

INSIGHTS FROM THE AVAILABLE EXPERIMENTAL ANIMAL TOXICOLOGICAL DATA

1. EXPLANATORY INTRODUCTION

1.1 This document is a summary of how HSE views the contribution that is made by the available experimental animal toxicology data to the assessment of the risk of lung cancer and mesothelioma caused by exposure to relatively low levels of different types of asbestos fibres.

1.2 It presents only a brief synopsis of the key issues. A crucial supporting document for this summary is the 1996 HSE publication "Review of Fibre Toxicology" (EH65/30), which was finalised following detailed consideration, input and support for publication from the WATCH committee at that time. EH65/30 is attached here. More recent findings from the last 10 or so years have also been taken into account in the summary now presented.

2. DOSE-RESPONSE DATA FROM EXPERIMENTAL ANIMAL CARCINOGENICITY STUDIES

2.1 Chrysotile, crocidolite and amosite forms of asbestos have each produced lung cancer and mesothelioma in the rat in long-term inhalation exposure studies.

2.2 Invariably in such studies the intention has been to create favourable conditions for any carcinogenic potential to be observed in the test system; indeed some of the available data come from the use of asbestos fibres as a positive control in the testing of other fibres for carcinogenic potential.

2.3 Within such experiments, the number of animals per group exposed to a particular dose level rarely exceeds 100, for practical (feasibility, cost) purposes. Hence (with a group size of 100) a positive result at a particular dose level entails a risk to those experimental animals, under the conditions of the study, of 1 in 100 (1%) or more; and negative findings in a particular group entail a risk of less than 1 in 100 (1%).

2.4 The consequence is that the available experimental animal carcinogenicity studies involving inhalation exposure to asbestos have focussed on airborne concentrations of asbestos fibres, producing incidences of tumour formation, very much higher than those of interest to the focus of the issue now being considered by WATCH. In such experiments, asbestos fibre concentrations ranging from about 100 fibres/ml up to 1000-2000 fibres/ml have generally been used (see table 3 of EH65/30). Most studies have used only one dose level; and there has been considerable variation between studies in the experimental conditions.

2.5 Asbestos experimental animal carcinogenicity studies employing other means of fibre administration share the same features, but with the added complication of extrapolation to the inhalation situation.

2.6 All of these factors create a position whereby the available experimental animal studies on the carcinogenicity of asbestos do not contribute usefully to assessing directly the risks of asbestos-induced cancers in humans exposed to relatively low concentrations (1 fibre/ml or less) of different forms of asbestos.

3. INFORMATION ON RELATIVE CARCINOGENIC POTENCY OF DIFFERENT ASBESTOS FIBRE TYPES FROM EXPERIMENTAL ANIMAL TOXICOLOGY STUDIES

3.1 It is generally accepted, with support from a substantial body of experimental evidence, that fibre durability in the body (biopersistence) is a crucial determinant in the ability of inhaled fibrous materials to exert adverse consequences in the respiratory tract and mesothelia.

3.2 Biopersistence studies conducted with different asbestos fibre types have shown that chrysotile is substantially less persistent than crocidolite and amosite in the lungs of experimental animals.

3.3 A range of different values and perspectives for the biopersistence of chrysotile have been reported, in different studies using different sources of chrysotile and experimental features. EH65/30 summarises work from Coin et al (1992), quoting clearance half-lives in rats of 10 days for chrysotile fibres of 4 μ in length and 114 days for fibres longer than 16 μ (page 21, para 3.25); and that of Rendall (1988) giving a clearance half-life for chrysotile in baboons of 90 days (pages 19-20, para 3.17). More recent studies by David Bernstein's group, using chrysotile from Canadian, Brazilian and USA sources, cite shorter clearance half-lives of just a few days (Bernstein et al 2004; 2005). Invariably, reported values for clearance half-lives for the amphiboles (crocidolite and amosite) introduced into the lungs of experimental animals have been very substantially larger, of the order of hundreds or thousands of days (EH65/30 page 19 para 3.15; Hesterberg 1998).

3.4 These experimental data and the underlying biological concepts support the epidemiological observation that the carcinogenic potency of amphibole forms of asbestos is appreciably greater than that of chrysotile. Because of the range of values cited for the clearance of chrysotile, there might be some variation in opinion as to just how wide is the difference in carcinogenic potency between chrysotile and the amphibole forms of asbestos.

4. INSIGHTS INTO THE UNDERLYING MECHANISM FOR ASBESTOS-INDUCED TUMOUR FORMATION FROM EXPERIMENTAL ANIMAL TOXICOLOGY STUDIES

4.1 EH 65/30, chapter 5, discusses in some detail the evidence and thinking at that time regarding the most significant behaviours of fibres within biological tissues

and the most likely processes underlying fibre-induced tumours. No newer evidence has emerged that changes significantly the perspective offered in EH65/30.

4.2 The balance of evidence, supported by prediction based on physicochemical characteristics, is that asbestos (and other) fibres do not express direct genotoxicity. The most likely chain of events giving rise to tumour formation involves incomplete phagocytosis by macrophages and consequent “frustrated clearance” activity establishing a state of inflammation, tissue damage and cell proliferation. Enhanced rates of cell proliferation predispose the tissues involved to transformation of cells (via mistakes in DNA replication) to a neoplastic state.

4.3 Such a concept suggests that, whatever the apparent shape of the dose-response curve at relatively high dose levels, it will not remain linear for its entire length, down to minute levels of exposure. Rather, there will be burdens of fibres that can be accommodated within the lungs without provoking an inflammatory response; such that a threshold will exist, below which inflammation and its consequences (including tumour formation) will not occur.

4.4 Unfortunately there is no experimental animal evidence that takes this line of thinking further forward towards identification of the location of this threshold and the associated exposure conditions, for any particular form of asbestos or tumour type.

REFERENCES (not covered in EH65/30)

Bernstein D et al (2004). The biopersistence of Brazilian chrysotile asbestos following inhalation. *Inhalation Toxicology* **16**; 745-761.

Bernstein D et al (2005). The biopersistence of Canadian chrysotile asbestos following inhalation: final results through 1 year after cessation of exposure. *Inhalation Toxicology* **17**; 1-14.

Hesterberg T W et al (1998). Biopersistence of synthetic vitreous fibres and amosite asbestos in the rat lung following inhalation. *Tox Appl Pharmacol* **151**; 262-275.