Consensus Summaries of Workshops

In order to increase the usefulness of this conference to the scientific, public policy and business communities, and in accord with the approach and philosophy of both the National Center for Toxological Research and the National Institute of Environmental Health Sciences, a Consensus Panel Workshop was convened during the course of the Second International Workshop on the In Vitro Effects of Mineral Dusts in which the expertise of the participants and attendees was focused on a number of questions. The questions were framed and selected by the organizing committee of the conference based upon their relationship to basic aspects of asbestos toxicity, the availability of sufficient information for discussion, and relevancy of the question to human exposure.

To help respond to these questions, panels were set up or more rapporteurs, who presented the questions, sought the opinions of the informed con-
ferees and coordinated the discussion. This summary of the question, the responses the-feto and the final consensus reached was written, edited and reviewed by the Chairman of the session and the rapporteurs of each panel and represents their combined opinions.

The questions were: (1) Are there different dimensional characteristics of fibers associated with different probabilities of developing a pleural tumor? (2) In view of the fact that smoking increases asbestos carcinogenesis, do the fibers merely exert their effect by passing the polycyclic aromatic hydrocarbons (PAH) into the cells? (3) Is there any threshold for the biological effects due to asbestos exposure? (4) Is it possible to extrapolate the risk of neoplasia induced by low levels of asbestos exposure from that induced by high dose levels?

Panel 1

RAPPORTEUR: Dr. S. E. Sykes

PANEL: Drs. E. G. Beck, R. C. Brown, M. Chamberlain and G. Oberdoerster

QUESTION: Are different dimensional characteristics of fibers associated with different probabilities of developing a pleural tumor?

CONSENSUS REPLY: There does appear to be an association between different probabilities of developing pleural tumors and fiber dimensions. However, this model is incomplete with regard to character-

izing various other factors that are included in the problem of the development of pleural tumors.

PERTINENT DISCUSSION: Dr. Oberdoerster summarized the data published in the literature by Stanton and Lazard (1) and Pott (2) on the relationship between a fiber’s dimensions and carcinogenic potency. In particular, he referred to Pott’s work, which indicates that the carcinogenicity factor depends on both fiber length and diameter assuming the fiber reaches a sensitive site. He pointed out, however, that the durability of the fiber in the tissue also has to be considered in evaluating the carcinogenicity factor.

Dr. Chamberlain emphasized the nature of the dose response curve showing the probability of pleural tumors versus the logarithm of number of fibers, >8 μm in length and thinner in diameter than some threshold between 0.25 and 1.5 μm, shown by Stanton and Lazard (1). The sigmoidal shape of this curve implies that a high tumor incidence can be obtained with a very low number of fibers. This was taken as evidence of the sensitivity of the test used for evaluating the carcinogenicity of mineral dusts.

Dr. Brown reminded the audience of disparity in the results of animal studies and the results of some epidemiological evidence. Anthophyllite miners in Finland were cited as a glaring example where no evidence of mesotheliomas could be found although the ability of fibers to reach the pleura was demonstrated by the occurrence of pleural fibrosis and pleurals (3). It was pointed out in discussion that competing risks, such as high lung cancer incidence from smoking, may mask the effects of asbestos. Dr. Brown also suggested that the best predictor of carcinogenesis of all the fiber parameters examined so far was the number of long thin fibers.

After a reminder from a member of the audience that the correlation of fiber size to carcinogenic potency was not valid for some types of asbestos fibers, some consideration was given to the work of Bertrand and Pezarat (4), who recalcuated the data of Stanton and Lazard using the aspect ratio (the ratio of length to width) of the injected fibers, and who emphasize the importance of this ratio in developing a pleural tumor. There was controversy over the technique used in this work and its validity.

Dr. Piggot emphasized the importance of the exposure route (injection or instillation [the usual experi-
mental routes] vs. inhalation) and the narrow range of surface properties in the fibers tested in understanding the effect of fiber size. In answer to the question of the availability of data on the fiber sizes seen in the lung after human exposure to asbestos, Dr. Bignon cited the results of Sebastian et al. (5) on the size of fibers found in the human pleura and lung. In humans, the fibers were very short and small in contrast to those in pleural injection studies in animals.

Dr. Beck noted that there were several parameters important for fiber cytotoxicity. The influence of fiber length is independent of the fiber used but durability in tissue was fiber type specific and depended on the composition of the fiber. Factors such as solubility, leachability, breakage and migration are important considering the long latency period for tumor development. For risk assessment he also stressed the necessity of characterizing the environmental factors important in toxicity and the importance of individuals especially sensitive to the effects of asbestos because of diminished adaption and suppressed immunity. The chemical properties of the fibers were referred to by another discussant.

Dr. Frank said that fiber dimension was only one factor in producing tumors. He proposed the consensus statement as the best and most reasonable statement about the question, which was accepted by the attendees.

Panel 2

RAPPORTEUR: DR. R. Davies

PANEL: DRS. R. C. Brown, M. J. W. Chang, C. Kandaswami and B. Mossman.

QUESTION: In view of the fact that smoking increases asbestos carcinogenesis, do the fibers merely exert their effect by passing the polycyclic aromatic hydrocarbons (PAH) into the cells?

CONSENSUS ANSWER: Although smoking increased asbestos carcinogenicity, it was questionable whether or not this was due to increased transport of the PAH into cells, since fibrous dusts could have a wide variety of effects on cell metabolism including the subsequent conjugation of PAH and repair of any genetic damage that might have arisen.

PERTINENT DISCUSSION: The panel members gave a brief outline of their recent research findings, which were presented in detail in their contributions to the general meeting. The work by Lakowicz and Bevan (6), demonstrating that the transport of a polycyclic aromatic hydrocarbon (PAH) into an artificial membrane of liposome was increased when the PAH was coated on a particulate, was successfully repeated and extended to show that the effect was more pronounced with asbestos than with non-fibrous particulates. It was pointed out, however, that PAH uptake into cells was not stimulated by fiber in the presence of serum.

Dr. Fisher raised the point that the technique used to coat particulate with PAH was an important factor in the observed biological effects. For example, coating fly ash with PAH beyond the level of a monolayer would result in a tremendous increase in PAH bioavailability. He stressed the necessity for simulating the real-world situation as closely as possible in coating techniques.

Dr. Brown noted that the work of Hammond et al. (7) had shown that ex-smokers had a higher cancer risk with exposure to asbestos than those who had never smoked, indicating that simultaneous exposure to cigarette smoke and asbestos, important if simply PAH transport was a key factor, was not necessary for increased cancer risk. He also asked whether asbestos increased smoking-stimulated carcinogenesis or smoking increased asbestos-stimulated carcinogenesis? Dr. Nolan questioned the role of PAH in smoking-induced carcinogenesis, and Dr. Bignon suggested that smoke works as a promoter rather than an initiator of carcinogenesis. Dr. Frank made the point that so little was known of the mechanisms of either asbestos or smoking induced carcinogenesis, or basic biological changes following inhalation of these agents, that the formulation of unequivocal response to the question was difficult and the consensus statement reflected that difficulty.

Panel 3

RAPPORTEURS: DR. S. Bignon and G. Fisher

PANEL: DRS. A. Brody, R. J. Emerson, A. Frank, B. Mossman, P. Sirois and J. Smith-Sonneborn

QUESTIONS: Is there any threshold for the biological effects due to asbestos exposure?

Is it possible to extrapolate the risk of neoplasia induced by low levels of asbestos exposure from that induced by high dose levels?

CONSENSUS ANSWER: The question of a threshold for biological effects was redefined to address the existence of thresholds for biological effects, lung fibrosis and neoplasia. As shown in Table 1, there was agreement that there is no threshold for biological effects of asbestos exposure since there were data presented that a single fiber may produce changes in lung epithelial and interstitial cells including calcifications in interstitial fibroblasts. If lung fibrosis is defined as a clinically evident entity, a threshold probably does exist. For neoplasia, differences of opinion on the relative importance of DNA repair mechanisms and the origin of neoplasia, plus the lack of relevant animal and human data allowed no consensus to be reached.
With regard to the possibility of extrapolation of risk from high dose levels to low chronic levels of exposure, it was agreed that the data were not generally available for either a generalized biological effect or fibrosis. It was generally agreed however, from an epidemiological standpoint, that the risk of neoplasia could be extrapolated from exposure information although, due to insufficient information, a quantitative dose-response model could not be promulgated.

| Endpoint       | Existence of Threshold | Possibility of Extrapolation |
|----------------|------------------------|------------------------------|
| Biological effect | No                     | No                           |
| Lung fibrosis   | Yes                    | No                           |
| Neoplasia      | No consensus           | Yes (but not at lower end)   |

**PERTINENT DISCUSSION:** To allow discussion of information relating to the nature of the dose-effect relationship for humans exposed to asbestos in the response to these two questions, and because of the overlap of their areas of concern, the two discussion groups were combined.

The problems of using experimental animal data were discussed. They included: a general dearth of long-term, low-level animal studies; lack of animal studies evaluating the significance of dose rate; the short duration of animal exposure when compared to human exposure; the long latency period for the expression of mesothelioma and lung carcinoma in humans; the interaction with cigarette smoking; difficulty with extrapolation from cell and organ culture data; and individual variability of genetic repair capabilities. Human data were deficient in the effect of the lack of quantitative exposure data (therefore the inability to define “dose”), the interaction of pre-existing health conditions and co-exposure to cigarette smoke.

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