Expert Group to Investigate Cot Death Theories: TOXIC GAS HYPOTHESIS

Comments by Barry A Richardson who developed the hypothesis

Penarth Research International Limited, June 1998

Introduction

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 deaths, although the term crib deaths is preferred in north America. Cot death rates increased steadily and in 1969 Beckwith proposed that *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 or 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; the reduction in infant deaths from respiratory diseases actually resulted from the introduction of improved antibiotics, and this same reduction is seen in other age groups and in countries such as Japan where SIDS was uncommon until recently and did not even appear in the statistics.

The cause of SIDS could not he identified despite intensive investigative research, although epidemiological studies were more successful, 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 indicates a single cause with many contributory factors. In 1989 Barry Richardson suggested that the primary cause of cot death might be toxic gases generated in mattress materials by the action of fungi and bacteria on phosphorus, arsenic and antimony compounds incorporated as fire retardents and biocides, an hypothesis which is entirely consistent with all the known features of SIDS. The disclosure of the hypothesis prompted some cot death researchers and organisations, particularly the Department of Health and the Department of Trade and Industry for England and Wales, to attempt to discredit the hypothesis. In March 1990 the Chief Medical Officer established an Expert Working Group under the chairmanship of Professor Turner to investigate the hypothesis. The Group report was eventually published in May 1991 and concluded that the hypothesis was unfounded, perhaps because the Group did not investigate the hypothesis thoroughly or because this was the conclusion that was desired by the Chief Medical Officer who had commissioned the enquiry.

Meanwhile it had been widely recognised that the Richardson hypothesis was completely consistent with all the known features of SIDS and precautions based on the hypothesis seemed

to have achieved a substantial reduction in the SIDS rate. These observations prompted programmes by the Cook Report on Independent Television broadcast on 17 November and 1 December 1994. These broadcasts prompted the Chief Medical Officer to establish a further Expert Group on 30 November 1994 chaired by Lady Limerick to investigate cot death theories. The final report of the Group was eventually issued on 21 May 1998. Although the title of the Group refers to Cot Death Theories, only the Richardson hypothesis on toxic gas generation was considered. The 365 pages of the final report comprise 12 chapters, 2 annexes and 4 appendices.

Chapter 1

Historical Background

This chapter does not justify any special comment, except that it is not explained that the developments since about 1950 described in paragraphs 1.5 and 1.6, including adoption of the terms *Cot Death* and *Sudden Infant Death Syndrome*, were prompted by increasing rates of unexpected and unexplained infant deaths. It is suggested that, before SIDS deaths were clearly recognised, they were usually classified as sudden respiratory deaths at home because these deaths decreased as SIDS deaths increased. However, respiratory deaths decreased in all age groups through the introduction of improved antibiotics and it is simply coincidence that respiratory deaths decreased when SIDS increased.

Chapter 2

The Toxic Gas Hypothesis

It is explained in the text that this chapter does not comprise the views of the Expert Group but is a synopsis of the report submitted to the Group by Richardson. The hypothesis is correctly summarised in 2.3 as *The primary cause of SIDS is poisoning by gaseous phosphines, arsines and stibines generated by deterioration of cot mattress materials by micro-organisms, particularly* Scopulariopsis brevicaulis, *an otherwise harmless fungus* and that the gases have an anticholinesterase action which causes *cardiac failure and vasodilatation* (actually vasodilation although it is the cardiac failure that is considered to be the cause of death). The summary is very poor and it is much better to refer to the summary, in pages 7 to 17 of the original Richardson report which appear at pages 251 to 261 of the Limerick report.

There seems to be deliberate confusion over the references to arsenic compounds. It is stated in this chapter that *Arsenic compounds are not used as fire retardants but may be found as a contaminant of antimony trioxide*, but it was never suggested in the Richardson hypothesis that arsenic compounds were used as fire retardents but that an arsenical compound OBPA was often incorporated into PVC as a biocide to limit degrade through insects such as termites and some micro-organisms and also to function as a hygiene agent. OBPA has not been commonly used in PVC cot mattress coverings in the British Isles but it has been extensively used in north America, as well as in cot mattresses issued to British service families.

There are also references in this chapter and throughout the report to the hypothesis depending on the generation of phosphine, arsine and stibine, that is the trihydrides of phosphorus, arsenic and antimony but the hypothesis actually refers to phosphines, arsines and stibines and thus includes compounds in which the hydrogen is replaced by alkyl or aryl groups.

Chapter 3

Scope of this Investigation

This chapter describes the approach of the Expert Group, and starts by emphasizing that anything found to indicate a risk to infants would be publicised, but this was not done; although appointed to investigate Cot Death Theories, the Group considered that only the Richardson hypothesis on toxic gas generation was worth investigating and did not at any time issue any warning that precautions should be taken to avoid any danger of toxic gas generation from mattresses by ensuring that mattresses did not contain phosphorus, arsenic or antimony compounds, or that mattresses were wrapped in polythene to isolate infants, although the Group recommended throughout and in the press release issued with the final report that the prone sleeping position should be avoided for infants, even though there is no known danger associated with the prone sleeping position provided there is no risk associated with mattress materials.

In other respects the chapter simply introduces the investigations which are subsequently reported in Chapters 4 to 11.

Chapter 4.

The Turner Report and subsequent work on the Toxic Gas Hypothesis (1991 to 1994)

In the abstract to this chapter it is stated that *The Turner Committee commissioned work that replicated Richardson's experiments using more sensitive analytical techniques* bot this is not true; the Turner work carried out by the Laboratory of the Government Chemist used larger vessels which reduced sensitivity and this was clearly demonstrated by the inability of the investigators to consistently detect arsines in experiments involving spiked samples. The Abstract also states that the Turner Group concluded that there was no evidence that toxic gases are produced by micro-organisms from antimony or phosphorus compounds in cot mattresses, but the Turner Group did identify antimony gases and phosphorus was not considered by the Group!

In paragraph 4.5 it is noted that the chemical content of mattresses involved in SIDS cases were similar to control mattresses, but why should this be surprising? The Richardson hypothesis does not suggest that there should be a difference, but that a toxic gas risk only develops if mattresses contain phosphorus, arsenic or antimony compounds, and a mattress has been in use for a sufficient period to allow active micro-organisms to develop; whether an infant using a mattress then dies or survives depends on secondary factors such us whether the infant is in the prone position which involves most intense exposure to generated gases and whether the infant is hyperthermic through overwrapping which increases the rate of gas generation, the overwrapping also trapping the infant in contact with the gas.

The experimental part of the Turner report indicated that an antimony gas had been detected but this was not mentioned in the text of the report, although it is acknowledged in paragraph 4.6 of this chapter. The Turner Group recommended that there should be further investigations into risks associated with fire retardent chemicals and the microorganisms found on cot mattresses but these further studies did not take account of the ability of many micro-organisms to convert phosphorus, arsenic and antimony compounds into phosphines, arsines and stibines.

In paragraph 4.21 it is admitted that the SIDS rate had been decreasing since 1989, even though the Department of Health 'Back to Sleep' campaign had not started until late 1991; Richardson's recommendations for mattress-related precautions were widely reported by the media from June 1989.

Paragraphs 4.22 to 4.25 refer to the Cook Reports. In 4.22 it is stated that slightly elevated concentrations of antimony were present in tissues from SIDS infants compared with controls but this is a gross misrepresentation of the facts; the antimony levels quoted in this paragraph were 0.007 ηg/g in SIDS compared with less than 0.0005 η/g in controls so that the level of antimony in SIDS was actually more than 14 times the level in controls.

Chapter 5

Repetition and Extension of Richardson's experiments on Microbiological Gas Generation

In the abstract to this Chapter it is stated that Richardson *agreed that the experiments, which were conducted at the Mycology Reference Laboratory in Bristol, followed his procedures* but this is not true. Richardson agreed that the experiments followed normal good practice but they differed from the Richardson experiments in several important respects. It is again stated incorrectly in this chapter that the Richardson hypothesis depends on the generation of the trihydrides phosphine, arsine or stibine but the hypothesis is actually concerned with phosphines, arsines and stibines, thus including compounds in which hydrogen is substituted by alkyl or aryl groups.

In the original Richardson experiments, small samples of mattress components, particularly PVC coverings, were placed on nutrient media in petri dishes and incubated. Any generated phosphines, arsines or stibines were detected using silver nitrate and mercuric bromide papers. Silver nitrate darkens when exposed to reducing gases but, before this darkening is developed by phosphines, arsines or stibines, faint colours can be seen which are characteristic of the gases, phosphines giving a lemon yellow colour and arsines and stibines giving a pinkish brown colour. If mercuric bromide papers are also included, they remain white except if arsine is present which causes a change to yellow, orange or red, depending on the concentration of arsines present. pH paper can be included, an alkaline reaction indicating that ammonia or amine may be present. Lead acetate paper can also be included to warn of the presence of significant amounts of hydrogen sulphide. The Bristol laboratory was warned by Richardson during meetings and in writing that the characteristic colour changes on silver nitrate could only be seen during the early stages before more general darkening developed, particularly on some media which generated a brownish sulphur darkening interfering with the colouration from arsines or stibines. Richardson also emphasized that the reactions were semiquantitative and that the sensitivity could be enhanced by using smaller test papers. However, larger papers could also be used to absorb any generated gas which could then be identified by analysis of the papers. Exposure of test papers for 5 days or more and subsequent chemical analysis was the method that was preferred by the Bristol laboratory who seemed reluctant to carry out the careful and frequent observations necessary to detect the early characteristic colourations on silver nitrate papers, although it is noted in paragraph 5.10 that colours developed after a few hours. The Group concentrated on investigation of the basic brownish darkening of the silver nitrate paper through the presence of sulphur compounds, largely ignoring the phosphorus, arsenic and antimony contents which cause characteristic early colourations of silver nitrate and mercuric bromide papers.

The medium used by the Bristol laboratory was malt and soya flour, a high nitrogen medium. During routine investigations of mattress materials Richardson used the same high nitrogen medium which encouraged growth of micro-organisms from the edges of pieces of PVC cot mattress coverings. On this high nitrogen media the dominant growth was a khaki coloured crinkly slime. Richardson identified this slime as an alternative growth form of *Scopulariopsis brevicaulis*, a fungus that grows in a typical hyphal or filamentous form on low nitrogen media. Richardson had considered that this fungus was most likely to be involved as it is common in the domestic environment and it is well known that it is able to generate arsines from arsenic compounds. Alternative growth forms have been described in the literature and Richardson considered that it is at least dimorphic, with the filamentous form developing on low nitrogen substrates and the slime on high nitrogen, although each growth form could be converted to the other simply by sub-culturing onto another medium, the classical way in which dimorphism is identified. It is not therefore surprising that the Bristol laboratory experiments produced slime growth which they identified as *Bacillus* sp. but it is surprising that they did not repeat their experiments on a low nitrogen medium which might have produced a filamentous growth which might have been more familiar to them as *Scopulariopsis brevicaulis*. Instead they used the high nitrogen medium plus chloramphenicol to suppress bacteria in the hope that, in the absence of the *Bacillus* slime, *Scopulariopsis* might develop.

During the Turner group investigation Richardson sent some isolates from cot mattress coverings to the International Mycological Institute for identification but they reported that the samples were contaminated with unidentified yeast slimes and they had difficulty in obtaining clean cultures. Richardson suspected that they were identifying the slime form of *S. brevicaulis* as this yeast and therefore sent them a sample of *S. brevicaulis* which had been obtained from them and sub-cultured onto a high nitrogen medium to give the slime growth but IMI still failed to identify the sample as S. brevicaulis. In the Bristol experiments the slime was identified as a *Bacillus* but it seems that there was no attempt, by sub-culture onto different media, to check whether it was an alternative form of growth; there is no reason why a fungus on one medium should not appear to be a bacterium when grown on another medium if an organism is truly polymorphic.

It is stated in paragraph 5.13 that Richardson relied throughout on colour changes in silver nitrate and mercuric bromide papers to identify generated gases but this is untrue; papers were also analysed to confirm that colour changes were related to the presence of phosphorus, arsenic or antimony.

In paragraph 5.28 it is stated that the results of the work at Bristol and Southampton were presented to Richardson in November 1995, but not for debate or consideration as a final paper had already been prepared and accepted for publication! There was a similar meeting in June 1996 to consider dimorphism in *Scopulariopsis brevicaulis* but which actually comprised presentation of the information in paragraphs 5.39 to 5.50 of this chapter.

The Bristol experiments did not assist in establishing whether the microbial generation of phosphines, arsines or stibines from cot mattress materials might be a primary cause of SIDS; they simply established that the Bristol laboratory and the Southampton University analyst who examined the test papers were unable to identify any phosphines, arsines or stibines that may have been generated.

Paragraphs 5.57 to 5.62 are concerned with a Q E D programme broadcast by the B B C on 21

March 1995. The programme was made by McDougal Craig Limited who asked Richardson's laboratory Penarth Research International Limited to carry out routine microbiological examinations on 19 samples of PVC cot mattress coverings. No information was provided on the samples, even analytical information was not provided and analysis was not requested. When the programme was broadcast it was observed that a scanning method of analysis had been used which detects particularly the surface finish on PVC fabric rather than the PVC itself and it was not therefore surprising that the analysis failed to detect the normal components in cot mattress PVC coverings! Test papers from the Penarth tests were analysed , according to paragraph 5.61, by Plymouth University using ICP-MS, 2 of the 19 papers giving 0.167 ηg/g, and 0.346 ηg/g antimony compared with 0.08-0.09 ηg/g in unexposed papers; these positive results confirming antimony mobilization were not reported in the programme. Similar microbial tests by Birthbeck College also gave positive antimony results on 4 tests according to paragraph 5.62 but again these were not reported but attributed to contamination. It is strange that all results which supported the Richardson hypothesis were suppressed!

Chapter 6

Laboratory Investigations of the Ability of Micro-organisms to Produce Volatile Products from Antimony and Phosphorus Compounds

The abstract to this chapter states that *Fungal (ie Scopulariopsis brevicaulis) generation of antimony and phosphorus trihydrides ((ie stibine and phosphine) from parent compounds in PVC cot mattress materials is a key requirement of the toxic gas hypothesis* but this is not correct as the hypothesis actually concerns the generation by any micro organisms of phosphines, arsines and stibines, that is compounds with alkyl and aryl groups as well as hydrogen.

lt is stated at 6.88 that *Although the Richardson hypothesis initially centered an the biovolatilisation of antimony it has also raised the question of possible phosphorus volatilisation to yield phosphine or methylated phosphorus derivatives* but this is incorrect. The original hypothesis in late 1988 and early 1989 assumed that the arsenical biocide OBPA was being used in cot mattress PVC coverings and that micro-organisms might convert this arsenic compound to toxic gaseous arsines. Investigations on cot mattresses indicated generation of arsines could not be identified and analysis showed that OBPA was not generally used in cot mattress PVC in the British Isles. It was suspected at that stage that the same biochemical processes might result in the generation of similarly toxic phosphines from the phosphorus and antimony compounds which were common y used as fire- retardents in cot mattress materials, phosphorus and antimony being the elements adjacent to arsenic in group Vb of the chemical periodic table.

This chapter ends with the statement that *Hence we conclude that there is no evidence from this research that phosphorus and antimony fire retardents in -PVC cot mattress covers are harmful to infants* but there is actually no evidence at all in the chapter concerning phosphorus and antimony fire retardents but only doubts that they can be converted into toxic phosphines or stibines by microbial action.

This chapter actually reports that some volatile antimony compounds were generated but under conditions which were not believed to be achieved in mattress materials, but also according to paragraph 6.53, when *Scopulariopsis brevicaulis* was present. Paragraphs 6.84-6.87 quote the views of Professor Cullen that microbial generation of methyl compounds and trihydrides of

arsenic and antimony is likely but of phosphorus is less likely; Professor Cullen of the University of British Columbia is the most knowledgeable person in the world on this subject.

Chapter 7

Toxins and the Sudden Infant Death Syndrome

In the abstract to this chapter it is stated correctly that *A critical component of the toxic gas hypothesis is that phosphine, arsine and stibine or their methylated derivatives, cause SIDS by inhibiting activity of cholinesterases ((ie they are anticholinesterases)* and their presence *results in increased levels of acetylcholine in the blood and subsequent cardiac failure in infants*. However, the abstract then notes that the features of SIDS are not compatible with acute poisoning by anticholinesterases and that SIDS babies also do not show evidence of haemolysis which is the hallmark of poisoning with arsine and stibine. The reason for these observations is that in infants anticholinesterases do not act in the same way as in adults but preferentially interfere with vagus cardiac control, the accumulation of acetylcholine in the blood causing slowing of the heart and eventual cardiac failure without any sign of abnormal illness or injury. There is no evidence of haemolysis which is a classical feature of arsine and stibine poisoning in adults because the haemolysis develops following protracted exposure to acute poisoning which is possible in adults but impossible in infants which die of cardiac failure before this stage is reached. Table 7.10 summarises the features of anticholinesterase poisoning in children but it is not specific to infants but includes children with age ranges of up to 7 or 11 years whereas SIDS is specific to infants. Table 7.11 is concerned with brain acetylcholinesterase activity in SIDS but it has not been suggested in the Richardson hypothesis that phosphines, arsines and stibines act on the brain in SIDS.

Paragraph 7.59 refers to phosgene which is a toxic gas which does not contain phosphorus, arsenic or antimony and which has never been implicated in the Richardson hypothesis; it seems to have been mentioned only to increase confusion. Similarly, paragraphs 7.88 - 7.99 refer to sulphur gases but these were identified as generated from some nutrient media during the microbial experiments and have never been implicated in the Richardson hypothesis.

Chapter 8

The Pathology of SIDS, Normal Infant Developmental Physiology and Insights into possible Pathophysiological Mechanisms

The purpose of this chapter seems to be to indicate that the normal features of SIDS are inconsistent with the Richardson hypothesis whereas many established SIDS features are actually consistent with the hypothesis, as is admitted, in the conclusions in paragraph 8.28.

Chapter 9

Antimony and Infant Health

The purpose of this chapter is apparently to discredit the investigations presented by the *Cook report* programmes in 1994 which indicated that antimony levels were much higher than normal in liver and blood in SIDS victims and the antimony level was very high in the hair of living

infants sleeping on PVC cot mattress covers containing high levels of antimony. Whilst various arguments are given for the high antimony levels occurring through contamination and natural exposure, none of these arguments are as convincing as the inhalation of stibines from mattress coverings containing antimony, particularly as antimony from natural sources occurs in infants at levels that are much lower than those found in the *Cook Report* investigations.

Chapter 10

Use of Fire Retardent Chemicals in Cot Mattress Materials and other Items

This chapter has the distinction within the report of containing the most incorrect information. In the abstract it is stated that *Antimony trioxide-containing fire retardents were not introduced in domestic cot mattresses until about 1988 and were used in many until 1994. This was a period during which the fall in the SID rate was the most rapid.* In fact, the fire retardent value of antimony in conjunction with chlorinated materials has been known for more than 50 years and antimony trioxide was already in use in PVC before it was first used as a covering for cot mattresses in about 1950. The Suggestion that antimony trioxide fire retardent was not introduced in domestic cot mattresses until about 1988 is utter nonsense. The antimony trioxide content was increased in PVC furniture coverings, including cot mattress coverings, in about 1984-1987 in preparation for the introduction of the Furniture and Furnishings (Fire) (Safety) Regulations 1988. Figure 10.1 actually indicates that the highest antimony concentrations occurred in mattresses which were thought to be purchased in 1988-1991 with the level then declining to a very low level by 1995-96; this figure also indicates a very low antimony level prior to 1988 but this is incorrect as the level from about 1950 to 1985 was about half the level adopted in about 1986. From about 1989 onwards there were changes in child care practices which reduced the SIDS rates despite continuing use of antimony, such as Richardson's well publicised advice in 1989 that new mattresses should be used for all new babies or old mattresses wrapped in polythene, a further decrease in the SIDS rate resulting from the introduction of the 'Back to Sleep Campaign' in late 1991.

Chapter 11

Epidemiology of Sudden Infant Death Syndrome in relation to Mr Richardson's Hypothesis

This chapter is an attempt to discredit any relationships between the use of phosphorus and antimony fire retardents, and advice by Richardson to adopt precautions to minimise the risk of SIDS through toxic gases generated from mattress materials. No explanation is given for the reduction of about 40% in the SIDS rate between 1988 and 1991 before the 'Back to Sleep' campaign was introduced, obviously a reluctance to admit that this was the period when there were few precautions against SIDS other than mattress related precautions recommended by Richardson. The chapter discusses the success of avoidance of the prone sleeping position in achieving reductions in SIDS rates in various countries, but fails to relate the prone sleeping position with most intense exposure to toxic gases generated from mattress materials.

In paragraph 11.39 it is reported that the Ministry of Defence advised that the arsenical preservative OBPA was not used in cot mattresses issued to British Army families but this is untrue; there were many analyses on army cot mattresses which showed that OBPA was used, and this was not particularly surprising as it was considered that OBPA was a valuable preservative and hygiene agent so that its use apparently represented good practice at the time.

Chapter 12

Conclusions and Recommendations

The report concludes that the toxic gas hypothesis was unsubstantiated, but this is not particularly surprising as the entire tone of the report indicates a reluctance to accept or even to seriously consider the toxic gas hypothesis but instead to attempt throughout to discredit the hypothesis. It is not acknowledged that the report indicates that antimony gases were generated by the activity of various micro-organisms, particularly the fungus *Scopulariopsis brevicaulis* which the Richardson hypothesis had suggested as the most likely organism to be involved.

The conclusions of the report might have been totally different if persons had been selected for the group who were enthusiastic to prove the hypothesis rather than discredit it.

Annex 1

Terms of Reference and Members of the Expert Group to Investigate Cot Death Theories

The group was chaired by the Countess of Limerick who was not independent but involved in the Foundation for the Study of Infant Deaths which actively promoted rejection of the hypothesis. A serious weakness in the formation of the group was the predominance of members with established ideas on causes of cot death and the presence of only one toxicologist, even though the hypothesis that the group studied was a toxicological matter.

Annex 2

Sources of Information

This annex is simply a list of persons who were interviewed by the group or corresponded.

Appendices

Appendices 3 and 4 (pages 243 to 298) comprises Mr Richardson's report whilst Appendix 2 (pages 299 to 310) comprises further reports and correspondence from Mr Richardson.

Appendices 3 and 4 (page 311 to 356) comprise reviews of the toxicology of antimony and other chemicals used in cot mattress materials, even though the Richardson hypothesis is specific to the toxic properties of phosphines, arsines and stibines which have not been previously recognized in the medical or scientific literature. Indeed throughout the report the Richardson hypothesis is criticised as a phenomenon which has not been previously identified or reported, but this is obviously the situation with all new discoveries! The difficulty in this case is that SIDS researchers consider that the Richardson hypothesis is unlikely because they are not familiar with the ability of microorganisms to convert harmless compounds into toxic gases, and there were no persons in the Group with special knowledge or experience of these processes.