down sleeping position should be avoided, and this prompted a reduction of about 40% in the cot death rate, sufficient to indicate that the prone position is a contributory cause of cot death but that the primary cause had not been identified.

There were many sudden unexpected infant deaths in the 19 century. Gosio, an Italian chemist investigating the rooms where the infants had died, noticed a garlic odour which he associated with the Marsh and Gutzeit analytical tests for arsenic. He also noticed that adults were ill with symptoms that he associated with arsenical poisoning, and he detected arsenic when he analysed finger nails and hair in which this element accumulates in chronic poisoning. He later detected arsenic in the air, and identified the source as wallpapers and carpets containing arsenical green pigments which were affected by dampness and a fungus Penicillium brevicaule, now known es Scopulariopsis brevicaulis. This gaseous arsenic was eventually identified as arsine and related alkyl compounds, and the risk of poisoning in this way was widely recognised; a Royal Commission on arsenic poisoning reported in 1904 that this gaseous poisoning was particularly sinister, difficult to diagnose, and probably undetected in most cases. Precautions were introduced, particularly the prohibition of arsenical pigments, and the last case of death from this cause was reported in the United Kingdom in 1932. Since then the risk of gaseous arsenical poisoning has been forgotten, except by the wood preservation industry in which the risk is potentially very high as arsenic compounds are used in situations in which fungal infections occur.

There has been a steady increase in cot death since about 1950. Various causes have been suggested but whilst it is now clear that some of these are contributory causes and appropriate precautions can reduce the cot death rate, the primary cause remained unidentified until 1989 when it was suggested that toxic gas generation from mattress materials might be involved. This hypothesis was prompted by Gosio's investigations in the 19 century into sudden unexpected infant deaths and the recognition that similar risks may be associated with deterioration of cot mattress materials. The purpose of this present study is to relate this hypothesis to other research as this is the only primary cause that has been proposed so far which is consistent with all the features of cot death, or sudden infant death syndrome.

2. COT DEATH; RESEARCH PROGRESS

The progressive increase in unexpected and unexplained infant deaths which prompted the adoption of the terms cot death in 1954 and sudden infant death syndrome in 1969, as well as the adoption of SIDS as a recognised cause of death in the International Classification of Diseases, also prompted increasingly detailed post-mortem investigations, but a cause of SIDS could not be identified. It was suggested that there might be many different causes of SIDS but this has not been established; on the contrary, research has identified a number of features which are consistently associated with SIDS, suggesting a single primary cause or discreet combination of causes, although several contributory factors have also been identified. In recent years these observations have prompted precautions which have in some cases achieved dramatic reductions in cot deaths, and the situation has now been reached when this apparently conflicting accumulation of research information can be collated to indicate the primary cause of SIDS, various contributory causes, and various conditions which increase the risk of SIDS. The research information is reported in detail in the Appendices.

Cot death or SIDS is a problem in most western-style countries with temperate or cooler climates. In western Europe and north America the annual SIDS rate varies between 1 and 4 per l,000 live births, but there is a distinct dependence on weather conditions; in England and Wales the rate varies from about 1.2 in the summer months to 3.5 in the winter months, and in north America the highest rates are associated with areas with the coldest winter weather. However, in Europe the rates in Sweden are only about 1.0, well below the average for western Europe, suggesting that both interior and exterior temperatures may be involved. The probable explanation is that, where intermittent heating is used as in the British Isles with cooler conditions at night, mothers tend to overwrap their babies during cold weather, and this can lead to hyperthermia or overheating when day-time temperatures are resumed early in the morning, a problem that does not affect Sweden where homes tend to be heated to a constant temperature in winter throughout the day and night.

SIDS is not recognised at all in many countries including Japan, Russia, China, Thailand, India and parts of Africa. It is often suggested that cot deaths occur in these countries and that they are attributed to some other cause, but this is not supported by statistical information. For example, SIDS is not recognised in Japan and the total infant mortality rate is approximately equal to the rate in England and Wales if the SIDS rate is omitted; the infant mortality rate in Japan is not high enough to include SIDS in any other group. There are, of course, unexplained infant deaths in all countries but there is a very sharp contrast between countries in which SIDS is recognised where the rate is 1 to 4 per l,000 births and countries in which it is not recognised where the rate is less than 0.1.

SIDS rates are low in Hong Kong, and amongst infants of African and Asian origin in England and Wales. It is sometimes suggested that SIDS rates in these communities are lower because of overcrowding and constant stimulus of the infant, but it is much more likely that they represent intermediate conditions between communities that are affected and those that are unaffected. In New Zealand the SIDS rate is relatively high at about 6 per 1,000 live births, but this comprises a comparatively low rate of about 1.6 amongst caucasian infants but an exceptionally high rate of about 11.7 amongst Maori infants. Similar high rates amongst aborigenes have been reported in Australia, suggesting an ethnic susceptibility such as a dietary factor, but more recent investigations have indicated a geographical distribution and a possible relationship with geological factors which will be described later in this chapter.

The SIDS risk is greatest for infants of 1 to 5 months in age, but there is a continuing risk up to about 14 months for infants that are particularly susceptible, such as those with low weight for their age; the greatest risk age range is slightly different in New Zealand at 0 to 5 months, a variation which is considered later. The risk is about 50% higher in boys than in girls, and higher in lower social groups, but lower for first born children.

The SIDS risk is higher in infants with low weight or low activity for their age, whatever the cause. Low infant weights may be attributed to retarded development or low birth weights due to premature or multiple births, or mothers who smoked or suffered anaemia or other inadequate pre-natal care. The SIDS risk is higher in families with poor economic conditions, such as unmarried mothers, young mothers, multiple births, second or subsequent children, lower social class, unemployment or other economic inadequacies, or parental alcoholism.

SIDS rates are higher in colder regions and much higher during colder weather. In countries where intermittent central heating is used infants usually die early in the morning when high daytime temperatures are resumed after low nightime temperatures. These observations are apparently related to excessive wrapping of infants in relation to their environmental temperature, apparently a protective response to external low temperature conditions.

Accidental or deliberate suffocation has always been considered the most likely cause of unexpected and unexplained infant death, and this suggestion has been repeated as recently as 1989, despite the enormous increase in recent years which obviously indicates a more recently developed cause of death. Detailed investigations have indicated that even suspicion of deliberate suffocation is rare, only about 1 or 2% of cot deaths, but the relationship with overwrapping, and the observation that SIDS victims are often found completely covered by bedding and sometimes at the bottoms of the beds, suggests that accidental suffocation might be involved, although overwrapping will also induce overheating or hyperthermia, and may also trap any toxic gases that are generated within the cot.

Whilst simple suffocation due to overwrapping is a possibility, suffocation can be caused by bedding in other ways. The nose and the mouth may be obstructed by a soft mattress, or by pools of vomit accumulated on an impermeable mattress covering such as PVC. 'Vented' mattresses, comprising foam covered only by netting, were introduced in the expectation that they would avoid this problem by allowing vomit to disperse, but the viscosity of vomit is too high and accumulations occur on the bottom sheet, whatever the nature of the mattress beneath. The vented mattresses probably represent one of the most harmful developments in cot bedding development as they rapidly become contaminated by perspiration, dribble and vomit which encourage heavy fungal infections and allergic reactions to associated spores and mites; there is a danger that infants become sensitised, reacting very severely to subsequent exposure to these allergens, an observation that perhaps explains the progressive increase in asthma in older children since these mattresses were introduced between 1975 and 1980. Additives in these inadequately covered foams such as fire retardants may also present toxic touching, sucking and breathing hazards, and recently preservatives and fire retardants in foams and mattress coverings have been identified as sources of toxic gases which are released through natural fungal deterioration. In England and Wales changes in mattress design and composition can be related to changes in the SIDS rates, and well publicised recommendations in June 1989 that new mattresses should be provided for all new babies (or old mattresses should be covered with polythene to isolate the babies from the mattress materials) prompted an increase of about 10 to 20% in new mattress sales, followed by a reduction in the SIDS rate of 15% in the last quarter of 1989 and a continuing reduction, reaching 43% by the last quarter of 1990.

This dramatic reduction in the SIDS rate suggests that poisoning by toxic gases from biodeterioration of mattress materials may be the primary cause of SIDS, and it is therefore appropriate to consider this hypothesis in more detail at this stage so that it can be related to other research. The air trapped in the bedding around a sleeping infant is saturated with moisture and, as this air is at a higher temperature than the air around the cot, condensation occurs within the bedding materials. This condensation disperses reasonably well from the bed coverings and does not present a problem, but it encourages development of micro-organisms on the mattress material, particularly Scopulariopsis brevicaulis, a common domestic

fungus which is encouraged to develop in the cot situation by the nitrogen content in perspiration. As it happens, this is the same fungus which was responsible for Gosio's disease and many unexpected and unexplained infants deaths in the 19 century, generating toxic arsine and related gases from arsenical pigments in wallpaper and carpets, as well as from the white arsenic (arsenious oxide) which was used as a rodent repellent in the horse hoof size used at that time beneath wallpaper. Arsenical preservatives such as OBPA are sometimes used in PVC cot mattress coverings, although not usually in the British Isles, but it has been found that the fungus can also generate phosphine, stibine and related toxic gases from phosphate and antimony trioxide fire retardant components. These gases are heavier-than-air and accumulate on the mattress. All these gases are extremely toxic even at low concentrations, and it is difficult to detect poisoning; in adults poisoning is usually diagnosed through changes in the red cells in the blood but these changes do not develop for 6 to 24 hours after severe acute poisoning and are not seen in SIDS, probably because infants die before these changes occur, perhaps because infant red cells, which are physiologically different from those in adults, are more resistant to this poisoning action.

Whether an infant is unaffected by these toxic gases or suffers irritation, illness or death depends on various contributory factors. Overwrapping in relation to the environmental temperature has already been mentioned as a contributory factor in SIDS. Overwrapping may trap toxic gases on top of the mattress and increase exposure, but will also cause overheating or hyperthermia. The toxic gases are generated by a biodeterioration process and the rate of generation is increased at higher temperatures; an increase from a normal cot temperature of 370C to a typical hyperthermia temperature of 420C or more may increase gas generation about 20 times. Infants sleeping in the prone position will be particularly exposed to accumulations of these heavier-than-air gases; the SIDS risk is much higher for infants that normally sleep in the prone position, SIDS victims are normally found in this position, and recommendations that this position should be avoided have achieved substantial reductions in the SIDS rate of up to 40% in the Netherlands, New Zealand, the State of Victoria in Australia and in the Avon area of England.

SIDS victims normally die on mattresses which have previously been used by other infants and in which fungal infections are well established; the SIDS rates are lowest in first born children and higher social groups es these are the most likely groups to use new mattresses. Reactivation by perspiration and warmth of an established fungal infection on a previously used mattress will usually take several weeks, and this is why SIDS is rare amongst babies of less than 1 month old; deaths amongst this very young age group are always associated with sleeping on a mattress in current use by an older infant in which fungal development and toxic gas generation is already activated. Headaches are the first symptom of poisoning, causing irritability in older infants who then dislodge their bed coverings, and this is why deaths are rare amongst infants of more than 5 months old, but the SIDS risk extends to about 14 months old for infants that are less active and less able to dislodge their bedding because they have low weight for their age or their activity is suppressed for some other reason. Mild and otherwise insignificant bacterial or viral infections can increase the SIDS risk in two different ways; hyperthermia is aggravated, and the administration of analgesics will suppress the headaches which cause irritability and prompt the infant to dislodge bedding and disperse the toxic gases, this observation explaining the suggestion many years ago that aspirin might be involved in cot death.

The prone or face down sleeping position may be involved in SIDS in other ways. The SIDS risk is reduced if the prone position is avoided and increased if the prone position is always used. It is also true that the supine or face up position is preferred in some of the countries where SIDS is not recognised, but in Japan increasing use of the prone position in recent years in accordance with north American practice has not resulted in the introduction of SIDS, although the Japanese community in north America suffers the same SIDS rate as other ethnic communities. In countries where SIDS is a problem the adoption of the supine position only reduces and does not eliminate SIDS. These observations suggest that the prone position is an important contributory factor but is not the primary factor in SIDS, an

important observation for the future as generally the prone sleeping position is preferred throughout the world as infants are more content, sleep more readily, cry less, move less and are less likely to suffer three month colic, and the prone position will be preferable once the SIDS risk has been eliminated. It is sometimes suggested that infants are more likely to choke on vomit accumulations on the mattress in the prone position and this is the reason why vented mattresses were introduced, yet it is obvious that an infant is much more likely to choke on vomit in the supine or face up position. Heat loss from the face is evidently important in temperature control, and the prone position may prompt overheating or hyperthermia, but not to the same extent as overwrapping.

The Suggestion that SIDS might be caused by unidentified respiratory infections seems to date from the introduction of SIDS statistics in about 1970, and the observation in England and Wales that the deaths attributable to SIDS and respiratory infections together remained almost constant (see Appendix 3, figure 1). However, closer investigation suggests that the progressive decrease in deaths attributable to respiratory infections is due to improved antibiotics as this r eduction is seen in all countries, including those in which SIDS is not recognised. There is no pathological evidence of respiratory disease as a primary cause of SIDS, but there is certainly evidence of a higher than average incidence of respiratory bacterial and viral infections in SIDS victims, suggesting that infants with these infections are at greater risk, or that medication associated with these infections increases the risk; the most likely explanation is that mild infections aggravate hyperthermia and increasing generation of toxic gases from the mattress materials.

An understanding of the possible poisoning actions of the toxic gases that are generated through biodeterioration of mattress materials provides a remarkable explanation for some of the other factors that have been found to be related to SIDS. Phosphine, arsine and stibine poisoning results in the formation of phosphonium, arsonium and stibonium cations in the blood which are weak bases and absorb acids. These cations absorb carbon dioxide, affecting the tonicity or osmotic pressure of the blood, and probably accounting for the red blood cell damage that is seen in adult cases 6 to 24 hours after severe acute poisoning. This red cell damage is not seen in SIDS, perhaps because infant red cells are more tolerant than adult red cells, but probably because longer exposure to rather lower gas concentrations is involved. The neutralisation of even a limited amount of carbon dioxide in this way is, however, significant as the carbon dioxide concentration in the blood is the most important factor in respiration control, and reduced carbon dioxide levels inhibit respiration. Overheating or hyperthermia which is also associated with SIDS usually prompts rapid breathing or hyperventilation which also reduces the carbon dioxide level in the blood, and these two factors may combine to cause protracted periods without breathing or apnoea. Cyanosis is often reported in SIDS victims which may be due to apnoea, although it is more likely to be due to catastrophic respiratory or cardiac failure; a survey indicated that SIDS is not particularly associated with infants in which periods of apnoea have been observed so that apnoea is unlikely to be the cause of SIDS, but it is obviously possible that a cause of SIDS may also be a cause of apnoea.

Organophosphorus pesticides and chemical warfare agents are well known nerve poisons. Nerves are joined by synapses in which acetylcholine generated from one nerve ending stimulates the next nerve in order to transmit the impulse, but the acetylcholine must be destroyed continously by an enzyme cholinesterase so that the next impulse and release of acetylcholine can be detected. Organophosphorus compounds interfere with this cholinesterase so that acetylcholine progressively accumulates, blocking nerve function and particularly brain function. Phosphine and the related alkyl compounds which are generated by biodeterioration of mattress materials containing phosphate plasticisers and fire retardants are the simplest organophosphorous compounds, and it is not therefore surprising that these compounds and their related arsenic and antimony compounds have been reported to possess this anticholinesterase activity. However, in infants acetylcholine has a particularly important function as it is released into the

blood by the vagus nerve as a means of moderating the heart beat, cholinesterase normally destroying the acetylcholine before the blood returns to the heart, but if the cholinesterase in the blood is destroyed by poisoning by phosphine, arsine, stibine or related alkyl compounds the acetylcholine progressively accumulates in the blood, eventually causing cardiac failure which is consistent with all the observed features of SIDS. Cardiac failure would obviously prevent the transmission of oxygen in the blood, and would explain the cyanosis that is often reported and the hypoxia or low oxygen level in the cells which is apparently always associated with SIDS. Alternatively hypoxia may be caused by interference with the oxygen transport system involving haemoglobin in the red blood cells, a poisoning action which has been reported for arsine but which would be equally understandable for phosphine and stibine. Interference in this way with haemoglobin may be associated with similar interference with the immunoglobins in the white cells, a poisoning action that has been described for arsine; interference with immunoglobins has been reported in SIDS with abnormal immunological responses to minor infections which have been attributed to immune system defficiency, perhaps a genetic defect, although toxic poisoning of the immunoglobins is an alternative explanation.

Enzymes such as cholinesterase are proteins which are easily poisoned by certain chemicals, but other enzymes are likely to be similarly affected. Glucose, an essential component in the blood which provides fuel for the body cells, is stored as glycogen in muscle and liver tissue, and interference with the glycogen storage and release process can have a profound effect on cell metabolism, particularly on brain cells which are most sensitive to glucose starvation. Glycogen storage disease is an enzyme dysfunction which can be genetic, but families affected by this problem do not seem to suffer a significantly higher SIDS rate. However, glycogen storage disease has been frequently diagnosed in SIDS victims, perhaps caused by poisoning of the enzyme systems. Fatty acid metabolism, which also provides energy and is enzyme dependent, can also suffer genetic deficiency, and affected families Suffer a much greater SIDS rate; the toxic gases phosphine, arsine, stibine and related alkyl compounds are continuously detoxified by the body and poisoning only occurs when the rate of absorption of these gases exceeds the rate of detoxification, interference with either of these metabolic processes probably increasing SIDS susceptibility by reducing the energy available for this detoxification process. However, interference with these metabolic processes is also likely to result in low body temperatures or hypothermia during cold weather; whilst hypothermia has been reported which would indicate faulty metabolism, either due to interference with one of these systems or the oxygen supply system, hyperthermia is usually reported in association with SIDS.

Muscle contraction also involves complex enzyme control. Deaths in anaesthesia are sometimes attributed to genetic dysfunctions in these systems, and it has been suggested that these dysfunctions may also be involved in SIDS. There is no evidence to indicate that SIDS is due to this disorder, but it is possible that the disorder may increase the risk of SIDS, particularly as it may aggravate overheating or hyperthermia, sometimes causing death by heatstroke. Hyperthermia is certainly important in SIDS, although it is unlikely that heatstroke is a primary cause. However, recent reports of twins in which one was a SIDS victim suggests that the other infant may suffer haemorrhagic shock encepalopathy syndrome; the symptoms of this syndrome are very similar to those of heatstroke, and it seems likely that both infants in each twin are affected by hyperthermia, but the twin on a previously used mattress dies through toxic gas generation whilst the twin on a new mattress survives but suf fers from heatstroke.

These observations have prompted various precautions over recent years. Some of these, such as breast feeding, avoiding smoking during pregnancy and the use of respiration monitors, have not significantly affected the SIDS rates, although they may be important in other respects. However, a recommendation in England in December 1984 that overwrapping should be avoided resulted in a distinct reduction in the SIDS rate in the first quarter of 1985, although this reduction was not maintained, presumably because parents were not continuously reminded of this recommendation. Avoidance of the prone or face down

sleeping position was recommended in the Netherlands in 1987 and resulted in a reduction in the SIDS rate of about 40%, and similar reductions have been achieved in Australia and New Zealand. A recommendation in England in July 1990 that overwrapping and the prone sleeping position should be avoided was also followed by a reduction in the SIDS rate, but a sharp reduction had been first observed a year earlier following recommendations that parents should provide a new mattress for every new child, or cover old mattresses with polythene, in order to avoid poisoning by toxic gases generated by biodeterioration of mattress materials.

3. COT DEATH; CONCLUSIONS AND RECOMMENDATIONS

It must be concluded that the primary cause of SIDS is generation of phosphine, arsine, stibine and related toxic gases through biodeterioration of mattress materials containing phosphorus, arsenic and antimony compounds. This hypothesis is consistent with all the established features of SIDS and is confirmed by five separate observations:-

1. lt is the only hypothesis that is consistent with most cases of SIDS. In initial investigations on 50 cases in England and Wales all the mattresses involved were found to contain phosphorus, arsenic or antimony, and all were generating volatile compounds of these elements. Further investigations indicated that all cot mattresses containing these elements generated these gases after several months in use, and whether infants were unaffected or suffered irritation, illness or death depended on contributory factors, sleeping in the prone position and overwrapping being most significant. All other hypotheses on the cause of SIDS apply to only a limited proportion of cases, but some are important contributory factors.

2. Blood antimony levels in SIDS victims who died on mattresses containing antimony and which were generating stibine were 2 to 5 times the normal maximum levels for infants, confirming poisoning. Similar analyses for phosphorus and arsenic are unrealistic because fatal dose levels for phosphine, arsine and related alkyl compounds are very low and cannot be detected in the presence of the much higher normal levels of these elements in blood and body tissues.

3. SIDS is not recognised in Japan where infant mattresses (futons) do not contain these elements. SIDS is a problem of western-style living, particularly in western Europe and northern America (including the Japanese communities in these countries), where arsenic is used in mattress preservatives, and phosphorus and antimony in fire retardants. Lamb fleeces are used for cot bedding in Australia and New Zealand where very high SIDS rates are associated with areas in which wool is likely to contain arsenic or antimony through sheep eating grass contaminated with soil containing these elements.

4. The cot death problem was first recognised in Europe and north America in about 1953, shortly after the introduction of PVC cot mattress coverings. The SIDS rate increased steadily as fire retardant and preservative systems involving phosphorus, arsenic and antimony were introduced to an increasing extent in all mattress materials, an increase in the SIDS rate in England and Wales from about 2.0 per 1,000 births in 1980-85 to about 2.3 in 1986-88 coinciding with the adoption of higher concentrations of fire retardants in preparation for the Furniture and Furnishings (Fire) (Safety) Regulations 1988.

5. SIDS rates have been substantially reduced through the adoption of mattress precautions. Media publicity for this hypothesis in June 1989 was used to promote the recommendations that a new mattress should be provided for every new infant or an old mattress should be covered with polythene to isolate the infant from the mattress materials. Many parents responded and mattress sales increased 10 to 20%, causing a progressive reduction in the SIDS rates for England and Wales of 15% in the last quarter of 1989 and 43% in the same quarter in 1990; the rates for the last quarters in 1986-88 averaged 2.68, reducing to 2.27 in 1989 and 1.54 in 1990.

In SIDS the most important poisoning effect of phosphine, arsine, stibine and related alkyl compounds is an anticholinesterase action, initially causing headache and irritability, but in extreme cases causing death through cardiac failure. Most infants in affected countries are exposed to these toxic gases but, whilst they may cause irritability, they do not cause death provided that the body is able to eliminate the poison at a sufficient rate. Death occurs only when overheating or hyperthermia results in a much higher rate of toxic gas generation, usually through overwrapping which also traps the gas around the infant,

and when sleeping in the prone or face down position results in particularly severe exposure to accumulations of these heavier-than-air gases on top of the mattress. The avoidance of overwrapping and particularly the prone position can substantially reduce but cannot eliminate SIDS.

SIDS will only be eliminated, or reduced in affected countries to the level that existed prior to 1950 and which still exists in unaffected countries such as Japan, by avoiding the elements phosphorus, arsenic and antimony in mattress materials. Components containing nitrogen should also be avoided as the biodeterioration process will generate ammonia from nitrogen compounds and, whilst ammonia is a less serious problem as it is lighter than air and easily disperses, it is very unpleasant for the infant and the biodeterioration can result in early mattress failure.

Phosphorus and antimony compounds are generally introduced in fire retardant components, and it is sometimes suggested that prohibition will make it difficult to conform with fire safety requirements. Fire retardants of this type, which are designed to inhibit fire initiation from a lighted match or cigarette, are not appropriate in cot mattresses in which fire initiation cannot occur as they are normally covered in use by bedclothes, and the introduction of improved fire safety standards in England and Wales has not therefore resulted in any reduction in casualties amongst children up to the age of 5 caused by fires in bedding materials; for many years there have been about 100 casualties annually in the United Kingdom but whilst there were about 5 fatalities these have now increased to about 15 with the introduction of more stringent fire safety requirements, probably because burning mattresses produce more toxic fumes if they contain fire retardants. There is therefore no justification for the use of fire retardants in cot mattresses but, if they must be used to satisfy inappropriate safety requirements, systems should be used which avoid the elements phosphorus, arsenic or antimony, and which are also less toxic than present systems in fire.

Changes in mattress composition to eliminate phosphorus, arsenic and antimony compounds will take some years to introduce, mainly for political rather than technical reasons. Meanwhile it is sensible to adopt appropriate precautions to minimise the SIDS risk by providing new mattresses for all new infants or by covering old mattresses with firmly secured polythene to isolate infants from the mattress materials, and also by avoiding the prone sleeping position and overwrapping.

On 31 October 1991 the Chief Medical Officer for England and Wales Dr K C Calman announced that his Department was adopting the recommendation that the prone position should be avoided and babies should be put to sleep on their sides or backs. He stated that this change in policy was being adopted following recommendations by an expert group appointed only 10 days earlier which had drawn his attention to the reductions in the SIDS rate that had been achieved in this way in New Zealand. This interest in the situation in New Zealand and the remarkably rapid response by Dr Calman and his expert group was apparently prompted by the broadcast on the same day of a television programme 'Every Mother's Nightmare' which was presented by Anne Diamond whose third son Sebastian had been a recent cot death victim and which emphasized the success which had been achieved in New Zealand in reducing the risk of cot death. Reductions in the SIDS rate through avoidance of the prone sleeping position are not unique to New Zealand but have been similarly achieved in the Netherlands, parts of Australia and in the Avon region in England, and it is obviously a matter of concern that unnecessary deaths have occurred simply because the importance of these recommendations was not recognised earlier. The prone sleeping position is a contributory factor in SIDS and avoidance will reduce but not eliminate the risk; the SIDS risk will only be eliminated or reduced to the insignificant level experienced in unaffected countries such as Japan by avoiding the primary cause which is the presence of phosphorus, arsenic and antimony compounds in cot mattress materials.

Apendix 1. RESEARCH ON SIDS

Sudden unexplained infant deaths first attracted attention in 1954 when Barrett described the unexpected deaths in sleeping quarters of apparently healthy infants, and suggested that the condition should be described as cot death; in north America crib death is preferred. The death rate increased steadily and the cause remained unidentified despite intensifying research. It was observed that most but not all deaths occurred during sleep, and not all in sleeping quarters, and in 1969 Beckwith proposed at a conference in the USA that The sudden death of any infant or young child which is unexpected by history, and in which a thorough post-mortem examination fails to demonstrate an adequate cause of death should be described as sudden infant death syndrome. This definition was adopted as code 798.0 under the International Classification of Diseases, and this new classification soon appeared in the mortality statistics for those countries in which SIDS is recognised.

SIDS rates continued to increase steadily, perhaps due to increasing recognition of SIDS with a corresponding reduction in other causes of death, but SIDS rates in some countries were too high to be explained in this way. One of the problems with SIDS is the frequent absence of any positive diagnosis; SIDS is, in effect, diagnosed by exclusion in the sense that it is unexpected in history and thorough necropsy fails to demonstrate an adequate cause, although there are now some pathological findings that are recognised as being characteristic of SIDS such as localized intrathoracic petechiae. The causes of SIDS remained unidentified, despite continuing investigative research, but a change in emphasis towards epidemiological studier achieved greater success in establishing the characteristic features of SIDS (Kelly & Shannon 1980; Kelly et al 1982; Golding et al 1985; Milner 1987; Southall et al 1987; Milner Ruggins 1989). Since 1984 various precautions have been recommended to reduce the risk and SIDS rates are now decreasing in several countries as a result, but it remains difficult to distinguish between primary causes, contributory causes and resulting symptoms.

This review of SIDS research considers the various hypotheses that have been proposed and the ways in which they relate to both the established epidemiological features and the precautions that have achieved reductions in the SIDS rates.

Epidemiology

The epidemiology of SIDS is considered in detail in Appendix 3. The main sources of statistical information are listed at the start of the bibliography in Appendix 4. SIDS rates increased steadily from about 1954 to 1990, perhaps due to improved recognition and reporting. The SIDS rates were about 2 to 4 per 1,000 live births in 1985-88 in western Europe, north America and most other western-style countries, but the rates were very low and SIDS was not recognised in Russia, China, Japan, Thailand, India and parts of Africa (Golding et al 1985; Morris 1986; Becroft & Mitchell 1989; Gordon 1989). The SIDS rates in Hong Kong, and amongst infants of African or Asian origin in England and Wales, were intermediate, apparently indicating intermediate style communities (Lee et al 1989; Balarajan et al 1989). It was suggested that overcrowding in homes in Hong Kong might be an advantage by providing an infant with a continous stimulus, an hypothesis that might also explain the lower SIDS rate amongst infants of African and Asian origin in England and Wales, but this does not explain why SIDS is not recognised at all in so many countries (Lee et al 1989).

The SIDS rate in New Zealand of about 6 per 1,000 live births was high compared with other western-style communities, but the rate amongst caucasian infants was actually lower at 1.6 and the rate amongst Maori infants was exceptionally high at 11.5 (Mitchell et al 1987). A similar high SIDS rate was reported amongst aborigines in Australia, suggesting an ethnic susceptibility, perhaps a dietary factor, although it has also been suggested that these figures might actually indicate a geographical distribution with the lamb fleeces that are traditionally used as cot mattresses in Australasia affected by soil geology (Richardson 1991a, b).

In the Netherlands it was observed that the SIDS rate had increased from 0.46 per 1,000 in 1969-71 to about 1.31 after 1978, and it was thought that this increase might be associated with a recommendation at a paediatric conference in 1971 that infants should sleep in the prone position (de Jonge et al 1989). It was suggested in 1987 that parents should avoid the prone position, and the SIDS rate dropped by about 40% (Englebert & de Jonge 1990). Similar recommendations in New Zealand and the State of Victoria in Australla achieved similar reductions (Beal 1988; Mitchell Engelberts 1991). Recommendations in England in July 1990 that overwrapping and the prone position should be avoided have also contributed to a progressive decrease in the SIDS rate, although the decrease was first observed a year earlier following recommendations in June 1989 that a new mattress should be used for every new child or old mattresses should be covered with polythene sheet to isolate the infant from the mattress (Fleming et al 1990; Richardson 1990, 1991a, b).

Statistical research in England and Wales indicates that the SIDS risk is highest between the ages of 1 month and 5 months, about 50% higher for boys than for girls, lower for first born infants than for subsequent infants and higher in lower social groups, and the risk is much greater during colder weather, both during the colder months and in colder parts of the same country (Froggatt et al 1971; Murphy Campbell 1987; Hereward 1991; Richardson 1991d). Various other factors have been identified but some of them can be grouped; for example, the risk is highest if an infant is one of a multiple birth, has a low birth weight, suffers retarded physical development, is born prematurely, has a mother who smoked or suffered anaemia during gestation, or a mother who suffered a low level of pre-natal care, but all these factors tend to result in infants with low weight and low activity for their age (Hutchinson et al 1979; Masterton et al 1987). Other factors that may be grouped are young mothers, unmarried mothers, one of a multiple birth, second or subsequent children, poor economic background and alcoholic parents, all perhaps tending to result in poor parental care but also low social and economic status; in England and Wales the risk increases with lower social status, but all these factors might also result in economic conditions which mean that the use of a new mattress is least likely (Richardson 1990, 1991a).

Bedding

Suffocation has always been suspected as a possible cause of SIDS (Meadow 1989). It is certainly true that SIDS victims are often found in the prone position completely covered by bedding and sometimes at the bottoms of their beds, conditions that would be consistent with suffocation but which are equally consistent with hyperthermia and increased exposure to toxic gases generated from mattress materials. Nasal obstruction is increased with some softer mattress materials (Emery Thorton 1968; Emery 1988). However, firmer mattrresses covered with impermeable fabric such as PVC may increase the danger of inhalation of vomit by prone infants; this has prompted the introduction in recent years of vented mattresses which comprise foam covered only by a net fabric, but these mattresses do not significantly improve the dispersal of vomit by absorption, and introduce the danger of allergic reactions to spores and mites associated with fungal infections developing on dribble and vomit accummulations in the foam filling materials (Richardson 1991a). Infants on vented mattresses may also be exposed to toxic components in mattress materials by touching, sucking or breathing absorption, or by generation of toxic gases through biodeterioration, toxic hazards that have increased in recent years through more extensive use of fire retardant or combustion modified materials.

Polyvinyl chloride (PVC) fabric was introduced as a covering for cot mattresses in about 1950 and soon gained widespread acceptance in western-style countries because it was easy to clean. Fire retardant additives were progressively introduced by prudent manufacturers, and were introduced more extensively with the progressive introduction of more stringent fire safety regulations. In England and Wales the Furniture and Furnishings (Fire) (Safety) Regulations 1988 were originally introduced to reduce fires initiated by lighted matches and cigarette ends in normal upholstered furnishings but they were later

extended to nursery furnishings. These regulations do not currently apply to cot mattresses which are not normally involved in fire initiation in this way, although they may be involved in subsequent fire spread, but the Regulations require all filling materials to be fire resistant even if they are used in cot mattresses, and cot mattress coverings are often used for other nursery furnishings and therefore require to be fire resistant. The progressive introduction of these Regulations has resulted in the use of higher concentrations of some fire retardant chemicals, and the introduction of fire retardant or combustion modified foams in vented mattresses where untreated foams were previously used. The fire retardant systems that have been used have been developed for adult furnishings and it is a matter of serious concern that the toxic risks through touching, sucking and breathing exposure in the cot mattress situation have not been recognised; mattress materials containing fire retardants and preservatives do not even conform to the safety regulations that apply to toys. The risks of toxic effects are greatly increased if mattress materials suffer biodeterioration; the generation of the extremely toxic gases phosphine, arsine, stibine and related alkyl compounds is considered in detail in Appendix 2.

Hyperthermia due to overwrapping in relation to the temperature of the surrounding environment was first suggested as a possible cause of SIDS in 1979 (Stanton 1984; Beal 1988; Stanton et al 1989; Nelson et al 1989). A recent controlled population study has confirmed that SIDS is associated with overwrapping and the prone sleeping position (Fleming et al 1990). Deaths occur particularly in the winter months and in cold climates when parents overwrap their infants in response to low external temperatures, although it has also been observed that many deaths in England and Wales occur early in the morning when the hyperthermia becomes more acute when intermittent central heating increases the accommodation temperature. Overheating is a common problem even with normal infants, about a quarter of them perspiring heavily and half of them throwing off all or some of their bed coverings (Bacon et al 1991). It is probable that the SIDS risk is higher in infants with lower weight and lower activity for their age because they have insufficient strength to dislodge their bed coverings in this way (Hutchinson et at 1979; Masterton et al 1987; Richardson 1990, 1991a). The risk of SIDS is also higher at the weekends when the infant is likely to remain undisturbed in its cot for a longer period (Morris 1986). The increase in SIDS coincides in some countries with improvements in accommodation comfort and higher temperatures in homes but, whilst higher average temperatures have been achieved at different rates in different countries, the SIDS rate has increased relatively steadily between 1950 and 1980 in most western-style countries but has remained unrecognised in eastern countries such as Japan despite similar accommodation temperatures. Hyperthermia can be aggravated if an infant is suffering from a minor and otherwise insignificant bacterial or viral infection. Hyperthermia is considered in more detail in a later section of this Appendix.

There is extensive evidence that hyperthermia is a contributory factor in SIDS. In 1990 it was suggested that hyperthermia might increase the activity of some natural fungal infections on cot mattresses, and also the rate of generation of the toxic gases that can be released from some mattress materials by micro-organisms (Richardson 1990, 1991a, b, c). The toxic gases that are generated in this way are heavier-than-air, and overwrapping will tend to trap these gases within the bedding as well as encouraging hyperthermia and greater gas generation. The higher SIDS rate amongst boys may be due to their higher metabolic rate and their greater susceptibility to hyperthermia when overwrapped.

Sleeping position

SIDS victims are usually found in their cots in the prone position, and it is now well established that the SIDS risk is greatly increased for infants who sleep in their cots in the prone position (Hassall & Vandenberg 1985; Beal 1988; McGlashan 1988; Davies et al 1989; Engelbert & de Jonge 1990a,b; Fleming et al 1991). The SIDS rate has been rather lower in the Nordic countries than in the rest of Europe, and in 1976 it was only 0.48 per 1,000 live births, but the supine sleeping position was preferred

at that time and the progressive adoption of the prone sleeping position resulted in a significant increase to 0.94 in 1984-86 (Norvenius 1988; Wennegren et al 1987). It was recognised in the Netherlands that the prone position had been adopted to an increasing extent following suggestions at a paediatric conference in 1971, and the SIDS rate increased from about 0.46 per 1,000 births in 1969-71 to about 1.31 by 1978 (de Jonge et al 1989). It was established in the Netherlands that the SIDS risk was about 2.2 times greater in infants that may be prone compared with those that are never prone, and 4.6 times greater in infants that are always prone, whilst in New Zealand the lateral position has been found to increase the risk 2.29 times and the prone position 7.44 times (Mitchell & Engelberts 1991). It was recommended in the Netherlands that parents should avoid the prone sleeping position; the use of the prone position reduced from 60% to less than 30%, and the SIDS rate then decreased by about 40% (Englebert & de Jonge 1990). Similar recommendations in New Zealand and the State of Victoria in Australia achieved similar reductions (Carpenter & Shaddick 1965; Beal 1988). Recommendations in England in July 1990 that overwrapping and the prone position should be avoided have contributed to a progressive decrease in the SIDS rate, although the decrease was first observed a year earlier following recommendations that every new infant should be provided with a new mattress or old mattresses should be covered with polythene to isolate the infant from the mattress materials; the prone position involves maximum exposure to any toxic heavier-than-air gases generated from the mattress (Engelbert & de Jonge 1990; Fleming at al 1990; Richardson 1990, 1991a, b; Berry 1991). The very low SIDS level in Hong Kong and the apparent freedom from SIDS in Japan may be due to the preference for sleeping infants in the supine position in these countries (Lee et al 1989).

The prone position may cause hyperthermia, the significant heat loss from the face in the supine position being prevented in the prone position, particularly if the infant is also overwrapped (Nelson et al 1989; Stanton et al 1989). However, the prone position may also obstruct the large blood vessels in the neck and cause. hypoxia (Gilles et al 1979; Levene & McKenzie 1990). It has also been suggested that the prone position may prompt apnoea, either because the infant is more contented in that position and sleeps more deeply, or because the position results in a higher body temperature (Scott 1990; Guntheroth & Spiers 1990). However, the situation is very confusing as there are just as many reports that the head position has no influence on hypoxia, and the prone position improves oxygenation and reduces apnoea (Lawson et al 1987; Wagaman et al 1979; Martin et al 1979; Dhande 1982). It is certainly well established that infants in the prone position are more content as they sleep more readily, they cry less, they move less and they are less likely to suffer from 3 month colic, and the prone position is usually preferred in neonatal units for these reasons (Illingworth 1954; Brackbill et al 1973; Engelberts & de Jonge 1990). It is sometimes suggested that the prone position increases the danger of choking on vomit, and this is the justification of the introduction of vented mattresses in place of mattresses covered by an impermeable fabric, but it is usually considered that the prone position is best and minimises the risk of choking on vomit (Southall et al 1991). The prone position may be associated with the development of nasal obstruction associated with viral or bacterial respiratory infections but, whilst these may be largely avoided in the supine position, other problems may develop; for example, babies with anatomical abnormalities such as Pierre Robin syndrome (abnormal tongue anchorage and reduced buccal cavity) can only survive in the prone position (Steinschneider 1975; Morris et al 1978; Guilleminault et al 1986; Emery 1988; Nicholl & o'Cathain 1988; Morris 1989; Milner & Ruggins 1989).

Whilst SIDS victims are usually found in the prone position and avoidance of the prone position can certainly lead to a reduction in the SIDS rate, the prone position is certainly not a primary cause of SIDS but is only a contributory cause. For example, in 1986-88 36% of infants in England were put to sleep in the prone position but only 24% in Scotland, yet the SIDS rate was slightly higher in Scotland during this period at ?.17 per 1,000 births compared with 2.03 for England and Wales (Shapiro et al 1990).

Respiratory and alimentary infections

It has been suggested that SIDS may be due to unidentified respiratory infections, an hypothesis that was prompted in the United Kingdom by statistical observations which appeared to indicate that the increasing incidence of SIDS was associated with an equivalent decrease in deaths due to respiratory disease (Knowelden et al 1984; see Appendix 3, Figure 1). The progressive reduction in deaths due to respiratory disease actually results from the introduction of improved antibiotics and is seen similarly in most other countries even where SIDS is not reported. Whilst some SIDS deaths were certainly classified as due to unidentified respiratory disease before the separate SIDS classification was introduced and fully recognised, a closer study of this statistical information reveals that most SIDS deaths were classified as 'unexplained' deaths and included in the 'other' classification.

There is no evidence that overwhelming respiratory disease is a cause of SIDS; indeed, if this was the case it would have been recognised and it would not have been necessary to introduce a separate SIDS classification for cause of death. However, it is generally accepted that there is frequently evidence of respiratory disease which may be a contributory factor in SIDS and which may explain the general malaise that is sometimes reported to effect SIDS victims shortly before death; for example, respiratory viral infections were identified in 38% of SIDS victims compared with only 16% of infants who had died of other non-respiratory causes (Gold et al 1961; Ray et al 1970; Urquhart & Grist 1972; Downham et al 1975; Scott et al 1978; Uren et al 1980). It has been suggested that SIDS occurs more frequently during RSV (respiratory syncytial virus) epidemics and whooping cough, yet the SIDS rate is low in Hong Kong despite a high rate of respiratory infection (Williams et al 1984; Davies 1985; Nicoll & Gardner 1988). In a recent study on 37 SIDS victims only 8% were considered to have indications of serious illness prior to death (Cole et al 1991). Whilst an unrecognised respiratory pathogen is a possible cause of SIDS, it must be concluded, as originally suggested in 1954, that acute respiratory inflammation or infection is unlikely to be the primary cause of SIDS, and observed pathological features suggest only mild irritation.

Mild viral or bacterial infections will aggravate hyperthermia caused by overwrapping (Milner & Ruggins 1989). Inflammation in the upper respiratory tract may also increase susceptibility to apnoea caused by closure of the airway on Inspiration; certainly viral infections are often associated with apnoea in otherwise healthy babies (Steinschneider 1975). Bacterial overgrowth of the nasopharynx observed in SIDS victims has also prompted the suggestion that bacterial infections, perhaps in association with viral infections, may generate toxins which may be a cause of SIDS, a suggestion that can be related to the higher incidence of SIDS in tue prone position in which bacterial secretions may accummulate in the upper respiratory passages (Morris et al 1987; Morris 1989). However, whilst these observations may be significant in some cases, it must be recognised that respiratory infections are not identified in the majority of SIDS victims.

A toxic infection would closely fit the SIDS age distribution with a peak at 3 to 4 months if temperature and immunological status are considered (Morris et al 1987; Murrell et al 1987; Bettelheim et al 1991). Microbial investigations on SIDS victims have detected significantly raised levels of streptococci and certain enterococci, as well as raised levels of Escherichia coli toxin and staphylococcal TSST-1 toxin (Morris et al 1987; Murrell et al 1987; Newbould et al 1989; Bettelheim 1990).

Immune system deficiency

It has been suggested that SIDS may be associated with immune system deficiencies. High concentrations of Ig A and particularly Ig G and Ig M have been found in the lungs of SIDS victims compared with babies dying from other non-respiratory causes (Forsyth et al 1989). These observations are considered to indicate an abnormal immunological response to a minor infection rather than an overwhelming

infection by an unidentified respiratory pathogen, these minor infections perhaps being more significant in relation to hyperthermia (Milner & Ruggins 1989). This abnormal immunological response may be associated with reported faulty formation of haemoglobin and immunoglobins, causing difficulty in transferring from foetal to adult haemoglobin with white cell defects causing difficulty in transferring from a foetal passive to an adult active immune system (Stewart 1989; Matthews & Fox 1989). It is possible that these haemoglobin and immunoglobins defects may be due to poisoning by the toxic gases that are generated by biodeterioration of some mattress materials; certainly arsine poisoning induces a reduced immunological response and phosphine and stibine can be expected to have a similar action, and whilst erythrocyte haemolysis is usually considered to be an esssential diagnostic feature of arsine poisoning in adults, an increase in white cell count may be more significant (Rosenthal et al 1989; Hong et al 1989).

Enzyme dysfunction

Various enzyme dysfunctions have been suggested as a cause of SIDS. Most of these hypotheses have been concerned with defective metabolism and particularly energy storage and utilization.

Glucose is an essential constituent in blood, providing the fuel for the body cells. The normal glucose concentration in blood is about 0.1% by weight, lower concentrations initially affecting the function of the nerve cells, particularly in the brain, and prompting muscular twitchings, convulsions and eventually death. Glucose is stored in muscle tissue and in the liver as glycogen, and enzymes are involved in both the storage and release processes. It has been suggested that SIDS might be due to type 1 glycogen storage disease which is caused by a deficiency of hepatic microsomal glucose-6-phosphatase, obstructing conversion of glycogen to glucose and prompting fatal hypoglycaemia (Cori & Cori 1952; Arion et al 1976; Nilsson et al 1978; Narisawa et al 1978; Arion et al 1980; Lange et al 1980; Burchell & Burchell 1980; Burchell & Burchell 1982; Nordlie et al 1983; Burchell et al 1985; Burchell et al 1987; Waddell & Burchell 1987; Waddell et al 1988; Burchell et al 1988; Countaway et al 1988; Emery et al 1988; Blair & Burchell 1988; Waddell et al 1989; Burchell et al 1989). Glucose-6- phosphatase is not a single enzyme but a complex comprising at least five different polypeptides; a glucose-6-phosphatase enzyme, a regulatory calcium binding protein, and three transport proteins designated T1, T2 and T3 which enable glucose-6-phosphatase, phosphate and pyrophasphate, and glucose respectively to cross the endoplasmic reticulum membrane. Raised hepatic glycogen levels have been detected in more than 25% of SIDS victims, with about 20% diagnosed as type la glycogen storage disease involving classic glucose-6-phosphatase deficiency, about 2% as type 1b disease involving T1 deficiency, and about 5% as type 1c involving T2 deficiency (Burchell et al 1989). Severe hypoglycaemia due to type 1 glycogen storage diseases may be a genetic defect, but investigations have suggested that families in which this defect is established do not suffer a significantly higher SIDS rate (Addison et al 1989).

Some sudden and unexpected infant deaths which might have been attributed to SIDS have been shown to involve genetic defects of fatty acid metabolism (Howat et al 1984; Howat et al 1985; Roe et al 1986; Duran et al 1986; Anon. 1986; Chalmers et al 1987; Harpey et al 1987a; Harpey et al 1987b; Allison et al 1988; Emery et al 1988; Burchell et al 1989). Faulty fatty acid oxidation due to medium-chain acyl coenzyme A dehydrogenase (MCAD) deficiency has been diagnosed in about 5% of SIDS victims, prompted by observations of fatty changes in the liver which are often associated with profound hypoglycaemia. MCAD deficiency is genetic, and the SIDS risk is higher in families in which this condition has been diagnosed (Addison et al 1989).

Interference with the enzymes involved in muscle contraction and relaxation has also been suggested as a possible cause of SIDS (Denborough 1989). Nerve impulses prompt the formation of IP3 at the muscle which releases calcium from the muscle cell, causing the protein in the muscle to contract. The increasing

calcium concentration outside the muscle cell then stimulates a phosphatase which breaks down the IP3 to IP2 which is inert, allowing the muscle protein to relax. Deficiency of the IP3 phosphatase results in protracted muscle contraction which is sometimes a cause of death in anaesthesia, but this condition is also associated with hyperpyrexia or hyperthermia, and death may be due to heat stroke, suggesting a link with SIDS in which hyperthermia is often observed.

Phosphoenolpyruvate carboxykinase deficiency in the liver has also been suggested as a cause of SIDS, but this hypothesis has not attracted any recent attention (Sturmer Susa 1980).

It has been suggested that SIDS might be caused by an anticholinesterase poison (Richardson 1991e, b). Acetyl choline is generated at nerve endings, stimulating the next nerve and providing continuity of impulse across a nerve synapse, although this system can only operate if cholinesterase is present which steadily reduces the aceteyl choline concentration so that the next impulse and release of acetyl choline can be detected. Acetyl choline is also released by the vagus nerve into the blood stream, regulating cardiac activity by inhibiting smooth muscle contraction. Cholinesterase in the blood normally ensures that acetyl choline is destroyed before the blood next enters the right atrium of the heart and receives more acetyl choline from the vagus nerve, but if the cholinesterase in the blood is depressed, acetyl choline will progressively accumulate, inhibiting cardiac contractions until death eventually occurs. Phosphine, arsine, stibine and associated alkyl compounds which are generated through biodeterioration of cot mattress materials containing fire retardents and preservatives are known to interfere with the central nervous system in adults through anticholinesterase action, but in infants this poisoning is more likely to result in cardiac failure, which would be completely consistent with SIDS with its absence of significant pathological features.

Enzymes are proteins, usually containing heavy metals, which can be inactivated by compounds such as cyanides which will complex with the heavy metals. Other poisons may be absorbed onto reactive sites on the molecule, destroying the enzymatic action; phosphine, arsine and stibine dissolve in blood to form phosphonium, arsonium and stibonium cations which can behave in this way but which, if present in sufficient concentration, may also condense onto blood glucose units, preventing glucose metabolism and prompting cell death (See Appendix 2).

Hyperthermia and hypothermia

Hyperthermia or hyperpyrexia is often observed in SIDS victims, and is usually attributed to overwrapping in relation to the temperature of the surrounding environment at the time of death. Hyperthermia does not seem to be a cause of death as the characteristic tissue damage associated with heatstroke is not normally observed, although there are reports that where twins are sleeping in the same room and one is a SIDS victim, the other often suffers haemorrhagic shock encephalopathy syndrome which has clinical and pathological features similar to heatstroke (Wadlington et al 1976; Bacon et al 1979; Trounce et al 1991; Bacon 1991). HSES may therefore result from hyperthermia and SIDS may be caused by hyperthermia in more sensitive individuals who die before development of the tissue damage which is characteristic of heat stroke, although it is more likely in twins that the SIDS victim was on a previously used mattress generating toxic gases and the HSES victim was on a new mattress free from toxic gas generation.

Hyperthermia prompts hyperventilation and a decreasing carbon dioxide tension in the blood which may in turn inhibit ventilation and prompt apnoea. The respiratory centre in the medulla is not well developed in young infants who depend instead on chemoreceptors in the carotid Sinus which react particularly to carbon dioxide tension, but hyperthermia may cause dysfunction of this respiratory chemoreceptor (Gozal et al 1988; Bacon 1991.

Whilst hyperthermia is certainly associated with SIDS and usually caused by overwrapping, aggravated by mild infections and other complications such as genetic phosphatase deficiency in muscle tissue, there is no evidence that hyperthermia is itself a cause of SIDS, but it is probably an important contributory factor, particularly in relation to the generation of toxic gases from mattress materials (see Appendix 2). Normal healthy infants affected by hyperthermia dislodge and remove bed coverings but weaker infants may not be able to react in this way and this may explain why the SIDS risk is greater for infants which are underweight for their age (Bacon et al 1991). Boys may be more sensitive to hyperthermia because of their higher metabolic rate and this may explain why the SIDS risk in boys is about 50% greater than in girls.

Whilst hyperthermia is reported in almost all SIDS victims, there have been some reports of hypothermia (Dunne Mathews 1988). Hypothermia may be due to inadequate wrapping in relation to the environmental temperature, but temperature control is very efficient in normal healthy infants and hypothermia is therefore is likely to be an indication of faulty metabolism, probably inefficient glycogen or fatty acid utilisation due to enzyme deficiency, perhaps a genetic defect.

Apnoea

The SIDS risk is higher in infants which are susceptible to prolonged apnoea, and cyanosis is often present in SIDS which indicates anoxaemia caused by cardiac or respiratory failure (Steinschneider 1975; Kelly et al 1986; Morris et al 1987; Kahn et al 1988). It has been suggested that the risk of SIDS can be predicted by investigations of apnoea and disorders of cardiac rythum but, in a survey of 9,000 infants, the 29 SIDS victims were not recorded as suffering previous apnoea or other respiratory abnormalities (Southall 1983; Southall et al 1985). It has not been established whether susceptibility to apnoea is a contributory factor in SIDS or whether the apnoea is prompted by a condition which is also a cause of SIDS.

Apnoea may be due to obstruction of the upper respiratory tract such as closure of the oropharynx and hypopharynx in inspiration to which an infant may be more susceptible in the prone position (Kahn et al 1988; Southall et al 1989). The risk of SIDS is higher in infants subject to prolonged apnoea, even if the attacks are not considered to be severe (Kelly et al 1986; Kahn et al 1988). Obstructive apnoea may be associated with respiratory infection and inflammation in the upper airway (Steinschneider 1975).

In adults the respiratory centre in the medulla is responsible for respiratory control, but this system is not well developed in young infants who depend instead on a respiratory centre in the carotid sinus. Overheating due to overwrapping may induce hyperventilation and a reduction in the carbon dioxide tension in the blood which may in turn inhibit ventilation and prompt apnoea. Poisoning by gases which will form bases in the blood will absorb carbon dioxide and similarly prompt apnoea (see Appendix 2).

Expiratory apnoea may cause arterial hypoxaemia and, in extreme cases, may induce cyanosis and hyperthermia, symptoms which are often associated with SIDS (Southall et al 1985; Dunne Mathews 1988).

Hypoxia

It has been observed that hypoxanthine concentrations in vitreous humour are very high in SIDS victims compared with infants dying from other nonrespiratory causes (Rognum et al 1988; Rognum Sangstad 1991). Hypoxanthine is formed from adenosine monophosphate by a catabolic process which is accelerated by hypoxia, so that these observations suggest hypoxic conditions at death. Hypoxia can be caused by various metabolic defects, by respiratory failure such as apnoea, or by cardiac failure, perhaps

caused by poisoning by toxic gases generated by mattress deterioration (Southall 1983; Southall et al 1985; Gozal et al 1988; Southall Samuels 1989; Richardson 1990, 1991 a, b; Bacon 1991). Oxygen monitors can detect the onset of hypoxaemia in infants but will not necessarily avoid SIDS; hypoxaemia may not be a cause of SIDS but may be simply an associated symptom (Poets et al 1991).

Allergic reactions

Exposure to spores and mites from fungal infections on bedding may cause sensitization and eventually fatal asthma attacks (Gravesen 1979; Homberg & Kallings 1980; Sundin 1983; Anon. 1984; Barr et al 1985; Holmberg 1985; Croft et al 1986; Milberg 1987; Richardson 1991a). Many of the fungal infections that develop on mattress materials are known to induce asthma in this way, but there is no evidence that this is a major cause of SIDS, although it would be consistent with observed hypoxia.

The incidence of asthma in older children in the British Isles has increased in recent years. This increase may be associated with increased exposure to heavier infections in the cot environment. Mattresses covered with easily cleaned impermeable PVC fabric are being progressively replaced by vented mattresses in which the foam filling is covered only by net, encouraging the development of heavy bacterial and particularly fungal infections where the exposed foam is affected by perspiration, dribble and vomit.

Mattress biodeterioration and toxic gas poisoning

Cot mattress materials become naturally infected in use by various microorganisms, particularly where affected by dribble and vomit, or by the perspiration and warmth of the sleeping infant. Some micro-organisms, particularly Scopulariopsis brevicaulis, are able to deteriorate mattress materials and generate the toxic gases phosphine, arsine, stibine and related alkyl compounds if suitable sources of phosphorus, arsenic and antimony are present (Richardson 1990, 1991a, b). Poisoning by these gases is consistent with the established features of SIDS, and this hypothesis is therefore reported in detail in Appendix 2. Recommendations in England in June 1989 that a new mattress should be provided for every new infant or old mattresses should be covered with polythene to isolate infants from the mattress materials were followed by an increase in new mattress sales and a substantial decrease in the SIDS rate (Richardson 1991d).

Other factors

Many possible causes of SIDS have been suggested. Prior to 1954 it was always considered that the most likely cause was deliberate or accidental suffocation, and it has been suggested as recently as 1989 that 2 to 10% of SIDS victims could have been smothered deliberately (Meadows 1989). Detailed studies of 988 infant deaths in 1976-79 identified only about 1% as infanticide and 1.5% as suspicious (Knowelden et al 1984). The SIDS rate at that time was about 2.0 per 1,000 live births and infanticide may therefore have accounted for up to 0.05 deaths per 1,000, about half of the sudden unexplained infant death rate prior to 1950 which was only about 0.1 per 1,000, a comparison that also explains the serious concern at the current SIDS rates, typically 2 to 4 per 1,000 in affected countries.

It has been frequently suggested that SIDS is caused by exposure to electromagnetic radiation. Strong electro-magnetic fields can affect persons, and some individuals are particularly sensitive to certain frequencies, but there is no evidence of consistency between SIDS and possible exposure to various forms of electro-magnetic radiation.

Congenital defects such as adrenal hypoplasia and islet hyperplasia have been suggested as possible causes of SIDS (Polak & Wigglesworth 1976; Russell et al 1977). However, whilst these conditions may be a primary or contributory cause in some individual cases, there is no evidence that they are generally associated with SIDS. Congenital enzyme deficiencies related to metabolism are much more likely causes of SIDS, and may be related to the observed islet hyperplasia, but they have still been observed in only a small proportion of SIDS victims.

Lethal toxic infections would be consistent with SIDS in terms of the peak age distribution of about 3 to 4 months when temperature and immunological status are considered (Morris et al 1987; Murrell et al 1987; Bettelheim et al 1991). Toxic respiratory and alimentary infections have been considered earlier.

Gaseous poisoning has also been proposed as a possible cause of SIDS. The association with overwrapping suggests that limited ventilation might result in an accumulation of carbon dioxide and increasing carbon dioxide tension in the blood which would prompt hyperventilation, but the respiratory chemoreceptor in the carotid Sinus in infants may be blocked in hyperthermia, preventing hyperventilation and allowing carbon dioxide to accumulate to dangerous concentrations. Excessive accumulations of carbon dioxide may result eventually in formation of carbon monoxide and methaemoglobin in the erythrocytes, obstructing oxygen transport in the blood, but carbon monoxide poisoning is unlikely as the gas is lighter-than-air and readily disperses from bedding, and the well established symptoms of carbon monoxide poisoning have never been reported in SIDS.

Ammonia, generated by bacterial degradation of urine, has also been suggested as a possible cause of SIDS but it is lighter-than-air and readily disperses from bedding; this is why it is noticed by parents. However, ammonia i3 the trihydride of nitrogen, an element in Group V/Vb of the chemical periodic table, and similar biodegradation of compounds containing the other elements in this group phosphorus, arsenic and antimony can generate much more toxic heavierthan-air gases which will accumulate on cot mattresses, particularly when an infant is overwrapped, presenting a particular hazard to infants sleeping in the prone or face down position (See Appendix 2).

Appendix-2 . MATTRESS BIODETERIORATION AND SIDS

It was recognised by Richardson in 1988 that microbial deterioration of plasticised polyvinyl chloride (PVC) containing an arsenical preservative might result in the generation of toxic arsine gas. It was suggested that this process might be a cause of sudden infant death. Investigations confirmed that used cot mattresses are naturally infected by fungi which can cause this gas generation and, whilst arsenical preservatives are not normally used in PVC cot mattress coverings in the British Isles, toxic phosphine, stibine and related alkyl gases can be similarly generated from the phosphate plasticisers and antimony trioxide that are used when fire resistance is required. Poisoning by toxic gases generated in this way is consistent with all the known features of SIDS. In March 1990 the Department of Health in the United Kingdom appointed a Group of Experts to enquire into the hypothesis.

The Richardson hypothesis

The Richardson hypothesis suggests that the primary cause of sudden infant death syndrome (SIDS) is poisoning by gaseous phosphine, arsine, stibine and related alkyl compounds generated by deterioration of cot mattress materials by micro-organisms, particularly Scopulariopsis brevicaulis. All cot mattresses become naturally infected in use by micro-organisms, and these toxic gases are generated from all mattress materials that contain phosphorus, arsenic or antimony compounds. Whether an infant is unaffected or suffers irritability, illness or death depends on various contributory factors (Richardson 1990,1991a,b).

Mattress biodeterioration and toxic gas generation

In the late 19 century an Italian chemist Gosio discovered that mysterious infant deaths and adult illnesses were caused by a gaseous form of arsenic which was generated by fungal deterioration of arsenical pigments in wallpapers and carpets, and white arsenic (arsenious oxide) used as a rodent repellent in horse hoof size (Gosio 1892,1893,1897; Sanger 1894a,b; Schmidt 1899; Biginelli 1900; Anon. 1932; Thom and Raper 1932). Poisoning by volatile arsenic compounds in this way was recognised as a particularly sinister form of arsenic poisoning which could not be readily detected and which was often attributed to food poisoning and incorrectly diagnosed as toxic jaundice or haemolytic anaemia (Anon. 1904; Hunter 1936; Doig 1958). The fungus involved was Scopulariopsis brevicaulis, known at that time as Penicillium brevicaule. This fungus, which is commonly found in the domestic environment, generates ammonia from nitrogen compounds such as proteins in meat, cheese and butter, as well as in damp leather and wool (Morton & Smith 1963; Onions 1966). Ammonia is nitrogen trihydride, derived from the nitrogen in the protein substrate, whilst Gosio's arsenic gas was identified as arsine or arsenic trihydride. Arsine and related alkyl compounds can also be generated by various fungi from arsenical wood preservatives (Richardson 1978). Group V/Vb of the periodic table comprises in sequence nitrogen, phosphorus, arsenic and antimony and it was not therefore surprising that S. brevicaulis should form trihydrides of both nitrogen and arsenic, but it was surprising that there seemed to be no reports in the literature of similar generation of the trihydride phosphine from the intermediate element phosphorus and perhaps also similar generation of stibine from antimony. Less volatile alkyl compounds would also be expected from the four elements; it has been suggested that Gosio's arsenic was trimethylarsine rather than arsine (Challenger 1945; Cullen & Reimer 1989).

Richardson observed that the microbial infections on used mattresses always included S. brevicaulis, as well as many other fungi and bacteria which were known to be pathenogenic or known to be associated with generation of spores and mites prompting allergic reactions such as asthma; Richardson recommended investigation of these other organisms (Gravesen 1979; Homberg & Kallings 1980; Sundin 1983; Anon. 1984; Barr et al 1985; Holmberg 1985; Croft et al 1986; Milberg 1987; Richardson 1991a).

S. brevicaulis infections were found to be concentrated in the parts of the mattress affected by the warmth and perspiration of the sleeping infant, development of this organism being prompted apparently by the presence of nitrogen compounds in the perspiration. S. brevicaulis was not only found on PVC cot mattress coverings but also on cotton, polyester and other covering fabrics and on the foams which are covered only by nets in some modern vented mattresses, the infections being concentrated in areas affected by perspiration, dribble and vomit. Pink staining was frequently observed, sometimes as an outline of the body of a sleeping infant, when the affected materials contained phosphates which prompt pink pigmentation in S. brevicaulis.

Richardson detected S. brevicaulis infections in samples of mattress material by placing them on a nitrogen-rich medium (malt/soya agar) on Petri dish plates, a medium that encouraged the spread of this fungus on the plate so that it could be readily identified; a nitrogen-rich medium also prompts the fungus to change from the normal hyphal or filamentous form to a slime form which is often incorrectly identified as a contaminant bacteria or yeast. Gases generated from these cultures were identified using silver nitrate and mercuric bromide (or chloride) papers secured over the edges of the Petri dishes. These trihydride gases are reducing agents and eventually cause darkening of the silver nitrate but, before this darkening develops, phosphine causes a bright yellow colouration whilst arsine and stibine cause a pink or brown colouration; the mercuric bromide paper enables the latter gases to be distinguished as arsine causes a yellow or orange colouration but phosphine and stibine cause no colour change. The related alkyl gases are not strong reducing agents but they cause similar but fainter colourations. The incubation temperature of about 22°C for these tests ensured that an antimony reaction indicated that only the trihydride stibine was present as the alkyl compounds are not volatile at that temperature, and arsenic and phosphorus reactions indicated that the trihydrides phosphine and arsine were most likely to be present, although theoretically the methyldihydride compounds might also be present. At normal cot mattress temperatures of about 37 °C the methyldihydride compound of antimony is also volatile, as well as the dimethylhydride and ethyldihydride compounds of phosphorus and arsenic. Doubts over the identity of the generated gases were prompted by reports which suggested that only alkyl compounds of arsenic are generated by biodeterioration, although it was not established that the trihydride was not also generated (Challenger et al 1933, Challenger 1945, Brahman & Foreback 1973, Cullen & Reimer 1989). The distinction between trihydrides and related alkyl compounds is actually irrelevant as all the compounds are toxic with similar poisoning actions.

Richardson obtained blood samples from SIDS victims. Antimony levels of 2.8, 4.8 and 1.9 ng/ml were found for infants who died on mattresses which were apparently generating only stibine; normal levels are 0.7 to 3.0 ng/ml in adults but less than 0.85 ng/ml in infants, so that there was an increase in blood antimony of about 2.0 ng/ml which could only be due to poisoning by stibine generated by biodeterioration of the mattress materials (Ward 1990). Analysis was limited to antimony because the known comparative toxicities of arsine and phosphine suggest that poisoning might increase arsenic and phosphorus levels in the blood by about 1.0 and 6.0 ng/ml respectively, but such increases would be undetectable with normal arsenic levels of 2.0 to 5.0 ng/ml and much higher phosphorus levels.

Polyvinyl chloride (PVC) cot mattress covers vary in composition but typically contain 55 to 60% PVC polymer and 30 to 35% plasticiser with 5 to 12% titanium dioxide and other pigments including antimony dioxide. Phosphate plasticisers and antimony trioxide have been used for many years to improve fire resistance, most fabrics containing either a phosphate plasticiser or antimony trioxide, although some contain both components. The concentrations of these fire retardants have increased progressively over the years, particularly in England and Wales with the introduction of the Furniture and Furnishings (Fire) (Safety) Regulations 1988 which prompted increases in the typical concentrations of phosphate plasticiser from 8 to 12% and of antimony trioxide from 1 to 4.5%. Phosphate plasticisers are generally

triarylphosphates such as trixylylphosphate and tricresylphosphate. Commercial antimony trioxide may contain up to 0.5% arsenical impurities. Biodeterioration of the plasticiser component in PVC particularly by Aspergillus niger and Streptomyces rubrireticuli has been extensively reported, but toxic gas generation through biodeterioration of components containing phosphorus, arsenic or antimony has not been previously considered (Klansmeier 1961, 1966, 1972; Yeager 1962, 1968).

Cotton, polyester, polypropylene and other woven fabrics used for cot mattress coverings often contain fire retardant components or are treated with fire retardants of various types such as ammonium phosphates and chlorophosphates. Boron compounds are sometimes used, although they are not common in the British Isles. Filling materials are also treated with various fire retardants, fibre fillings using the same fire retardants as for woven fabric coverings. Fire retardant foam fillings have only been generally introduced in England and Wales since about 1985 in order to conform with the Furniture and Furnishings (Fire) (Safety) Regulations 1988 and such foams are now often described as 'Combustion Modified'. Some foams contain fire retardants similar to those used in woven fabrics, particularly chlorophosphate esters, sometimes with the addition of small amounts of antimony trioxide which improves fire retardancy by reaction with the chlorine content, but many combustion modified foams rely on graphite or melamine components to achieve sufficient fire resistance.

Although wool clothing, bedding and carpets are often 'proofed' against damage by moth and other insects with insecticide treatments, preservatives are not normally used on furnishing fabrics in the British Isles as other fabrics are not significantly at risk from insect attack and the risk of microbial deterioration is very small in a normal dry domestic environment. However, PVC intended for use in the sub-tropics and tropics is sometimes protected from termite and microbial attack using an arsenical biocide 10,10'oxybisphenoxyarsine (OBPA), and in some countries such as Japan boron compounds are used which function as fire retardants as well as preservatives against microbial deterioration.

The presence of phosphorus, arsenic and antimony compounds in mattress materials can be directly related to SIDS rates. In Japan where SIDS is unknown infant mattresses (futons) are manufacturered from cotton alone and do not contain any of these elements. In England and Wales where phosphorus and antimony fire retardents are used the SIDS rate stabilized at about 2.0 in 1980, but later increased to a new level of about 2.3 in 1986-88 when use of fire retardents increased in preparation for the introduction of the Furniture and Furnishings (Fire) (Safety) Regulations 1988; these regulations did not strictly apply to cot mattresses, even after they were later extended to nursery furnishings, but all filling materials were required to be fire resistant and all covering materials were also used for other nursery furnishings where they were required to be fire resistant. SIDS rates are higher, typically about 4.0, where arsenical preservatives are used such as OBPA, and these rates increase even further where fire retardents based on phosphorus and antimony compounds are used in addition to arsenical preservatives; the SIDS rate amongst armed service families in England and Wales is about 6.0 because they use issue mattresses containing both fire retardents and OBPA preservative. Lamb fleeces are often used as cot mattresses in Australia and New Zealand, and result in exceptionally high SIDS rates up to 20.0 in some areas, apparently where the wool contains arsenic or antimony acquired through sheep feeding on grass contaminated with soil containing these elements.

Phosphorus in plasticisers and fire retardants, arsenic present as impurities in antimony trioxide and in the biocide OBPA, and antimony in antimony trioxide fire retardants are the sources of the extremely toxic phosphine, arsine, stibine and related gases that have been identified, but these gases can only be generated by an organism such as S. brevicaulis if sufficient energy is available. Generally the micro-organism must have access to an hydrocarbon, although some energy can also be obtained by deterioration of nitrogen or even phosphorus compounds. In PVC the chlorine groups provide some

protection for the PVC polymer itself and the plasticiser therefore forms the main nutrient in biodeterioration, but if nitrogen compounds are present from perspiration or urine, or as ammonium phosphate or melamine fire retardant components, development of S. brevicaulis is particularly encouraged. This organism will convert nitrogen compounds to the trihydride ammonia which is also toxic but disperses readily as it is lighter than air but, if sufficient energy is available, it will also generate phosphine, arsine or stibine from any phosphorus, arsenic or antimony compounds that are present. Generation of these gases is therefore usually associated with deterioration of the plasticiser and progressive development of brittleness, particularly where development of this fungus is encouraged by the warmth and perspiration of the infant. On other fabrics and fillings a variety of micro-organisms will develop on areas affected by perspiration, dribble or vomit but including S. brevicaulis so that again phosphine, arsine or stibine may be generated if suitable sources of phosphorus, arsenic and antimony are accessible to the organism.

Mattress biodeterioration can only occur if sufficient moisture is present within the affected materials. The air around an infant in a cot is saturated with moisture and the relative humidity of the air is therefore 100%. There is a temperature gradient between the interior and exterior of the cot through the bedding and mattress materials, and diffusion of this saturated air towards the exterior will result in cooling and interstitial condensation within these materials, providing the moisture which is necessary for the development of microbial infections and mattress biodeterioration (Richardson 1991c). Interstitial condensation is more severe if the saturated internal air is at a higher temperature, as in infant hyperthermia prompted by viral or bacterial infection or overwrapping.

Toxicology of Group V/Vb trihydrides and related compounds

Nitrogen, phosphorus, arsenic, antimony and bismuth are elements of increasing atomic weight which form Group V/Vb in the periodic classification of the elements. It is well known that many micro-organisms are able to convert nitrogen compounds such as protein into the trihydride ammonia and related alkyl compounds or amines. This ability to generate trihydrides is particularly well developed in the fungus S. brevicaulis which is able to utilize nitrogen from a wide variety of sources including nitrate and ammonium compounds, as well as urea, proteins and nitrogen polymers such as melamine. S. brevicaulis and several other organisms can similarly generate phosphine, arsine, stibine and related alkyl compounds from substrates containing phosphorus, arsenic and antimony, although it seems that S. brevicaulis is most active in this respect if nitrogen compounds are also present, presumably because they stimulate the enzymatic processes that are involved. Generation of these hydrides and related alkyl compounds in the cot environment introduces a toxic hazard which varies according to the compounds that are involved.

Ammonia, phosphine, arsine and stibine are gases with densities of 0.65, 1.17, 2.68 and 4.29 relative to air. Mothers are usually aware of ammonia generation as the pungent odour and low density mean that it is readily detected above the cot, but phosphine, arsine and stibine are denser than air and odourless, and accumulate on top of the mattress, particularly if the infant is well wrapped. The alkyl compounds of phosphorus, arsenic and antimony are denser than the trihydrides but at normal cot temperatures of 37 °C only the methyldihydride compounds of all three elements and the dimethylhydride and ethyldihydride compounds of phosphorus and arsenic are volatile. Phosphine, arsine and stibine are colourless and odourless, although their associated alkyl compounds have distinctive odours which are often attributed to the trihydrides themselves. Thus the standard toxicological literature usually states that phosphine has a 'dead fish' or 'garlic' odour, arsine is more distinctly 'garlic', and stibine odour is usually described only as 'very unpleasant'. The threshold limit values (occupational exposure limits assuming 8 hours exposure) for phosphine, arsine and stibine are usually quoted as 0.3, 0.05 and 0.1 ppm

respectively, indicating extreme toxicity; these gases are about 300, 2,000 and 1,000 times more toxic than carbon monoxide which has a TLV of 100 ppm (Anon. 1989; Anon. 1990). The garlic odour associated with arsine is only usually detectable at concentrations well in excess of the TLV.

It has been reported that it is difficult to tonfirm that an infant has absorbed sufficient phosphine, arsine or stibine to cause death (Richardson 1991a, b). Blood samples from three infants who died on mattresses which appeared to be generating only stibine were found to have antimony levels of about 2.8, 4.8 and 1.9 ng/ml, compared with normal ambient levels of 0.7 to 3.0 ng/ml in adults but less than 0.85 ng/ml in infants (Ward 1990). These results suggest that the blood antimony level was increased by about 2.0 ng/ml by stibine poisoning, although the normal maximum level of 0.85 ng/ml in infants probably includes some contribution from mattress stibine in non-fatal situations. The known comparative toxicities of arsine and phosphine would suggest that poisoning might increase arsenic and phosphorus levels in the blood by about 1.0 and 6.0 ng/ml respectively but such increases would be undetectable with normal arsenic levels of 2.0 to 5.0 ng/ml and much higher phosphorus. levels. These calculations would suggest that lethal doses of phosphine, arsine and stibine in infants might be 60, 10 and 20 ng/Kg body weight respectively. Mixtures of gases are probably additive in effect because of their identical mode of action. These gases are eliminated by excretion in urine and significant toxic effects only develop when the rate of gas absorption exceeds the rate of elimination; hyperthermia in an infant increases the rate of gas generation from mattress materials. Antimony levels in urine can be used to monitor exposure in infants; arsenic may be checked in the same way, but normal phosphorus levels in urine are too high for this element to be monitored.

The typical symptoms of arsine poisoning in adults are well known (Hunter 1936; Josephson et al 1951; Doig 1958; Teitelbaum & Kier 1969; Hocker & Bradshaw 1970; Cooper 1974; Pinto 1976; Kleinfeld 1980; Selzer & Ancel 1983; Polson et al 1983; Dreisbach 1983; Tver & Anderson 1986; Plunkett 1987; Moorman et al 1987; Houg et al 1989; Rosenthal et al 1989). Poisoning by phosphine and stibine is not so frequently reported and is not described in such detail in the literature but they are exceedingly poisonous heavier-than-air gases with the same mode of action and symptoms as arsine; the main differences arise only through differences in density and toxicity (Fairhall 1947; Cooper 1974; Wilson et al 1980; Dreisbach 1983; Polson et al 1983; Tver & Anderson 1986; Plunkett 1987; Misra et al 1988). Phosphine, arsine and stibine are much more toxic than other phosphorus, arsenic and antimony compounds, perhaps because they are not so readily eliminated by methylation and excretion (Braman & Foreback 1973; Cullen & Reimer 1989). Poisoning by these gases is usually diagnosed in adults through erythrocyte haemolysis and Heinz body formation, but haemolysis only develops 6 to 24 hours after severe acute exposure and such symptoms are not normally associated with SIDS. If phosphine, arsine and stibine are a cause of SIDS, death must result from some other action before erythrocyte haemolysis develops, either because infant erythrocytes are more resistent to haemolysis or because infants are more susceptible to some other poisoning action; there are several reports of phosphine and arsine poisoning causing child fatalities but only illness in adults (Gosio 1892, 1893, 1897; Sanger 1894a, 1894b; Schmidt 1899; Anon 1932; Thom & Raper 1932; Wilson et al 1980).

Poisoning by phosphine, arsine and stibine results in the accummulation in the blood of phosphonium, arsonium and stibonium ions which are weak bases and absorb carbon dioxide; they can change the tonicity or osmotic pressure of the blood in this way, a process that probably accounts for the erythrocyte haemolysis observed in adults which usually develops 6 to 24 hours after severe poisoning by these gases, although lysis may be associated with chemical modification of the haemaglobin which might also explain the observations of hypoxia in SIDS; certainly arsenic has been identified in erythrocytes as dimethylarsinate (Fowler & Weisberg 1974; Cullen & Reimer 1989). The removal of carbon dioxide from the blood will also reduce stimulation of respiration, through the respiratory centre in the carotid Sinus in infants Tather than in the medulla that is involved in adults, and it is not therefore surprising that

suppression of respiration is sometimes reported as a feature of poisoning by these gases, although it is not known whether carbon dioxide neutralisation is involved or a direct action of the toxic trihydride gases on the chemoreceptors associated with respiratory control. Phosphine, arsine and stibine are also reported to cause depression of the central nervous system which may indicate an anticholinesterase action which would cause cardiac inhibition and vasodilation in infants through progressive accummulation of acetylcholine from the vagus nerve, a mechanism that would be completely consistent with SIDS as it would be undetectable, except as hypoxia which is actually observed in SIDS, and which would also explain certain unusual observations such as death a few minutes after lifting the infant from the cot. (Cooper 1974; Kleinfeild 1980; Rognum et al 1988). The anticholinesterase action of organophosphorus pesticides and chemical warfare agents is well known and congestive cardiac failure reported for phosphine, but these gases may also interfere with other enzyme systems, such as those involved in glycogen and fatty acid metabolism, and in muscle contraction (Klimmer 1969; see Appendix 1). Phosphonium, arsonium and stibonium cations may also condense onto blood glucose units in the 1 and 6 positions, preventing glucose utilisation and causing irritation of the central nervous system followed eventually by death; organotin and organolead cations have a similar action (Richardson 1969, 1988).

If poisoning by phosphine, arsine, stibine and related alkyl gases is the main cause of SIDS, the risk can be completely avoided only by eliminating phosphorus, arsenic and antimony from mattress materials. However, whilst most infants are apparently exposed to this poisoning in western-style communities, as well as in Australia and New Zealand where fleeces containing arsenic and antimony are used as cot mattresses, other contributory factors will decide whether an infant is unaffected or suffers irritability, illness or death. The rate of gas generation will depend on the activity of the Scopulariopsis brevicaulis infection. SIDS is almost always associated with previously used mattresses in which the infection has become well established during the previous use and reactivated by the new use, so that first children are least at risk as they are more likely to use new mattresses, and lower social class groups are more at risk because they are more likely to use previously used mattresses (Richardson 1990, 1991a,d). SIDS is mainly associated with infants older than 1 month as it usually takes several weeks to reactivate an infection on a previously used mattress to a sufficient extent for it to generate significant amounts of toxic gas, and deaths at less then 1 month generally occur on mattresses which are in current use by an older infant, typically when a family with a very young infant is visiting friends or relatives. SIDS is unusual at ages of more then 5 months and very rare at ages of more than 14 months; the first sign of poisoning by these gases is a headache which causes irritability, an older and stronger infant dislodging the bedding and dispersing the gas, SIDS cases at more than 5 months involving weaker infants, generally those that are underweight or unwell. It has been suggested that bacterial and viral infections increase the SIDS risk but higher temperatures caused by these infections will increase the rate of toxic gas generation and analgesic medication will suppress the headache which warns of poisoning by these gases, reducing irritability and increasing the risk of death.

Phosphine, arsine, stibine and their related alkyl gases are heavier then air and accumulate on top of the mattress, death being associated particularly with sleeping in the prone or face down position. Overwrapping traps gas around the infant but also results in hyperthermia or overheating, prompting increased fungal activity and gas generation; the rate of gas generation increases about 20 times if the cot temperature increases from 37 °C to and hyperthermic temperature of about 42 °C (Richardson 1991a). Hyperthermia can also be aggravated by mild and otherwise insignificant viral or bacterial infections (Milner Ruggins 1989). Hyperthermia through overwrapping is more likely in male infants because of their higher metabolic rate; the SIDS rate for males is about 55% higher than for females. In twins it has been observed that if one is a SIDS victim the other may Suffer from haemorrhagic shock encephalopathy syndrome (Trounce et al 1991). It is probable that both infants were similarly affected by hyperthermia, that one infant was on a previously used mattress suffering active biodeterioration and

toxic gas generation which caused death diagnosed as SIDS, whilst the survivor was affected by intensifying hyperthermia; the symptoms of HSES are similar to those of heatstroke (Bacon 1991).

Recommendations to parents that the prone or face down sleeping position should be avoided can significantly reduce the SIDS risk; in the Netherlands, New Zealand, the Avon area in England and the State of Victoria in Australia this precaution alone has reduced the SIDS rate by about 40% (Engelbert & de Jonge 1990). Recommendations in 1990 that the prone position and overwrapping should be avoided may have achieved a similar reduction in the SIDS rate in England and Wales, although the reductions were actually observable a year earlier, following recommendations that a new mattress should be provided for every new infant or old mattresses should be covered to isolate the infant from the mattress materials (Fleming et al 1990; Richardson 1990). However, these precautions will only remain effective whilst parents are continuously reminded, and the SlDS risk can only be permanently reduced by totally prohibiting mattress materials containing phosphorus, arsenic or antimony compounds.

The Turner Report

In England the Department of Health established an expert working group in March 1990 to investigate the Richardson hypothesis that SIDS is caused by gaseous phosphine, arsine, stibine and related alkyl compounds generated by biodeterioration of cot matress materials. Their report was issued on 12 June 1991 (Anon. 1991).

The group instructed the Laboratory of the Government Chemist and the International Mycological Institute to repeat the investigations on which the hypothesis was based, but the LGC results were considered to be inconclusive; they had modified the experimental methods and they were unable to consistently detect arsenic gases even when they were expected to be generated from samples spiked with arsenic, and they detected an antimony gas which could only be present if the hypothesis is correct. The group reported that the generation of phosphine was unlikely on theoretical grounds, whereas the established generation of ammonia and arsine actually suggests that it would be surprising if phosphine was not similarly generated. The group considered that poisoning by phosphine, arsine, stibine or related toxic gases was unlikely in SIDS as erythrocyte haemolysis, the most common symptom of poisoning reported in adults, had not been observed, ignoring the possibility that infants may die before the development of haemolysis because they are more sensitive than adults to some other poisoning action or because infant erythrocytes, which are physiologically different from adult erythrocytes, may be more resistant to haemolysis. The group did not commission any investigations which might have confirmed that SIDS may be caused by poisoning by the toxic gases that had been reported, despite reports of blood analyses which indicated high antimony levels in SIDS victims who had died on mattresses apparently generating antimony gases. The group reported but ignored the significant reduction in the SIDS rate in England and Wales that had followed recommendations that new mattresses should be provided for every new child (or old mattresses should be covered with polythene to isolate the child from the mattress materials) and the group did not even report the much larger decreases that occurred in 1990.

It is not surprising that the group reported that the hypothesis was unproven through lack of any independent supporting data as the group ignored any data and avoided any investigations that might have confirmed the hypothesis. However, the group recommended that the potential toxicity of additives in mattress materials and their breakdown products should be investigated, emphasizing the possible significance of arsenic contamination of the antimony trioxide which is used as a fire retardant additive and the risk of formation of toxic volatile compounds. The group recommended that the hazards associated with microbial contamination should also be investigated.

Appendix 3- EPIDEMIOLOGY OF SIDS

SIDS rates increased steadily from about 1953 when this condition was first recognised as cot death to 1987, perhaps due to improved recognition and reporting. The SIDS rates were about 2 to 4 per 1,000 live births in 1985-88 in western Europe, northern America and most other western-style countries, but the rates were very low and SIDS was not recognised in Russia, China, Japan, Thailand, India and parts of Africa (Golding et al 1985; Morris 1986; Becroft & Mitchell 1989; Gordon 1989). The SIDS rates in Hong Kong, and amongst infants of African or Asian origin in England and Wales, were intermediate, apparently indicating intermediate style communities (Lee et al 1989; Balarajan et al 1989). It was suggested that overcrowding in homes in Hong Kong might be an advantage by providing an infant with a continous stimulus, an hypothesis that might also explain the lower SIDS rate amongst infants of African and Asian origin in England and Wales, but this does not explain why SIDS is not recognised at all in so many countries (Lee et al 1989).

Figure 1 shows the accumulative postneonatal deaths for England and Wales (OPCS Monitor DH3 91/1). In this diagram each cause of death is represented by the areas between the lines. The SIDS rate has increased steadily since 1970 when this cause of death was first of ficially recognised but has remained reasonably constant since about 1981. SIDS deaths prior to 1970 were included in one or more of the other groups, and the way in which this diagram is presented has prompted the suggestion that they were previously diagnosed as respiratory diseases. Whilst it is probably true that some sudden infant deaths were diagnosed as unidentified respiratory problems and therefore included in this group, unexplained deaths would normally be included in the top 'other' group in this diagram. The progressive reduction in respiratory diseases can be attributed to improved antibiotics and can be seen in mortality rates in all countries, including those in which SIDS is not recognised. A reduction in the 'other' group from about 1.3 prior to 1973 to 0.8 after 1976 can certainly be attributed to the introduction of the SIDS classification, but the steady increase in SIDS after 1976 without any proportionate reduction in the 'other' group indicates that SIDS rates have since been increasing, reaching a reasonably constant level in 1982-85, and then increasing to a slightly higher level in 1986-88. In 1989 there was a significant reduction in the infant mortality rate, due entirely to a substantial reduction in the SIDS rate, which continued in 1990.

This recent reduction in the SIDS rate in England and Wales is shown in more detail in figure 2 which also shows quarterly rates, demonstrating very pronounced seasonal fluctuations; it is well established that the risk is much greater during the colder months and in colder parts of the same country (Froggatt et al 1971; Murphy & Campbell 1987; Hereward 1991; Richardson 1991d). Temperatures are not easy to relate statistically to SIDS rates but it has been suggested that domestic fuel consumption is the best measure of 'coldness', and a relationship can certainly be established in this way, as shown in figure 3 (Richardson 1991d). Low external temperatures apparently induce excessive overwrapping and hyperthermia, but if hyperthermia is involved it is also likely that SIDS rates during the summer months (quarters 2 and 3) are higher than indicated by this relationship. The line on figure 3 is therefore drawn beneath the points for these two quarters but through the main cluster of points for the winter quarters 1 and 4, an arrangement which is consistent with an element of domestic fuel consumption which is not related to space heating, as well as a proportion of the SIDS rate which may be actually related to other factors. The points for the end of 1989 and the whole of 1990, particularly the last quarter in 1990, are very low relative to the line established for previous quarters, indicating that there is some factor which applied from about the third quarter of 1989 onwards which progressively reduced the SIDS rate; in June 1989 it was suggested that toxic gas generation through mattress biodeterioration might be involved, and parents were recommended to use a new mattress for every new baby (new mattress sales increased between 10 and 20%) or cover old mattresses with polythene to isolate the infants from the mattress materials (Richardson 1990, 1991a, b, d). This diagram also indicates that the SIDS rate for the first quarter of 1985 was lower than expected; in December 1984 it was recommended to parents that overwrapping should be avoided (Stanton 1984).

Detailed studies of the SIDS statistics for England and Wales indicate that the risk is highest between the ages of 1 month and 5 months, about 50% higher for boys than for girls, and about 60% lower for first born infants than for subsequent infants; there is little variation between social status for first born infants, but a higher risk for lower social classes for subsequent infants (Richardson 1991d).

Various other factors have been identified but some of them can be grouped; for example, the risk is highest if an infant is one of a multiple birth, has a low birth weight, suffers retarded physical development, is born prematurely, has a mother who smoked or suffered anaemia during gestation, or a mother who suffered a low level of pre-natal care, but all these factors tend to result in infants with low weight and low activity for their age. Other factors that may be grouped are young mothers, unmarried mothers, one of a multiple birth, second or subsequent children, poor economic background and alcoholic parents, all perhaps tending to result in poor parental care but also low social and economic status, but all these factors may also result in economic conditions which mean that the use of a new mattress is unlikely (Richardson 1990, 1991a).

The SIDS rate in New Zealand of about 6 per 1,000 live births was high compared with other western-style communities, but the rate amongst caucasian infants was actually lower at 1.6 and the rate amongst Maori infants was exceptionally high at 11.5 (Mitchell et al 1987). A similar high SIDS rate was reported amongst aborigines in Australia, suggesting an ethnic susceptibility, perhaps a dietary factor, although it has also been suggested that these figures might actually indicate a geographical distribution with the lamb fleeces that are traditionally used as cot mattresses in Australasia containing arsenic or antimony through sheep feeding on grass contaminated with soil containing these elements (Richardson 1991a, b).

In the Netherlands it was observed that the SIDS rate had increased from 0.46 per 1,000 in 1969-71 to about 1.31 after 1978, and it was thought that this increase might be associated with a suggestion at a paediatric conference in 1971 that infants should sleep in the prone position (de Jonge et al 1989). It was recommended in 1987 that parents should avoid the prone position, and the SIDS rate dropped by about 40% from 1.13 in 1987 to 0.76 in 1988 (Englebert de Jonge 1990). Similar recommendations in New Zealand and in the State of Victoria in Australia achieved similar reductions in the SIDS rate (Beal 1988; Mitchell Engelberts 1991). It was established in the Netherlands that the SIDS risk was about 2.2 times greater in infants that may be prone compared with those that are never prone, and 4.6 times greater in infants that are always prone, whilst in New Zealand the lateral position has been found to increase the risk 2.29 times and the prone position 7.44 times (Mitchell Engelberts 1991). Recommendations in England in July 1990 that overwrapping and the prone position should be avoided have also contributed to a progressive decrease in the SIDS rate (from 3.7 to 1.8 in the Avon area involved in the experiment), although a decrease throughout England and Wales was first observed a year earlier following recommendations in June 1989 that a new mattress should be used for every new child, or old mattresses should be covered with polythene sheet to isolate the infant from the mattress (Fleming et al 1990; Richardson 1990, 1991a, b; Berry 1991).

It has also been suggested that the preference for the supine rather than prone sleeping position in Japan and China may be responsible for the apparent freedom from SIDS in these countries, but choice of sleeping position only affects the rate without eliminating SIDS, and the prone position was used in the British Isles before SIDS was recognised in about 1952 and is being adopted in Japan to an increasing extent without SIDS becoming a problem (Lee et al 1989). The infant mortality rate in Japan is about 5.2 per 1,000 live births, compared with about 8.6 for England and Wales in 1986-88. The lower rate in

Japan is explained almost entirely by the absence of sudden infant deaths which account for about 2.3 in England and Wales; the largest single item in Japan is congenital abnormalities at 1.7 (twice the rate for England and Wales of 0.8) but even this item is much too small to conceal unrecognised sudden infant deaths. It must be concluded therefore that sudden infant deaths do not occur in Japan. These research studies suggest that the probable explanation for this difference is the fact that the futons or mattresses used by Japanese infants are free from the elements phosphorus, arsenic and antimony which have been identified as sources of toxic gases and the cause of SIDS (Richardson 1990, 1991a,b,d).

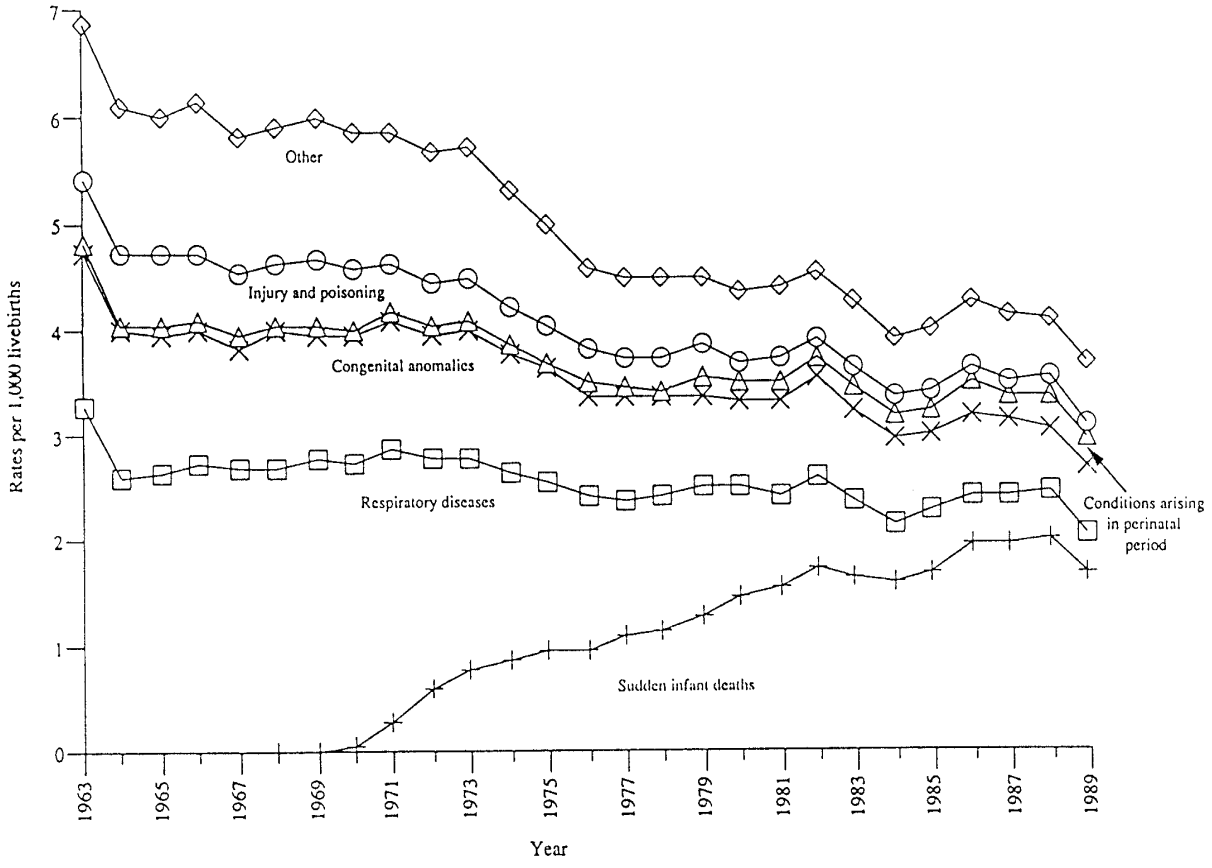

Figure 1. Cumulative postneonatal deaths by selected causes, England and Wales, 1963-1989
(Source: OPCS Monitor DH3 91/1; Crown Copyright 1991)

Cot Death: must babies still die?

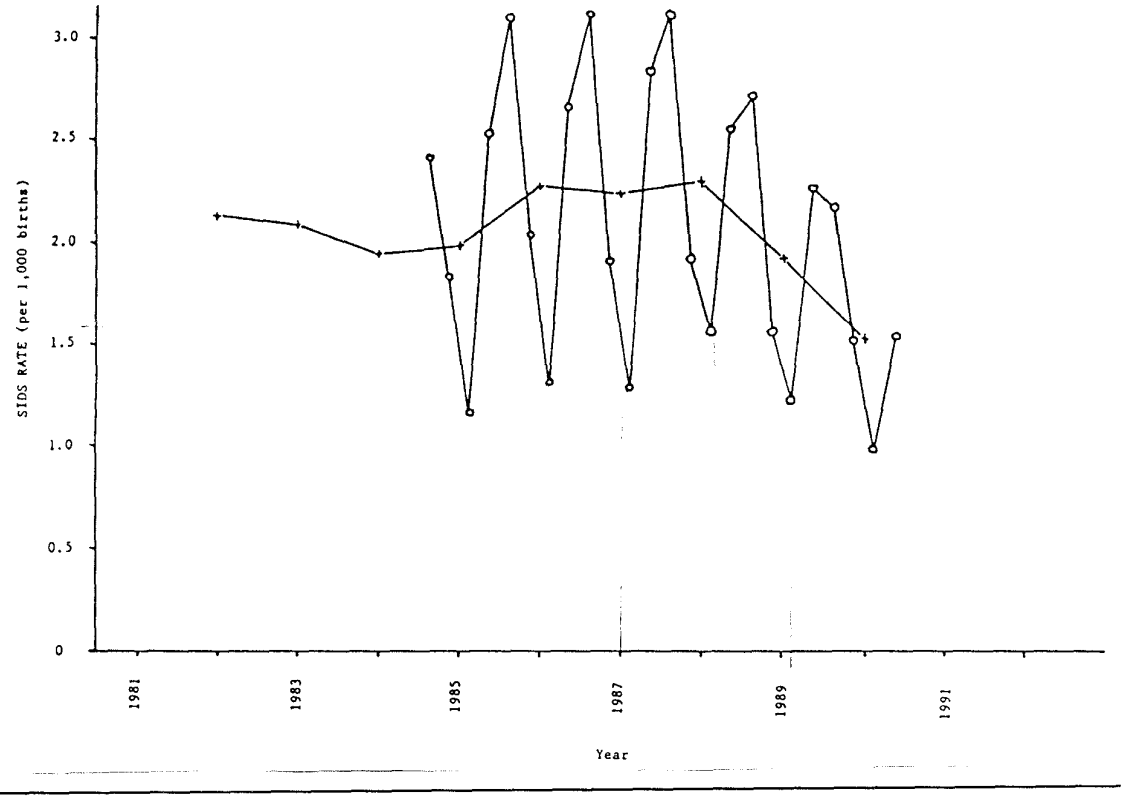

Figure 2. Annual and quarterly SIDS rates for England and Wales (OPCS statistics)

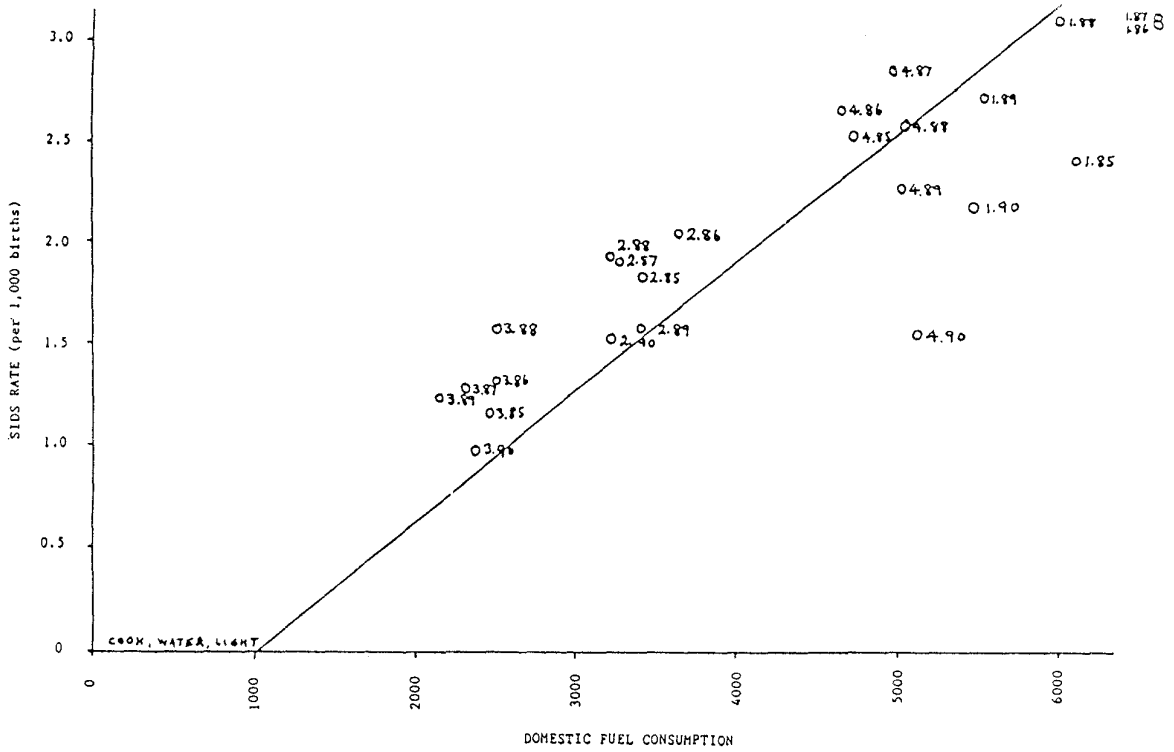

Figure 3. Quarterly SIDS rates related to 'coldness' represented by domestic fuel consumption

Appendix 4. BIBLIOGRAPHY ON SIDS

Statistical information on SIDS in England and Wales is derived from OPCS Monitors DH3 80/3 (1971-78), DH3 82/1 (1979-80), DH3 84/1 (1981-82), DH3 85/4 (1983-84), DH3 88/3 (1985-87) and DH3 91/1 (1988-89), Office of Population Censuses & Surveys, London. Domestic Fuel Consumption is derived from the Monthly Digest of Statistics, HMSO, London.

Statistical information on infant death rates in Japan is published in Vital Statistics, Statistics & Information Dept., Ministry of Health & Welfare.

Statistical information on infant deaths in the United States of America is published by the National Center for Health Statistics.

Addison G M, Besley G T N & Leanard J V (1989). Sudden infant death and glycogen storage disease. Lancet 334:1389.

Allison F, Bennett M 5, Variend S Engel P C (1988). Acylcoenzyme A dehydrogenase deficiency in heart tissue from infants who died unexpectedly with fatty change in the liver. Br Med J 296:11-2.

Anon. (1904). Royal Commission an Arsenical Poisoning; Final Report. London, HMSO (1845, 1848, 1869).

Anon. (1932). Gaseous arsenic from wall-plaster. The Analyst 57:163-164.

Anon. (1984). Mogel i byggnader; en kunskapsoversikt. Socialstyrelsen redovisar, 11,37s.

Anon. (1986). Sudden infant death and inherited disorders of fat oxidation Lancet 328:1073-5.

Anon. (1989). Occupational exposure limits HSE Guidance note EH40/89 London, HMSO.

Anon. (1990). Threshold limit value for chemical substances and physical agents and biological exposure indices.

Amer Conf Gov Ind Hyg, Cincinnati.

Anon. (1991). Sudden infant death syndrome (SIDS); Report of the expert working group enquiring into the hypothesis that toxic gases evolved from chemicals in cot mattress covers and cot mettresses are a cause of SIDS. (The Turner Report). London, HMSO.

Arion W 3, Ballas L M, Lange A J & Wallin B K (1976). Microsomal membrane permeability and the hepatic glucose-6-phosphatase system. J Biol Chem 251:49017.

Arion W J, Lange A J, Walls H E Ballas L M.(1980). Evidence of the participation of independent translocases for phosphate and glucose-6-phosphate in the microsomal glucose-6-phosphatase system. J Biol Chem 255:10396-406.

Bacon C J, Scott D & Jones P (1979). Heatstroke in well-wrapped infants. Lancet 313:422-5.

Bacon C J (1991). Haemorrohagic shock encephalopathy and sudden infant death. Lancet 337:1048.

Bacon C J, Bell S A, Clulow E E & Beattie A B (1991). How mothers keep their babies warm. Arch Dis Child 66:627-32.

Balarajan R, Soni Raleigh V & Botting B (1989). Sudden infant death syndrome and postneonatal mortality in immigrants in England and Wales. Br Med J 298:716-720.

Baranov A A (1991). Maternal and child health problems in the USSR. Arch Dis Child 66:542-5.

Barr A R M, Hutchens M E & David J (1985). Mycotoxins; a potential hazard to health in domestic dwellings. J Inst Wood Sci 10:120-121.

Barrett A M (1954). Recent advances in paediatrics (ed. Gairdner D), London, Churchill 301-20.

Bass M, Kravath R E & Glass L (1986). Death-scene investigation in sudden infant death. N Engl J Med 315:100-5.

Bass M (1989a). Sudden infant death syndrome. Br Med J 298:1267.

Bass M (1989b). The fallacy of the simultaneous sudden infant death syndrome in twins. Am J Forensic Med Pathol 10:200-5.

Bass M & Hass R (1991). Sudden infant death in Thailand and Alaska. Lancet 337:304-5.

Beal S (1988). Prone or supine for pre-term babies? Lancet 332:512.

Beal S (1988). Sleeping position and sudden infant death. Med J Aust 149:562.

Becroft D M 0 & Mitchell E A (1989). Trends in unexpected infant deaths. Lancet 333:673.

Berry J (1991). (press report). Daily Telegraph, London 18 June 1991.

Bettelheim K A, Dwyer B W, Smith D L, Goldwater P N & Bourne A J (1990). Toxigenic Escherichia coli associated with sudden infant death syndrome. Scand J lnfect Dis 22:467-76,

Bettelheim K A, Smith H, Goldwater P N, Morris J A, Murrell TGC, Sweet C & Weaver S A (1991). Sleeping position and cot death. Lancet 338:192

Biginelli P (1900). Composizione e costituzione chimica del gas arsenicale delle tappezerie. Atti R Accad Lincei Rendic CI Sc Fis Math e Nat, 9:210-214 & 242249.

Blair J N R Burchell A (1988). The mechanism of histone activation of the hepatic microsomal glucose-6-phosphatase system: a novel method to assay glucose-6-phosphatase activity. Biochem Biophys Acta 964:161-7.

Brackbill Y, Douthitt T C & West H. (1973). Psychophysiological effects in the neonate of the prone versus the supine placement. .1 Pediatr 82:82-4.

Braman R S & Foreback C C (1973). Science 182, 1247.

Burchell A & Burchell B (1980). Stabilisation of partially purified glucose-6- phosphatase by fluoride; is enzyme inactivation caused by dephosphorylation? FEBS Lett 113:180-4.

Burchell A & Burchell B (1982). Identification and purification of a liver microsomal glucose-6-phosphatase. Biochem J 205:567-73.

Burchell A, Burchell B, Monaco M, Walls H E & Arion W J (1985). Stabilisation of glucose-6-phosphatase activity by a 21,000 dalton hepatic microsomal protein. Biochem J 230:489-95.

Burchell A, Jung R T, Lang C C, Bennett W & Shepherd A N (1987). Diagnosis of type la and type 1c glycogen storage diseases in adults Lancet 329:1059-62.

Burchell A, Waddell I D, Countaway J L, Arion W J & Hume R (1988). Identification of the human hepatic microsomal glucose-6-phosphatase enzyme. FEBS Lett 242:153-6.

Burchell A, Bell J E, Busultil A Hume R (1989). Hepatic microsomal glucose-6-phosphatase system and sudden infant death syndrome. Lancet 334:291-4.

Carpenter R G Shaddick C W (1965). Role of infection, suffocation and bottlefeeding in cot death; an analysis of some factors in the histories of 110 cases and their controls. Br J Prev Soc Med 19:1-7.

Challenger F, Higginbottom C & Ellis L (1933). The formation of organometalloidal compounds by microorganisms. Part 1: Trimethylarsine and dimethylarsine. J Chem Soc 95.

Challenger F Ellis L (1935). J Chem Soc 396.

Challenger F (1945). Biological methylation. Chem Rev 36, 315. Challenger J & Higginbottom C. (1935). J Biochem Soc 29:1757.

Chalmers R A, English N, Hughes E A, Nobel-Jamieson C & Wigglesworth J S (1987). Biochemical studies on cultured skin fibroblasts from a baby with long chain acyl CoA dehydrogenase deficiency presenting as sudden neonatal death. J Inherit Metab Dis 10:260-2.

Cole T Gilbert R E, Fleming P 3, Morley C Rudd P T & Berry P J (1991). Baby check and the Avon infant mortality study. Arch Dis Child 66:1077-8.

Collier H 0 J (1971). Sudden death in infancy. Lancet 297:343.

Cooper P (1974). Poisoning by Drugs and Chemicals 3rd edition, London, Alchemist,

Cori G T Cori C F (1952). Glucose-6-phosphatase of the liver in glycogen storage disease. J Biol Chem 199:661-7.

Countaway J L, Waddell 1 D, Burchell A & Arion W J (1988). The phosphohydrolase component of the hepatic

microsomal glucose-6-phosphatase system is a 36.5 kilodalton polypeptide. .1 Biol Chem 263:2673-8.

Croft W A, Jarvis B B & Yatawara C S (1986). Airborne outbreak of trichothecene toxicosis. Atmos Env 20:549-552.

Cullen W R & Reimer K J (1989). Arsenic speciation in the environment. Chem Rev 89, 713-764.

David T W E (1950). Geology of the Commonwealth of Australia. London, Edward Arnold, 299.

Davies D P (1985). Cot death in Hong Kong: a rare problem? Lancet 326:13461349.

Davies D P. Cheng J Y C & Lee N (1989). Cot death and prone sleeping position. Br Med .1 298:1519.

de Jonge G A & Engelberts A C (1989). Cot death and sleeping position. Lancet 334:1149-50

de Jonge G A, Engelberts A C, Koomen-Liefting A J M & Kostense P J (1989). Cot death and prone sleeping position in The Netherlands. Br Med J 298:722.

Denborough M (1989). Fatal thermal injury. Med .1 Aust 150:608.

Dhande V G, Katwinkel J & Darnall R A (1982). Prone position reduces apnea in preterm infants. Pediatr Res 16:285A.

Doig A T (1958). Arseniuretted hydrogen poisoning in tank cleaners Lancet 272:88-92.

Downham M A P S, Gardner P S, McQuillan J & Ferris J A J (1975). Role of respiratory viruses in childhood mortality. Br Med J 269:235-9.

Dreisbach R H (1983). Handbook of Poisoning, 1 1th edition. Los Altos, Lange,

Dunne K P & Matthews T G (1988). Hypothermia and sudden infant death syndrome. Arch Dis Child 63:438-40.

Duran M, Hofkamp M, Rhead W J, Sandubray J M Wadman S K (1986). Sudden child death and healthy affected family members with medium chain acyl-coenzyme A dehydrogenase deficiency. Pediatrics 78:1052-7.

Emery J L Thornton J A (1968). Effects of obstruction to respiration in infants, with particular reference to mattresses, pillows, and their coverings. Br Med ..T 255:209-13.

Emery J L (1988a). Sleeping position, cot mattresses, and cot deaths. Lancet 332:738-9.

Emery J L (1988b). Trends in unidentified infant deaths in Sheffield. Lancet 332:1121-3.

Emery J L, Howat A 3, Variend S Vawter G F (1988). Investigation of inborn errors of metabolism in unexpected infant deaths. Lancet 332:29-31

Emery J L (1989). Is sudden infant death syndrome a diagnosis? Br Med J 299:1240.

Engleberts A C & de Jonge G A (1990a). Bedding and sleeping position in sudden infant death syndrome. Br Med J 301:493.

Engelberts A C & de Jonge G A (1990b). Choice of sleeping positions for infants. Arch of Dis in Childhood 65:462-7.

Fairhall L T & Hyslop F (1947). Toxicology of antimony. Pub HIth Rep (Supp) 195:1-41.

Fleming P J, Gilbert R, Azaz Y, Berry P J, Rudd P T, Stewart A & Hall E (1990). Interaction between bedding and sleeping position in the sudden infant death syndrome: a population based case-control study. Br Med J 301:85-9.

Forsyth K D, Weeks S C, Koh L, Skinner J Bradley J (1989). Lung immunoglobulins in the sudden infant death syndrome. Br Med J 298:23-6.

Fowler B A & Weissberg J B (1974). Arsine poisoning. N Eng] J Med 291:1171-4.

Froggatt P, Lynas M A & Mackenzie G (1971). Epidemiology of sudden unexpected death in infants ('cot death') in Northern Ireland. Br J Prev Soc Med 25: 119-34.

Gilbert R E, Fleming P J, Azaz Y & Rudd P T (1990a). Signs of illness preceding sudden unexpected death in infants. Br Med J 300:1237-9.

Gilbert R E, Fleming P J, Berry J E M & Rudd P (1990b). Signs of illness preceding sudden infant death. Br Med J 301:45-6.

Gilles F H, Bina M & Sotrel A (1979). Infantile atlantoocipital instability: the potential danger of extreme extension. Am J Dis Child 133:30-7.

Gold E, Carver D H, Heineberg H, Adelson L Robbins F C (1961). Viral infection: a possible cause of sudden unexpected death in infants. N Engl J Med 264:53-60.

Golding 3, Limerick S & MacFarlane A (1985). Sudden infant death; patterns, puzzles and problems. Shepton Mallet, Open Book Publishing,

Goldwater P N, Williams V, Bourne A J Byard R W (1990). Sudden infant death syndrome: a possible clue to causation. Med J Aust 153:59.

Gordon R R (1989). Trends in unexpected deaths in Sheffield. Lancet 333:106

Gordon R R (1990). Bedding and sleeping position in sudden infant death syndrome. Br Med J 301:493.

Gosio B (1892). Azione di alcune muffe sui composti fissi d'arsenico. Riv d'Igiene e San Publ 3:201-230 & 261-273.

Gosio B (1893). Action de quelques moisissures sur les composes fixes d'arsenic. Arch Ital Biol 18:253-265.

Gosio B (1897). Zur Frage, wodurch die Giftigkeit arsenhaltiger Tapeten bedingt wird. Ber Deuts Chem Ges 30:1024-1026.

Gozal D, Colin A A , Daskalovic V I & Jaffe M (1988). Environmental overheating as a cause of transient respiratory chemoreceptor dysfunction in an infant. Pediatrics 82:738-40.

Gravesen S (1979). Fungi as a cause of allergic disease. Allergy, 34:135-154.

Guilleminault C, Heldt G, Powell N & Riley R (1986). Small upper airway in nearmiss sudden infant death syndrome infants and their families. Lancet 327:402-7.

Guntheroth W G & Spiers P S (1990). Bedding and sleeping position in the sudden infant death syndrom. Br Med J 301:494

Harpey J P, Charpentier C, Coude M, Divoy P & Paturnean-Jouas M (1987a). Sudden infant death syndrome and multiple acyl-coenzyme A dehydrogenase deficiency, ethylmalomic-adipic aciduria, or systemic carnitine deficiency. Pediatr 110:881-4.

Harpey J P, Charpentier C & Paturnean-Jouas M (1987b). Fatty acid betaoxidation defects and sudden infant death. Lancet 329:163.

Hassall I B & Vandenberg M (1985). Infant sleep position: a New Zealand survey. NZ Med J 98:97-9.

Hassall I B (1986). Sudden infant death syndrome - a serious New Zealand problem. NZ Med J 99:233-234.

Hereward M C (1991). (Interview report). Population Center, University of North Carolina at Chapel Hill.

Hocken A G & Bradshaw G (1970). Arsine poisoning. Br J Ind Med 27:56-60.

Holmberg K (1985). Halsoeffekter av mogelkontaminering i svenska bostader. Byggforskningsradet rapport R36,99s.

Holmberg K & Kallings L-0 (1980). Allergisk alveolit orsakad av mogel och termofila aktinomyceter. Lakartidningen, 77:39-44.

Hong H L, Fowler B A & Boorman G A (1989). Hematopoietic effects in mice exposed to arsine gas. Tox App Pharm 97:173-82.

Hoppenbrouwers T, Calub M, Arakawa K & Hodgman J E (1981). Seasonal relationship of sudden infant death syndrome and environmental pollutants. Am J Epidemiol 113:623-35.

Howat A J, Bennett M 3, Variend S & Shaw L (1984). Deficiency of medium chain fatty acylcoenzyme A dehydrogenase presenting as the sudden infant death syndrome. Br Med .1 288:976.

Howat A J, Bennett M 3, Variend 5, Shaw L & Engel P C(1985). Defects of metabolism of fatty acids in the sudden infant death syndrome. Br Med J 290:1771-3.

Hunter D (1936). Industrial Toxicology of Today. Pharm J 137:514-15.

Hutchinson A A, Ross K R & Russell G (1979). The effect of posture on ventilation and lung merchanics in preterm and light-for-date infants. Pediatrics 64:429-32.

Josephson C 3, Pinto S S & Petronella S J (1951). Arsine: electrocardiographic changes produced in acute human poisoning. Arch Ind Hyg Occ Med 4:43-52.

Illingworth R S (1954). Three months colic. Arch Dis Child 29:165-74.

Jones A M & Weston J T (1976). The examination of the sudden infant death syndrome: investigatative and autopsy protocols. .1 Forensic Sci 21:833-41.

Kahn A, Blum D, Rebuffat, et al (1988). Polysomnographic studies of infants who subsequently died of Sudden Infant Death Syndrome. Pediatrics 82:721-727.

Kelly D H & Shannon D C (1980). Epidemiology clues to the etiology of SIDS. Am .1 Pub Hlth 70:1047-1048.

Kelly D H & Shannon D C (1982). Sudden infant death syndrome and near sudden infant death syndrome: a review of the literature 1964 to 1982. Pediatr Clin North Am 29:1241-61.

Kelly D H, Golub H, Carley D & Shannon D (1986). Pneumograms in infants who subsequently died of Sudden Infant Death Syndrome. J Pediatr 109:249-254.

Klausmeier R E & Jones W A (1961). Microbial degradation of plasticizers. Dev Ind Microbiol 2:47-53.

Klausmeier R E (1966). The effect of extraneous nutrients on the biodeterioration of plastics. Monograph 23, Soc Chem Ind 232-243.

Klausmeier R E (1972). Results of the second interlaboratory experiment in biodeterioration of plastics. Int Biodet Bull 8:(1):3-7.

Kleinfeld M J (1980). Arsine poisoning J Occup Med 22:12:820.

Knowelden J, Keeling J & Nicholl J (1984). Report of a Multicentre Study of Postnatal Mortality. Dep Hlth Soc Sec, London.

Lange A J, Arion W Beaudet A L (1980). Type 1b glycozen storage disease is caused by a defect in the glucose-6-phosphate translocase of the microsomal glucose-6-phosphatase system. J Biol Chem 255:8381-4.

Lawson B. Anday E, Guillet R, Wagerle L C, Chance B Delivoria-Papadopoul M (1987). Brain oxidative phosphorylation following alteration in head position in preterm and term neonates. Pediatr Res 22:302-5.

Lee M, David D P Chan Y F (1988). Prone or supine for preterm babies. Lancet 331:1322.

Lee N N Y, Chan Y F, Davies D P, Lau E Yip D C P (1989). Sudden infant death syndrome in Hong Kong; confirmation of low incidence Br Med J 298:721.

Legge T M (1918). Arsenic poisoning. Ann Rep Chief Insp Fact Worksh Gr Brit, 67-68.

Levene S McKenzie S A (1990). Transcutaneous oxygen saturation in sleeping infants: prone and supine. Arch Dis Child 65:524-6.

Lewak N, van den Berg B J Beckwith J B (1979). Sudden infant death syndrome risk factors. Clin pediat 18:404-411.

Limerick S (1984). Sudden Infant Death (1): Epidemiology. Nursing Times 80:28-29.

MacDonald J R, Mathison D A & Stevenson D D (1972). Aspirin intolerante in asthma. Allergy Clin Immunol 50:198.

McGlashan N D (1988). Sleeping position and SIDS. Lancet 332:106.

Marshall T K (1972). Epidemiology of cot deaths: The Northern Ireland study. J Forensic Sci Soc 12:575-579.

Martin R J, Herrell N, Rubin D Fanaroff A (1979). Effect of supine and prone positions on arterial oxygen tension in the preterm infant. Pediatrics 63:528-31.

Masterton 3, Zucker C & Schulze K (1987). Prone and supine positioning effects on energy expenditure and behaviour of low birth weight neonates. Pediatrics 80:689-92.

Matthews T G & Fox G P P (1989). Lung immunoglobulins in the sudden infant death syndrome. Br Med J 298:522.

Meadow R (1989). Suffocation and sudden infant death syndrome. Br Med J 299:178-9.

McBride B C Wolfe R S (1971) Biochem 10:4312-7.

Milberg P (1987). Mikroorganismer i byggnader, en litterarurstudie over arter, forekomst och miljokrav. Sv Lantbruksuniv, Inst f virkeslara, Uppsats 164.

Milner A D & Ruggins N (1989). Sudden infant death syndrome. Br Med J 298:689-90.

Milner A D (1987). Recent theories on the cause of cot death. Br Med J 295:1366-8.

Misra U K, Bhargava S K, Nag D et l (1988). Occupational phosphine exposure in Indian workers. Toxicol Lett 42:257-63.

Mitchell E A, Hassall I B Becroft D M 0 (1987). Postneonatal mortality review in Auckland; two years experience. NZ Med .1 100:269-272

Mitchell E A & Engelberts A C (1991). Sleeping position and cot deaths. Lancet 338:19 2.

Mitchell E A, Scragg R, Steward A W et l (1991). Results from the first year of the New Zealand cot death study. N Z Med J 104:71-6.

Moorman M P, Moorman C R, Hardisty J F et al (1987). Arsine: Toxicity data from acute and subchronic Inhalation exposures. Env Hlth Pers 75:145.

Morris 3 A (1986). Increased risk of sudden infant death syndrome in older infants at weekends. Br Med J 293:566.

Morris 3 A, Haran D & Smith A (1987). Hypothesis; Common bacterial toxins are a possible cause of the sudden infant death syndrome. Med Hypotheses 22:211-22.

Morris 3 A (1989). Sudden infant death syndrome. Br Med J 298:958.

Morton F J & Smith G (1963). The genera Scopulariopsis Bainer, Microsacus Zukal, and Doratomyces Corda. Mycol Paper 86, London, Com Myc Inst.

Murphy J F, Newcombe R G & Sibert 3 R (1982). The epidemiology of sudden infant death syndrome. J Epidemiol Com Hlth 36:17-21.

Murphy M G F & Campbell M J (1987). Sudden infant death syndrome and environmental temperature: an analysis using vital statistics. J Epidemiology Community Health 41,63-71.

Murrell T G C, Inglam B E, Moss J R& Taylor W B (1987). A hypothesis concerning Clostridium perfringens type A enterotoxin (CPE) and sudden infant death syndrome (SIDS). Med Hypoth 22:401-13.

Narisawa K, Igarashi Y, Otomo H & Tada K (1978). A new variant of glycozen storage disease type 1 probably due to a defect in the glucose-6-phosphate transport system. Biochem Biophys Res Commun 83:1360-4.

Nelson E A S, Taylor B J & Weatherall I L (1989). Sleeping position and infant death bedding may predispose to hyperthermia and the Sudden Infant Death Syndrome Lancet 333:199-200.

Newbould M J, Malam J, McIllmurray J M, Morris J A, Telford D R & Barson A J (1989). Immunohistological localisation of staphylococcal toxic shock syndrome (TSST-1) antigen in sudden infant death syndrome J Clin Pathol 42:935-9.

Nicholl J P Gardener A (1988). Sleeping position and SIDS. Lancet 332:106.

Nicoll A & Gardner A (1988). Whooping cough and unrecognised postperinatal mortality. Arch Dis Child 63:41-7.

Nilsson 0 S, Arion W J,Depierre J W, Dallner G & Ernster L (1978). Evidence for the involvement of a

glucose-6-phosphate carrier in microsomal glucose-6- phosphatase activity. Enr J Biochem 82:627-34.

Nordlie R C, Sukalski K, Munoz J M Baldwin J J (1983). Type 1c, a novel glycogenesis. J Biol Chem 258:9739-44.

Norvenius S G (1988). Sudden infant death syndrome in Sweden in 1973-1977 and 1979. Acta Paediat Scand (Supp) 333:1-138.

Onions A H S (1966). Scopulariopsis brevicaulis. CMI descriptions of Pathogenic Fungi and Bacteria - No 100.

Peterson D R, van Bell G, Chinn N M (1979). Epidemiologic comparisons of the sudden infant death syndrome with other major components of infant mortality. Am J Epidemiol 110:699-707.

Peterson D R, van Bell G & Chinn N M (1982). Sudden infant death syndrome and maternal age. J Am Med Ass 247:2250-2252.

Pinto S S (1976). Arsine poisoning: Evaluation of the acute phase. J Occ Med 18:633-5.

Plunkett E R (1987). Handbook of Industrial Toxicology 3rd edition, London, Edward Arnold.

Poets C F, Samuels M P, Noyes J P, Jones K A & Southall D P (1991). Home monitoring of transcutaneous oxygen tension in the early detection of hypoxaemia in infants and young children. Arch Dis Child 66:676-82.

Polak 3 M & Wigglesworth J S (1976). lslet-cell hyperplasia and sudden infant death. Lancet 308:570-1.

Polson C J, Green M A & Lee M R (1983). Clinical Toxicology 3rd edition. London, Pitman.

Ray C G, Beckwith J B, Heberstreit N M Bergham A B (1970). Studies of the sudden infant death syndrome in King Country, Washington: 1. The role of viruses. JA MA 211:619-23.

Richardson B A (1969). Action mechanisms of some organometallic preservatives. Proc Ist Int Biodet Sym 498-505.

Richardson B A (1970). Tributyltin wood preservatives. Rec Ann Conv BWPA.

Richardson B A (1978). Wood preservation. London, Construction Press & Longmans.

Richardson B A (1988). Organotin wood preservatives; activity and safety in relation to structure. Proc AWPA.

Richardson B A (1990). Cot mattress biodeterioration and SIDS. Lancet 335:670.

Richardson B A (1991a). Mattress biodeterioration and toxic gas generation; a possible cause of sudden infant death. Clin Ecol 8:1

Richardson B A (199lb). Mattresses and cot death. Lancet 337:1285

Richardson B A (199lc). Humidity in buildings, micro-organisms and toxic gas generation. Complementary Med Res 5(2):116-9.

Richardson B A (1991d). Sudden infant death syndrome; decreasing SIDS rates in England and Wales. Tech Note September 1991 Penarth Res Int Ltd, Guernsey, C I. Presented in lecture Cot deaths: the ultimate answer? at Scottish Agricultural College, Auchincruive, 3 September 1991.

Rintahaka P J & Hirvonen J (1986). The epidemiology of sudden infant death syndrome in Finland in 1969-1980. Forensic Sci Int 30:219-233.

Roe C R, Millington D S, Maltby D A & Kinnebrew P (1986). Recognition of medium chain acyl-coA dehydrogenase deficiency in asymptomatic siblings of children dying of sudden infant death or Reye-like syndromes. J Pediatr 108:13- 8.

Rognum T 0, Sangstad, Oyasaeter S Olarsen B (1988). Elevated levels of hypoxanthine in vitreous humor indicated prolonged cerebral hypoxia in victims of Sudden Infant Death Syndrome. Pediatrics 82:615-7.

Rognum T 0 & Sangstad 0 D (1991). Hypoxanthine levels in vitreous humor: evidence of hypoxia in most infants who died of sudden infant death syndrome. Pediatrics 87:306-10.

Rooney C I F, Rodrigues L C & Campbell 0 M R (1991). Cot deaths and single parents. Lancet 338:192-3.

Rosenthal G 3, Forb M M, Germolec D R et l (1989). Effect of subchronic arsine Inhalation on immune function and host resistance. Inhal Toxicol l:113-27.

Russell M A, Optiz J M, Viseskul C, Gilbert E F & Bargman G J (1977). Sudden infant deaths due to congenitgal adrenal hypoplasia. Arch Pathol Lab Med 101:168-9.

Sanger C R (1894a). On the formation of volatile compounds of arsenical wall papers. Proc Am Acad Arts Sci, 21:112-147.

Sanger C R (1894b). On chronic arsenical poisoning from wall papers and fabrics. Proc Am Acad Arts Sci, 21:148-177.

Schmidt H R (1899). Uber verschimmelte Tapeten. Diss Erlangen.

Scott D .J, Gardner P S, McQuillan J, Stanton A N & Downham M A P S (1978). Respiratory viruses and cot death. Br Med J 276:12-3.

Scott S (1990). Bedding and sleeping position in the sudden infant deaths syndrome. Br Med J 301:493-4.

Selzer P M & Ancel M A (1983). Chronic arsenic poisoning masquerading as pernicious anemia. West .J Med 139:219-20.

Shapiro C M, Fossey E & Peck D F (1990). Cot deaths and sleeping position. Lancet 335:226-7

Simson L R Brantley R E (1977). Postural asphyxia as a cause of death in sudden infant death syndrone. J Forensic Sci 22:178-87.

Smith G (1969). An introduction to Industrial Mycology. London, Edward Arnold, 6th edition.

Southall D P (1983). Identification of infants destined to die unexpectedly during infancy; evaluation of predictive importance of prolonged apnoea and disorders of cardiac rythum or conductance. Br Med J 286:1092-6.

Southall D P, Talbot D G, Johnson P et l (1985). Prolonged expiratory apnoea; a disorder resulting in episodes of severe arterial hypoxaemia in infants and young children. Lancet 326:571-7.

Southall D P Stebbens V & Shinebourne E A (1987). Sudden and unexpected death between 1 and 5 years. Arch Dis Child 62:700-5.

Southall D P & Samuels M P (1989). Respiratory infections, hypoxaemic episodes and sudden infant deaths - possible pathways in prevention? Matern Child Hlth 210-7.

Southall D P, Croft C, Stebbins V, et al. (1989). Detection of sleep associated dysfunctional pharyngeal obstruction in infants. Eur J Pediatr 148:353-9.

Southall D, Stebbens V & Samuels M (1991). Bedding and sleeping position in sudden infant death syndrome. Br Med J 301:492.

Spiers P S (1983). Sibling birthweights and maternal age in SIDS cases. Growth 47:104-108.

Standfast S J, Jereb S & Janerich D T (1979). The epidemiology of sudden infant death in Upstate New York. J Am Med Ass 214:1121-1124.

Standfast S 3, Jereb S & Janerich D T (1980). The epidemiology of sudden infant death in Upstate New York: II: Birth characteristics. Am J Pub Hlth 70:1061-1067.

Stanton A N (1984). Overheating and cot death. Lancet 324:8413:1199-201.

Stanton A N, Scott D J Downham M A P S (1989). Is overheating a factor in some unexpected infant deaths? Lancet 333:1054-7.

Steinschneider A (1975). Nasopharyngitis and prolonged sleep apnea. Pediatrics 56:967-71.

Steward A M, (1989). Sudden infant death syndrome; faulty maturation of haemoglobin and immunoglobins. Br Med .J 298:521-2.

Sturner W Q & Susa J B (1980). Sudden infant death and liver phosphoenolpyruvate carboxykinase deficiency. Forensic Sci Int 16:19-28.

Sundin B (1983). Fukt och mogel 1 byggnader. Medicinska effekter; VVS och energi,12:45-46.

Teitelbaum D T & Kier L C (1969). Arsine poisoning. Arch Env Hlth 19:133-43.

Thom C & Raper K B (1932). The arsenic fungi of Gosio. Science 76:548-550.

Tonkin S (1975) Sudden infant death syndrome: a hypothesis of causation. Pediatrics 55:650-61.

Tonkin S L & Partridge J (1979). The pharyngeal effect of partial nasal obstruction. Pediatrics 63:261-71.

Tonkin S L (1986). Infant mortality: epidemiology of cot-deaths in Aukland. NZ Med J 99:324-6.

Tough S C & Butt J C (1991). Cot deaths and single parents. Lancet 337:1490.

Trounce J Q,Lowe J, Lloyd B W & Johnston D 1 (1991). Haemorrhagic shock encephalopathy and sudden infant death. Lancet 337:202-3.

Tver D F Anderson K A (1986). Industrial Medicine Desk Reference. New York & London, Chapman & Hall.

Uren E C, Williams A L, Jack I & Raes J W (1980). Association of respiratory virus infections with sudden infant death syndrome. Med J Aust i:417-9.

Urquhart G E D & Grist N R (1972). Virological studies of sudden, unexplained infant deaths in Glasgow 1967-1970. .1 Clin Pathol 25:443-6.

Waddell I D & Burchell A (1987). A direct assay for each translocase of the hepatic microsomal glucose-6-phosphatase system. Biochem Soc Trans 15:1125-6.

Waddell I D, Lindsay J G Burchell A (1988). The identification of T2, the phosphate/pyrophosphate transport protein of the hepatic microsomal glucose-6- phosphatase system. FEBS Lett 229:179-82.

Waddell I D, Hume R & Burchell A (1989). A direct method for the diagnosis of type 1b and 1c glycogen storage disease. Clin Sci 76:573-9.

Wadlington W B, Tucker A L, Fly F & Freen M C (1976), Heatstroke in infancy. Am J Dis Child 130:1250-1.

Wagaman M Shutack J G, Moomjian A S, Schwartz T G, Shaffer T H E & Fox W W (1979). Improved oxygenation and lung compliance with prone positioning of neonates. J Pediatr 94:787-91.

Ward N I (1990). Private communication.

Wennegren G, Milerad J, Lagercrantz H et l (1987). The epidemiology of sudden infant death syndrome and attacks of lifelessness in Sweden. Acta Paediatr Scand 76:898-906.

Williams A L, Uren E C Bretherton L (1984). Respiratory viruses and sudden infant death. Br Med J 288:1491-3.

Williams G J (1965). Economic Geology of New Zealand Melbourne, Aust Inst Mining & Metallurgy 186.

Williams T G (1990). Guilt feelings about "cot death". The Times (7 Aug) 11.

Wilson R, Lovejoy F H, Jaeger R J & Landrigan P L (1980). Acute phosphine poisoning abroad a grain freighter. JAMA 244:148-150.

Wood J M (1974). Science 183:1049-52.

Yeager C C (1962). Pink staining in polyvinychloride. Plastics World 20:14.

Yeager C C (1968). Laboratory and service tests for PVC. Proc Ist Int Biodet Symp 151-161.