SUMMARY AND SYNTHESIS OF PART III. CARCINOGENICITY AND RELATED GENOTOXIC EVENTS

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Introduction

A number of important new findings are presented in this section from which a few conclusions were drawn and many new (and old) questions were posed; partial answers to these questions were in some cases available and new directions for research were evident. These conclusions, questions and answers (when available) are discussed below.

Conclusions and Questions

(1) Cell culture systems with mammalian cells now exist to study and compare toxic, mutagenic and transforming abilities of mineral dusts.

Several contributors (as indicated by the parentheses) present data which indicates that it is possible to determine the biological effects (including induction of cell transformation) of mineral fibers in mammalian cells including fibroblasts (Hesterberg, Lechner, Brown), epithelial cells (Nettesheim, Lechner) rat mesothelial cells (Patérou) and human mesothelial cells (Lechner). Thus, new model systems to study the mechanism(s) of action of mineral fibers are available.

(2) Asbestos fibers directly transform some cells in culture.

The important new findings that asbestos fibers induce neoplastic transformation of cells in culture (Hesterberg, Lechner and Patérou) indicate that direct cellular effects of mineral fibers are likely to play a role in asbestos carcinogenicity. The basis for the induction of these heritable changes by mineral dusts is an important area for future research. It is interesting to note that while evidence exists that asbestos transforms certain fibroblastic cells (Hesterberg) and rat (Patérou) and human mesothelial cells (Lechner), the results with other cell types, for example human bronchial epithelial cells (Lechner), rat tracheal cells (Nettesheim) and a mouse fibroblast cell line (Brown), are less definitive. These findings suggest important cell type
differences, which may be useful for determining critical cellular changes for transformation.

(3) Is asbestos an initiator and/or promoter?

This important question cannot be addressed by in vitro studies. Initiation and promotion are phenomena defined by in vivo models. The demonstration that asbestos transforms cells in culture does not prove that asbestos is an initiator. Furthermore, the lack of promoting activity of asbestos in cell culture models does not obviate a promoting role for mineral fibers in vivo. It should also be kept in mind that initiation and promotion do not fully describe the neoplastic process in vivo. Later stages of tumor progression involve heritable phenotypic changes in cells which are not affected by tumor promoters (Slaga et al. 1984; Hennings et al. 1983; Barrett 1985). It is possible that induction of cell transformation in cells in culture is more analogous to a late stage of tumor development in vivo and that some agents like asbestos are active in this stage of carcinogenesis.

(4) How does asbestos transform cells in culture?

Now that it has been demonstrated that asbestos induces heritable phenotypic changes associated with neoplastic transformation, the understanding of the mechanism of this effect is obviously important. The answer to this question is not yet known, but some of the data presented in this session can be used to begin evaluation of this question. Listed below are several additional questions which directly bear on this specific problem.

(5) What is the relationship between toxicity and transformation?

This is an important question from a practical as well as mechanistic standpoint since cellular toxicity assays have been extensively used to study different mineral fibers. The results to date, which are few, indicate a general correlation between induction of cell transformation and reduction in colony-forming efficiency for mineral fibers, but this association is less strong with nonfibrous dusts, such as silica, which transform cells at non-toxic doses (Hesterberg). Two complexities in analyzing this relationship are the marked cell type differences in toxicity response to mineral