UNION CARBIDE

INTERNAL CORRESPONDENCE

(F): Metals Div : Asbestos

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Subject Asbestos Toxicology

The IRDA item "Further Evidence that Asbestos is not Genotoxic" is interesting, but I am not certain that anything of practical value regarding control of exposure to asbestos in commercial usage can be derived from it at this point in time.

It is generally accepted that carcinogenesis is a multi-stage process. Furthermore, since 60-90% of human cancer is attributable to environmental factors, a major proportion should be preventable. The problem with this is that few cancers are attributable to single factors and most are the result of a complex interaction between environmental factors and human host factors.

The term carcinogen is used by some researchers to refer only to agents that are tumor initiators and act through genotoxic mechanisms. Promoters and other co-factors function through other mechanisms collectively called epigenetic mechanisms. The work reported in the IRDA note is very interesting, but the extent to which the in vitro findings can be related to human exposures to asbestos fibers cannot be determined. In the human being, as opposed to cell culture material, the extent of DNA damage in a target cell depends on such factors as the specific metabolism of carcinogens in the organ involved, the cells' permeability to particular metabolites and tendency to accumulate them and the extent of residual DNA damage after the cellular repair mechanisms have had their effect. The experiments cannot replicate the complex interactions between a multiplicity of environmental factors and human host factors. However, if asbestos fibers are not genotoxic, and if the mechanism whereby cancer arises in asbestos exposed persons is the result of epigenetic mechanisms, the next experiment should be aimed at establishing dose-response relationships within various time-frames. Promoters require repeated prolonged exposure to produce a response and this is sometimes erroneously thought of as indicating the existence of a no-effect level. In fact, if the stimulus is applied frequently enough and for long enough the response will be elicited. The

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only limiting factor is time! Time for induction of a response will obviously also vary with frequency of stimulation and size of dose. In other words, there is no such thing as a no-effect level.

My opinion, for what it is worth, is that the only safe way to handle asbestos is to reduce exposure to the lowest possible level or to find suitable substitutes for it. Only time will tell in the human organism whether an exposure level has been determined which, given sufficient time, fails to induce or promote cancer. Perhaps the information we seek can be obtained from studies of body burden in persons known to have been exposed to asbestos, whose exposures have been adequately documented and who died of causes unrelated to asbestos.

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