FORUM

The need for standardised testing procedures for all products capable of liberating respirable fibres: the example of materials based on cellulose

Industrial society has a great requirement for fibrous materials. The use of animal and vegetable fibres for weaving dates from prehistoric times and modern industry uses both naturally occurring and man made mineral fibres in very large quantities, some for specialised woven products. A major use of fibres during the present century has been as fillers or reinforcing agents in moulded cement or plastic products. The property of finely divided fibres of low density to occupy a great volume has made them particularly useful in insulation where air trapped within the fibrous mass provides the main barrier to heat transfer.

Asbestos was the first major fibrous product to be marketed at the end of the 19th century, a time when controls in the workplace environment were non-existent. Without precautions, the mining of asbestos and the manufacture of various asbestos based products resulted in extremely high amounts of asbestos dust being generated and the inhalation of this rapidly proved to be highly pathogenic. Heavy exposure to respirable asbestos dust was shown as early as 1907¹ to cause lethal pulmonary fibrosis (asbestosis) and subsequently asbestos was found to be carcinogenic, causing pulmonary carcinomas² and mesotheliomas.³

Data accumulated over the past three decades has shown that mesotheliomas are particularly associated with exposure to the amphibole asbestos types crocidolite and amosite and more than 90% of asbestos use has always been chrysotile. Also, epidemiological studies have failed to find asbestos related disease in workers in whom exposure has been less than 30 fibre-years except in some specialised textile operations. Despite this, the reaction of society to the realisation that in some circumstances asbestos can be dangerous has been to eliminate its use wherever possible and to use other types of fibre, particularly man

made vitreous fibres, cellulose insulation, and synthetic organic fibres.

Man made vitreous fibres comprise rock wool, slag wool, and glass wool, and glass filament as well as ceramic fibres. Fibres of this type were first manufactured in the middle of the 19th century, even before the widespread use of asbestos, but production expanded greatly after the first world war with the increased demand for insulation for industrial equipment and for buildings. When the first studies into the health effects of fibres of insulation wool were undertaken in the 1930s, the concern was not with carcinogenesis but with tuberculosis and with upper respiratory effects perceived likely because of irritation. In many cases, fibre diameters have been so large that most dust generated has not been respirable but a small proportion of respirable material is always found and because thin fibres can produce a greater volume to weight ratio in the final products, there has been a tendency, for some uses, to reduce diameters as far as possible. During the 1960s it was assumed that the carcinogenicity of asbestos was unique to this family of minerals and that man made fibres could be safely used by industry without a hazard and without the dust controls that had become mandatory in the asbestos industry. This opinion continued until publication of work from two laboratories showing that some man made mineral fibres, when injected into the pleural or peritoneal cavities of rats, could produce mesotheliomas as often as asbestos. These studies had been undertaken to examine which properties of a fibrous dust cloud were most closely associated with tumour production and showed that fibre geometry was extremely important; those dust samples containing the most long thin fibres were the most carcinogenic. Maximum carcinogenicity was found with fibres $> 8 \mu\text{m}$ in length and $< 0.025 \mu\text{m}$ in diameter.⁴⁻⁷

This finding that fibres other than asbestos could be carcinogenic prompted widespread epidemiological studies of groups of workers manufacturing man made vitreous fibres and a great deal of animal experimentation, including long term inhalation studies, was also undertaken. In general the results have been reassuring. Small but definite

increases in incidence of lung cancer have been found in some workers in the rock wool and slag wool industry⁸ and in the manufacture of glass wool.⁹ These increases were limited, however, to very early production processes and for rock wool and slag wool workers it has been suggested that the problem could be related to the use of slags containing copper and arsenic.¹⁰ Also, no relation between amount of fibre exposure and carcinogenicity could be established and smoking habits could not be taken into account. The International Agency for Research on Cancer in 1988¹¹ considered that there was "inadequate" evidence of carcinogenicity of glass wool and glass filament in humans. For rock wool and slag wool the evidence was considered "limited". Results from long term inhalation studies have confirmed this position for most fibres with no increase in pulmonary tumours occurring in rats after exposure to various glass wool preparations, slag wool, and rock wool.¹²⁻¹⁶ Two man made fibre types that have proved carcinogenic in experimental animals after inhalation are ceramic fibre¹⁷⁻¹⁸ and aramid fibre.¹⁹ These results, coupled with studies relating to chemical dissolution of fibres²⁰⁻²² have led to the general theory that a fibre will be carcinogenic if it has the critical dimensions required and the durability to remain in lung tissue for long periods. Many man made vitreous fibres dissolve quite quickly in lung tissue but most ceramic fibres do not.

These findings should have resulted in the understanding that before the marketing of any new fibre product, evidence ought to be produced concerning its ability to liberate respirable fibres and the ability of these fibres to survive in lung tissue. A product liberating durable respirable fibres needs to be manufactured and used with strict dust controls. It is disappointing to find that this procedure is not being adopted and some fibre products are being manufactured and promoted as safe when this really means that they are untested. A current example of this concerns the increasing use of materials based on cellulose fibres.

Cellulose fibres are now used in place of asbestos to impart structural strength to cement products and of course have long been the basis of

numerous paper and cardboard materials. Most of the manufacturing processes are either enclosed or undertaken wet and a dust hazard is unlikely but the disintegration of such products while dry may be different. One study (Dodgson J, personal communication), examined the liberation of respirable fibres from a series of cellulose products subjected to mechanical disruption, by the standard test of Schneider and Smith.²³ All manufactured products examined liberated respirable fibres, mainly in the range of 1–4 fibres/ml whereas three samples of pure chrysotile asbestos subjected to the same treatment liberated on average 20 fibres/ml. One cellulose product, however, liberated 18 fibres/ml.

Most of the cellulose fibre used is derived from wood and wood dust is a known carcinogen, causing nasal cancer in exposed persons.²⁴ It is likely that this site of tumour formation predominates rather than the lung because of the large size of the particles of wood dust generated by most forms of carpentry. An excess of respiratory cancer has been recorded, however, in some populations of wood workers.^{24–26} Exposure to wood dust can cause other diseases as well, particularly asthma and loss of lung function and dermatitis.²⁷

Few studies have been undertaken on populations of workers exposed to cellulose fibres after their separation from wood but one case control study of 299 malignancies among paper mill workers has been reported.²⁸ There was a significant excess of lymphatic and haematopoietic malignancies and a non-significant excess of stomach cancer. An excess of cancers of the lymphopoietic system was found in a proportional mortality analysis of 1010 deaths of workers in the pulp and paper industry.²⁹ The authors also reported a general excess of cancer, largely of lung cancer (observed = 30 cases, expected = 19.9 cases, $p = 0.02$) but they did not have information on smoking habits.

A Swedish team has reported on a study of a soft paper mill production plant.^{30–32} The odds ratios for mortality from chronic obstructive pulmonary disease and from asthma among the exposed workers were significantly increased. There was no excess of malignancies. A morbidity study found a dose related irritation

of the upper respiratory tract. A decrease in vital capacity of the lung was associated with long term exposure to dust. Increased elastic recoil pressure and a decreased residual volume were reported among the exposed workers, findings considered by the authors to be non-specific reactions to the heavy exposures to paper dust in the mill.

The mortality of 1271 employees of an American cellulose fibre production plant has been studied.³³ Excess mortality was found for cancers of the liver and biliary tract (four observed, 0.70 expected, SMR 5.75 with 95% confidence interval 1.82–13.78), for the buccal cavity and pharynx (two observed, 0.87 expected) and for melanoma (two observed, 0.88 expected). The last two were not significantly raised. The authors were primarily concerned with the effects of exposure to methylene chloride rather than that related to cellulose fibres.

On the experimental side, a study of the ability of industrial cotton dust to produce emphysema after intratracheal injection in hamsters, included a sample of pure cellulose dust as a control.³⁴ The experimental regime was twice weekly injections of dust in saline at a dose of 0.75 mg/100 g for six weeks followed by an eight week recovery period before the animals were killed. Animals treated with the cotton dust, which contained endotoxin, showed mild centrilobular emphysema. Cellulose treated animals by contrast showed fibrosing granulomas and patchy thickening of alveolar septa.

Cellulose fibre dust is also toxic to mouse macrophages *in vitro*.^{35–36} Samples derived from pure cellulose fibre, including one in which the particle size was in the respirable range, caused the release of more lactic dehydrogenase than similar doses of chrysotile or crocidolite. Cellulose fibre was also found to stimulate the release of inflammatory materials from macrophages. Cells treated with cellulose released similar amounts of plasminogen activator and interleukin 1 as those treated with asbestos. Cellulose proved more powerful than asbestos in stimulating the release of the inflammatory agents prostaglandin PGE₂ and leucotrine LTC₄. Control dusts including glass and rock wool preparations produced a much lower response.

Whereas separated and relatively pure cellulose fibre itself may well be harmful to lung tissue, in many manufacturing processes chemicals are added to cellulose fibre to produce the final product. This raises the potential for an increase in hazard compared with the original material. One group of products for which this could cause concern is cellulose fibre insulation for buildings. These materials are derived mainly from finely shredded newspapers or other printed documents and are applied by an air blowing process. This process is likely to maximise the generation of respirable dust and dust concentrations as high as 20 mg/m³ have been reported by the National Institute for Occupational Safety and Health.³⁷ To reduce the fire hazard from the use of cellulose in domestic buildings, fire retardant chemicals are added. These fire retardants are most often boric acid or borax but cellulose insulation may also contain the hazardous chemicals sodium hydroxide, sodium sulphide, formaldehyde, chlorine, fluorine, lead, iron, and sulphur compounds as well as cadmium, nitric acid, and methane. The material may also contain dyes, resins, gums, talc, various solvents, and printing inks. Of these, lead and cadmium compounds and formaldehyde are known carcinogens^{38–41} and there has been concern in the printing industry at concentrations of polyaromatic hydrocarbons in some of the inks used. These are extremely potent carcinogens.

Boric acid itself is a toxic material and can be lethal to humans when ingested in gram quantities. It is not considered that the inhalation of cellulose insulation dust could approach this lethal toxicity but the heavily impregnated respirable cellulose dust will liberate the readily soluble boric acid in significant amounts in lung tissue. Symptoms of sublethal toxicity to boric acid include abdominal pain, liver, kidney, and lung disfunction and severe exfoliative dermatitis.^{42,43} The drinking of water with a high boron content has been reported to reduce sexual function in human males⁴⁴ and similar effects have been reported in men who work in boric acid production plants.⁴⁵ Here symptoms included decreased seminal volume, low sperm count and motility, and increased seminal

fructose.

Animal experimentation has confirmed that boric acid can cause severe reproductive toxicity, mainly in males.⁴⁴⁻⁴⁸ These studies found reproductive defects in rats fed boric acid or borax at doses ranging from 60 to 700 mg/kg. Similar results have been reported in male gerbils.⁴⁹ Studies in the National Toxicology Program⁵⁰⁻⁵¹ treated CD-1 Swiss mice and B6C3F1 mice with high doses of boric acid by ingestion and confirmed previous results. Doses for the CD-1 mice were 600 or 1500 mg/kg and for the B6C3F1 mice doses ranged between 1420 and 2860 mg/kg. In both studies, testicular atrophy and decreased sperm production were dose related.

As well as reproductive defects, developmental toxicity has also been reported from studies with rodents.⁵² Swiss mice and Sprague Dawley rats were fed diets containing boric acid. Doses were between 250 and 1000 mg/kg for mice and 70-330 mg/kg for rats. A dose related increased incidence of resorption and malformed fetuses was recorded in both species.

Boron compounds do not seem to be carcinogenic on their own. Sprague Dawley rats treated by ingestion with up to 60 mg/kg/day of boron as borax or boric acid showed no increases in incidence of tumours.⁴⁶ Dogs were also included in this study and gave negative results but the two year latency period allowed is too low to determine carcinogenicity in this species. No increased incidence of tumours was found in mice treated with 5 ppm of boron in drinking water for their lifespan.⁵³

Feeding studies at much higher doses were undertaken in B6C3F1 mice in the National Toxicology Program.⁵⁰ Doses of up to 100 mg/kg/day of boron as boric acid were administered for 103 weeks but caused no increase in incidence of tumours.

Only one experimental study has been reported with dust from cellulose insulation materials themselves. Rats were treated by inhalation for 28 days with an aerosol generated from cellulose building insulation of which about 40% was respirable by the rats.⁵⁴ Target doses were 100, 500, and 2000 mg/m³. Animals were killed at the end of the inhalation period

when dose related pulmonary changes were found. There was diffuse macrophage infiltration throughout the pulmonary parenchyma with the macrophages enlarged and with foamy cytoplasm. Some areas showed alveolitis and epithelial cell hyperplasia with some small areas consolidated with granulation tissue. Within granulomas there was evidence of collagen deposition.

This report indicates that there is a need for full toxicological testing of dust from cellulose building insulation and indeed dust from pure cellulose fibre as well. With any respirable fibre, a potential for carcinogenicity must be a major concern. The present state of our knowledge indicates that the only acceptable method for carcinogenicity testing of fibrous products is by long term inhalation. Because of the short lifespan of laboratory animals, which limits the time available for the build up of harmful fibres in the lung, the dose used must be much higher than that applicable to humans and if possible should exceed 100 respirable fibres/ml with lengths greater than 10 µm. Dust administration should be for at least 12 months with a full lifespan follow up. Studies undertaken should include an examination of the durability of inhaled fibres in the lung—that is, the ability of a significant proportion of deposited fibres to remain for long periods without chemical dissolution or removal by macrophages. With dust from cellulose building insulation, chemical additives are likely to be hazardous as well as the fibres themselves. In this case, the dust concentration used should be at least 20 mg/m³ of respirable dust as this is a concentration to which humans are known to be exposed. The rat is usually considered the best available experimental model for fibre related disease because with asbestos at least it readily develops pulmonary fibrosis and pulmonary carcinomas.⁵⁵⁻⁵⁶ Hamsters on the other hand, although they produce less fibrosis and fewer carcinomas, produce mesotheliomas more often than the rat¹⁸ and a really thorough study should include both species.

Only when the results of these long term experiments are available will it be known whether or not respirable cellulose fibres are sufficiently hazardous to require strict dust controls

during manufacture and use and whether products like shredded paper insulation materials, which have to be installed by an extremely dusty process, are safe to use at all.

JMG DAVIS

*Institute of Occupational Medicine Ltd,
Registered Office, 8 Roxburgh Place,
Edinburgh EH8 9SU*

- 1 Murray M (1907), referred to by Cooke WE. Pulmonary asbestosis. *BMJ* 1927;2:1024-5.
- 2 Doll R. Mortality from lung cancer in asbestos workers. *BMJ* 12:81-6.
- 3 Wagner JC, Sleggs CA, Marchand P. Diffuse pleural mesothelioma and asbestos exposure in North Western Cape Province. *Br J Ind Med* 1960; 17:260-71.
- 4 Stanton MF, Wrench C. Mechanisms of mesothelioma induction with asbestos and fibrous glass. *J Natl Cancer Inst* 1972;48:797-821.
- 5 Stanton MF, Layard M, Tegeris A, Miller M, May M, Kent E. Carcinogenicity of fibrous glass: Pleural response in the rat in relation to fiber dimension. *J Natl Cancer Inst* 1977;58:587-603.
- 6 Pott F, Friedrichs KH. Tumoren der Ratte nach IP Injektion faserförmiger Stube. *Naturwissenschaften* 1972;59: 318-32.
- 7 Pott F. Some aspects on the dosimetry of the carcinogenic potency of asbestos and other fibrous dusts. *Staub-Reinhalt Luft* 1978;38:486-90.
- 8 Saracci R. Ten years of epidemiologic investigations on man-made mineral fibers and health. *Scand J Work Environ Health* 1986;12 (suppl 11): 5-11.
- 9 Enterline PE, Marsh GM, Henderson V, Callahan C. Mortality update of a cohort of US man-made mineral fibre workers. *Ann Occup Hyg* 1987; 31:625-56.
- 10 Cherie J, Dodgson J. Past exposures to airborne fibers and other potential risk factors in the European man-made mineral fiber production industry. *Scand J Work Environ Health* 1986;12 (suppl 1):26-33.
- 11 International Agency for Research on Cancer. *Monographs on the evaluation of carcinogenic risks to humans. Vol 43. Man made mineral fibres and radon.* Lyon: IARC, 1988.
- 12 McConnell EE, Wagner JC, Skidmore JW, Moore JA. A comparative study of the fibrogenic and carcinogenic effect of UICC Canadian chrysotile B asbestos and glass microfibre (JM 100). In: *Biological effects of man-made mineral fibres—proceedings of a symposium.* Copenhagen: World Health Organisation, 1992;234-52.
- 13 Wagner JC, Berry GB, Hill RJ, Munday DE, Skidmore JW. Animal experiments with MMM(V)F—effects of inhalation and intrapleural inoculation in rats. In: *Biological effects of man-made mineral fibres—proceedings of a symposium.* Copenhagen: World Health Organisation, 1982;207-33.
- 14 Le Bouffant L, Daniel H, Henin JP, et al. Experimental study on long-term effects of inhaled MMMF on the

- lungs of rats. *Ann Occup Hyg* 1987; 31:765-91.
- 15 Muhle H, Pott F, Bellman B, Takenaka S, Ziem V. Inhalation and injection experiments in rats to test the carcinogenicity of MMMF. *Ann Occup Hyg* 1987;31:755-65.
 - 16 Smith DM, Ortiz LW, Archuleta RF, Johnson NF. Long-term health effects in hamsters and rats exposed chronically to man-made vitreous fibres. *Ann Occup Hyg* 1987;31: 731-55.
 - 17 Davis JMG, Addison J, Bolton RF, Donaldson K, Jones AD, Wright A. The pathogenic effects of fibrous ceramic aluminium silicate glass administered to rats by inhalation or peritoneal injection. In: *Biological effects of man-made mineral fibres—proceedings of a symposium*. Copenhagen: World Health Organisation, 1982:303-22.
 - 18 Hesterberg TW, Mast R, McConnell EE, et al. Chronic inhalation toxicity of refractory ceramic fibres in Syrian Hamsters. In: Brown RC, Hoskins JA, Johnson NF, eds. *Mechanisms of fibre carcinogenesis*. New York: Plenum Press, 1991:531-8.
 - 19 Lee KP, Kelly DP, O'Neal FO, Shadler JC, Kennedy GL. Lung response to ultrafine kevlar aramid synthetic fibrils following two year inhalation exposure in rats. *Fundam Appl Toxicol* 1988;11:1-20.
 - 20 Leineweber JP. Solubility of fibres in vitro and in vivo. In: *Biological effects of man-made mineral fibres. Report of a WHO/LARC meeting*. Copenhagen: World Health Organisation, 1984: 81-102.
 - 21 Forster H. The behaviour of mineral fibres in physiological solutions. In: *Biological effects of man-made mineral fibres. Report of a WHO/LARC meeting*. Copenhagen: World Health Organisation, 1984:27-60.
 - 22 Bellmann B, Muhle H, Pott F, König H, Klöppel H, Spurny K. Persistence of man-made mineral fibres (MMMF) and asbestos in rat lungs. *Ann Occup Hyg* 1987;31: 693-711.
 - 23 Schneider T, Smith ED. Characteristics of dust clouds generated from old MMMF products. Part II. Experimental approach. In: *Biological effects of man-made mineral fibres. Report of a WHO/LARC meeting*. Copenhagen: World Health Organisation, 1984:31-44.
 - 24 International Agency for Research on Cancer. *Monographs on the evaluation of carcinogenic risks to humans*. Vol 25. *Wood, leather and some associated industries*. Lyon: IARC, 1981.
 - 25 Acheson ED. Nasal cancer in the furniture and boot and shoe manufacturing industries. *Prev Med* 1976;5: 295-315.
 - 26 Goldsmith DF. *Respiratory disease in the North Carolina furniture industry: a pilot study* (doctoral dissertation). Chapel Hill NC: University of North Carolina, 1983. (University Microfilms, Ann Arbor MI, 1984.)
 - 27 Goldsmith DF, Shy CM. Respiratory health effects from occupational exposure to wood dusts. *Scand J Work Environ Health* 1988;14:1-15.
 - 28 Rinsky RA. *Hazard evaluation and technical assistance report* 1990. Cincinnati: National Institute for Occupational Safety and Health, 1990. (No HETA-89-020-L2070. Boise Cascade, Rumford, Maine.)
 - 29 Solet D, Zoeloth SR, Sullivan C, Jewett J, Michaels DM. Patterns of mortality in pulp and paper workers. *J Occup Med* 1989;31:627-30.
 - 30 Jarvholm B, Thoran K, Brodin I, et al. Lung function in workers exposed to soft paper dust. *Am J Ind Med* 1988;14:457-64.
 - 31 Thoran K, Jarvholm B, Morgan U. Mortality from asthma and chronic obstructive pulmonary disease among workers in a soft paper mill: a case-referent study. *Br J Ind Med* 1989;46:192-5.
 - 32 Ericsson J, Jarvholm B, Norin F. Respiratory symptoms and lung function following exposure in workers exposed to soft paper tissue dust. *Int Arch Occup Environ Health* 1988;60:341-5.
 - 33 Lanes SF, Cohen A, Rothman K, Dreyer NA, Soden KJ. Mortality of cellulose fibre production workers. *Scand J Work Environ Health* 1990;16:247-51.
 - 34 Milton DK, Eodleski JJ, Feldman HA, Greaves IA. Toxicity of Intracheally Instilled cotton Dust, Cellulose and Endotoxin. *Am Rev Respir Dis* 1990;142:184-92.
 - 35 Godelaine D, Beaufay H. Comparative study of the effect of various fibres on the secretion of plasminogen activator by murine peritoneal macrophages. In: Mossman BT, Begin RO, eds. *Effects of mineral dusts on cells*. Berlin: Springer-Verlag, 1989;30:93-101. (NATO ASI Series H Cell Biology.)
 - 36 Godelaine D, Beaufay H. *In vitro effects of asbestos and substitutes on macrophages*. Final report 1989. Brussels: International Institute for Cellular and Molecular Pathology, 1989.
 - 37 National Institute for Occupational Safety and Health. *Health hazard evaluation report*. Cincinnati: US Dept of Commerce, National Technical Information Service, 1985. (HETA, 84-213:391-1619.)
 - 38 International Agency for Research on Cancer. *Monographs on the evaluation of carcinogenic risks to humans*. Vol 2. *Some inorganic and organometallic compounds*. Lyon: International Agency for Research on Cancer, 1973.
 - 39 International Agency for Research on Cancer. *Monographs on the evaluation of carcinogenic risks to humans*. Vol 23. *Some metals and metallic compounds*. Lyon: International Agency for Research on Cancer, 1980.
 - 40 International Agency for Research on Cancer. *Monographs on the evaluation of carcinogenic risks to humans*. Vol 29. *Some industrial chemicals and dyestuffs*. Lyon: International Agency for Research on Cancer, 1982.
 - 41 International Agency for Research on Cancer. *Monographs on the evaluation of carcinogenic risks to humans*. Supplement 7. Lyon: International Agency for Research on Cancer, 1987.
 - 42 American College of Toxicology. Final report on the safety assessment of Sodium borate and boric acid. *Journal of the American College of Toxicology* 1983;2:87-125.
 - 43 Siegel E, Wason S. Boric acid toxicity. *Pediatric Clinics of North America* 1986;33:363-7.
 - 44 Krasovskii GN, Varshavskaya SP, Borisov AI. Toxic and gonadotropic effects of cadmium and boron relative to standards for these substances in drinking water. *Environ Health Perspect* 1976;13:69-75.
 - 45 Tarasenko NY, Kasparov AA, Smirnova EM, Ananov BV. *Gig Sanit* 1971;37:27-32.
 - 46 Weir RJ, Fisher RS. Toxicologic studies on borax and boric acid. *Toxicol Appl Pharmacol* 1972;23:351-64.
 - 47 Lee IP, Sherins RJ, Dixon RL. Evidence for induction of germinal aplasia in make rats by environmental exposure to boron. *Toxicol Appl Pharmacol* 1978;45:577-90.
 - 48 Beyer KH, Bergfeld WF, Berndt WO, et al. Final report on the safety assessment of sodium borate and boric acid. *Journal of the American College of Toxicology* 1983;2:87-125.
 - 49 Sharma MP, Mathur RS, Mehta K. Effect of borax on the testis of the Indian desert gerbil. *Experientia* 1978;34:1374-5.
 - 50 National Toxicology Program. *Toxicology and carcinogenesis studies of boric acid in B6C3F1 Mice*. Research Triangle Park, NC: US Department of Health and Human Services, 1987. (NTP-TR 324. NIH publ No 88-2580.)
 - 51 National Toxicology Program. *Final Report on the reproductive toxicity of boric acid in CD-1 Swiss Mice*. Research Triangle Park, NC: National Institute of Environmental Health Sciences, 1990. (NTP report 90-105.)
 - 52 Heindel JJ, Price CJ, Field EA, et al. *Developmental toxicity of boric acid in mice and rats*. *Fundam Appl Toxicol* 1992;18:266-77.
 - 53 Shroeder HA, Mitchener M. *Life term effects of mercury, methyl mercury and nine other trace metals on mice*. *J Nutr* 1975;105:452-8.
 - 54 Hadley JG, Kotin P, Bernstein DM. Subacute (28 day) repeated dose inhalation of cellulose building insulation in the rat. *The Toxicologist* 1992;12:225 (abstract).
 - 55 Wagner JC, Berry G, Skidmore JW. The effects of the inhalation of asbestos in rats. *Br J Cancer* 1974; 29:252-69.
 - 56 Davis JMG, Beckett ST, Bolton RE, Collings P, Middleton AP. Mass and number of fibres in the pathogenesis of asbestos-related lung disease in rats. *Br J Cancer* 1978;37:673-88.

Accepted 7 September 1992