Approaches to Characterizing Human Health Risks of Exposure to Fibers

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Naturally occurring and man-made (synthetic) fibers of respirable sizes are substances that have been identified by the U.S. Environmental Protection Agency (U.S. EPA) as priority substances for risk reduction and pollution prevention under the Toxic Substances Control Act (TSCA). The health concern for respirable fibers is based on the link of occupational asbestos exposure and environmental erionite fiber exposure to the development of chronic respiratory diseases, including interstitial lung fibrosis, lung cancer, and mesothelioma in humans. There is also considerable laboratory evidence indicating that a variety of fibers of varying physical and chemical characteristics can elicit fibrogenic and carcinogenic effects in animals under certain exposure conditions. This paper discusses key scientific issues and major default assumptions and uncertainties pertaining to the risk assessment of inhaled fibers. This is followed by a description of the types of assessment performed by the U.S. EPA to support risk management actions of new fibers and existing fibers under TSCA. The scope and depth of these risk assessments, however, vary greatly depending on whether the substance under review is an existing or a new fiber, the purpose of the assessment, the availability of data, time, and resources, and the intended nature of regulatory action. In general, these risk assessments are of considerable uncertainty because health hazard and human exposure information is often incomplete for most fibers. Furthermore, how fibers cause diseases and what specific determinants are critical to fiber-induced toxicity and carcinogenicity are still not completely understood. Further research to improve our knowledge base in fiber toxicology and additional toxicity and exposure data gathering are needed to more accurately characterize the health risks of inhaled fibers. — *Environ Health Perspect* 105(Suppl 5):1329–1336 (1997)

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Introduction

A major goal of the U.S. Environmental Protection Agency (U.S. EPA) is the prevention, reduction, or elimination of harmful pollutant releases into the general environment. Naturally occurring and man-made (synthetic) fibers of respirable sizes are substances that have been identified as priority substances for risk reduction and pollution prevention. The health concern for respirable fibers is based on the link of occupational asbestos exposure and environmental erionite fiber exposure to the development of chronic respiratory diseases, including interstitial lung fibrosis, lung cancer, and mesothelioma in humans (*1*). Moreover, there is extensive experimental evidence indicating that a variety of fibers of varying physical and chemical characteristics can elicit fibrogenic and carcinogenic effects in laboratory animals under certain exposure conditions (*2,3*).

The U.S. EPA's Office of Pollution Prevention and Toxics (U.S. EPA/OPPT) is responsible for the evaluation of human health risk from occupational, consumer, and environmental exposure to respirable fibrous particles, and the development of regulation under the Toxic Substances Control Act (TSCA) to prevent, reduce, or eliminate these potential risks. TSCA authorizes the U.S. EPA to restrict or prohibit the manufacture, processing, distribution, use, or disposal of chemical substances already in commerce, and of new substances when there is a reasonable basis to conclude that any such activity poses an unreasonable risk to human health or the environment. TSCA also empowers the agency to require the manufacturers and processors of a chemical to develop the necessary toxicity and exposure data, if the agency determines that there is significant human or environmental exposure to such chemical, or that such chemical may pose an unreasonable risk but lacks sufficient data to take action. TSCA, however, requires the U.S. EPA to consider and weigh health and environmental risks, potential costs and benefits, and availability of alternative materials or technologies before taking any risk reduction actions.

This article describes the risk assessment approaches utilized by the U.S. EPA/OPPT in characterizing human health risks of exposure to new and existing fibers i.e., fibers that are listed on the TSCA inventory other than asbestos. This paper begins with a brief overview of the general principles of human health risk assessment and a discussion of the major scientific issues, uncertainties, and default assumptions pertaining to the risk assessment of inhaled fibers, and of research needs to improve the scientific basis for future risk assessments. This is followed by a description of the types of assessment performed by the U.S. EPA/OPPT to support risk management actions of new fibers and existing fibers under TSCA. Attention is focused on the kinds of scientific information and key factors that are considered in the hazard and dose–response assessments of the risk assessment process. Exposure assessment is only briefly addressed. The risk assessment of asbestos conducted by the U.S. EPA will not be discussed here, as it can be found elsewhere (*4*).

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Abbreviations used: IT, intratracheal instillation; MF, modifying factor; MOE, margin of exposure; NOAEL, no observed adverse effect level; OPPT, Office of Pollution Prevention and Toxics; PMN, premanufactured notice; RCF, refractory ceramic fiber; ROS, reactive oxygen species; SNUR, significant new use rule; TSCA, Toxic Substances Control Act; UFs, uncertainty factors; U.S. EPA, U.S. Environmental Protection Agency; WOE, weight of evidence.

General Principles of Risk Assessment

Risk assessment involves the analysis and synthesis of the entire knowledge base on an environmental agent to characterize the anticipated risk from human exposure to the agent. The U.S. EPA has followed the basic National Research Council risk assessment paradigm (*5,6*) as a foundation for its human health risk assessment guidance (*7–9*). Risk assessment consists of four components: hazard identification, dose-response relationship assessment, exposure assessment, and risk characterization.

The U.S. EPA's risk assessment guidelines contain detailed guidance on the application of default assumptions, i.e., science policy choices, and the associated uncertainties. It is generally accepted that default assumptions are necessary tools in performing risk assessment to bridge the gaps in general scientific knowledge and in data for a particular agent. Default assumptions are developed generically, not on an agent-by-agent basis. The intent is that default positions are taken for all agents unless case-specific data clearly indicate that the default assumption is no longer plausible and another inference position may be more appropriate.

Hazard identification is a qualitative assessment of available scientific data to make an informed judgment about the potential adverse human health effects posed by an agent. The principal question is what is known about the capacity of an environmental agent for causing adverse effects in humans, and under what exposure conditions an identified adverse effect may be expressed. The U.S. EPA uses a weight of evidence (WOE) approach to evaluate the potential human health effects of an agent. Information for this WOE evaluation is derived from available studies in humans and laboratory animals on the agent and on structurally related substances, together with other relevant information such as chemical and physical properties, toxicokinetic data, results of short-term assays for biochemical, molecular, genetic, and cellular effects, and any other mechanistic data.

Because human data are not always available, most hazard evaluations are, of necessity, based on animal data. Consequently, a major default assumption in hazard assessment is that an agent causing adverse effects in laboratory animals will also have the potential to cause adverse effects in humans unless the available data prove otherwise. In addition, in the absence of evidence to the contrary, data from animal studies in the most sensitive animal species are used for dose–response assessment purposes. The underlying scientific basis for this default assumption is the possibility that human sensitivity is as high as the most sensitive responding animal species.

The dose–response assessment evaluates the quantitative relationship of exposure and dose to the degree of response in existing studies in which adverse health effects have been observed. When environmental exposures of interest are outside the range of observation, extrapolations are necessary to estimate the likelihood of adverse effects in populations potentially at risk, if it is deemed appropriate and scientifically supportable.

Because cancer and noncancer effects historically are believed to occur by different modes of action, different approaches to dose–response relationship assessment have been developed. It is believed that most cancers, if not all, develop as a consequence of mutations of critical genes. Because a single chemical–DNA interaction may lead to a mutation, and because cancer is thought to arise from single cells, it follows that any dose of an agent may be associated with some finite risk. This has led the agency to employ a default procedure that cancer risk should be estimated by a linear, nonthreshold dose–response approach when the mode of action is not known, supportive of linearity, or is insufficient to support a nonlinear or threshold mode of action (*8*). It is recognized that such extrapolation does not necessarily give a realistic prediction of the risk but is consistent with the agency's goal to provide an estimate of the upper limit to risk.

In contrast, based on our understanding of homeostatic and adaptive mechanisms, the default approach for dose–response assessment of noncancer toxicity, i.e., toxicity other than cancer and gene mutations, assumes an identifiable threshold below which effects are not observable (*10,11*). It should be noted, however, that future case-specific knowledge of the mechanisms of chemically induced toxicity and carcinogenicity may blur this distinction between approaches for noncancer toxicity and carcinogenicity.

The exposure assessment identifies the likely sources of human exposures to the environmental agent, environmental pathways for exposure (e.g., air, water, soil, food), potential routes of exposure (e.g., oral, dermal, inhalation), populations at risk, including those of highly exposed groups and highly susceptible groups, and estimates exposure and dose levels that impact the exposed individuals or populations. The exposure assessment relies on many kinds of information, some based on actual measurements and some developed using predictive models and surrogate data.

Risk characterization, the last step in risk assessment, is the integrated analysis of the preceding three steps in risk assessment to reach a conclusion about the nature and magnitude of expected risk. The predicted risk can be qualitative (e.g., high or low probability) or quantitative (e.g., one in a million probability of occurrence). Risk characterization also includes a discussion of the confidence, limitations, and uncertainties of the risk assessment, given the constraints of available data, and the state of scientific knowledge, significant issues, and scientific assumptions and policy choices.

It should be noted that not every U.S. EPA risk assessment contains all four components. The scope and depth of the risk assessment depend on the availability of scientific data, resources, and time, the purpose of the assessment, any legislative mandates, and the nature of the intended regulatory action.

Issues in Risk Assessment of Inhaled Fibers

The following section discusses some key scientific issues and uncertainties to be kept in mind when assessing the potential health risk from exposure to fibers. These include *a*) the incomplete knowledge of how certain mineral fibers cause disease in humans and laboratory animals and which specific fiber properties are important in influencing their biologic and toxicologic effects; *b*) the limitations of available experimental models to accurately predict adverse outcomes in humans; and *c*) the lack of reliable data on human exposures to a wide variety types of fibers of concern. All of these factors contribute in part to the uncertainties of the risk assessment process.

Mechanisms of Fiber-induced Toxicity and Carcinogenicity

Although there have been significant advances in our knowledge about the health effects of asbestos and other fibers in recent years, the mechanisms by which mineral fibers cause fibrogenic and carcinogenic effects in humans and laboratory animals are not clearly understood. Fiber-induced fibrogenesis appears to arise from a chronic inflammation process that involves the release of cellular mediators (e.g.,

lysosomal enzymes, arachidonic acid metabolites, neutral proteases, cytokines, growth factors, chemotactic factors, or reactive oxygen species [ROS]) by activated alveolar macrophages and other inflammatory cells. These events are believed to be followed by the proliferation of fibrolasts and deposition of collagen within the alveolar spaces and the interstitium.

With regard to fiber-induced carcinogenicity, several hypotheses have been proposed. These include: *a*) DNA damage by ROS induced by fibers; *b*) direct DNA damage by physical interactions between fibers and target cells; *c*) enhancement of cell proliferation by fibers; *d*) fibers that elicit a chronic inflammatory reaction, which leads to prolonged release of ROS, cytokines, and growth factors; and *e*) fibers that act as cocarcinogens or carriers of chemical carcinogens to the target tissue. It is likely that all of these mechanisms contribute to the carcinogenicity of fibers because all these effects have been observed in various *in vitro* systems of human and mammalian cells using different types of fibers (*12*).

The role of fiber-induced fibrosis in carcinogenesis is not clear. Macrophage lysis and chronic inflammation induced by fiber exposure may not only lead to lung fibrosis but also to the development of some lung tumors in rats. Other rat lung tumors, however, appear to have no relationship to fibrotic scar.

Critical Determinants of Fiber Toxicity and Carcinogenicity

Current scientific knowledge indicates that a major determinant of fiber toxicity and carcinogenicity is fiber dimension. There is extensive evidence relating to the importance of fiber size in lung deposition and clearance of fibers, which in turn govern the bioavailability of fibers at target tissues (*13*). Fiber diameter is the major determinant for the deposition of fibers. Only fibers less than about 3.5 μm in diameter can reach the alveolar spaces. Fiber length also influences the deposition and clearance of fibers. Fibers longer than 20 μm are more readily deposited by interception at airway bifurcations. In general, short fibers (< 5 μm) are cleared more rapidly than long fibers (> 5 μm). Fiber size also plays an important role in relation to cellular mechanisms of toxicity and carcinogenicity. Long fibers of a given fiber type are generally more biologically active than shorter fibers, regardless of the measured biological end points such as cytoxicity, cell transformation, or aneuploidy. Furthermore, long fibers (> 5 μm) are more carcinogenic and fibrogenic than short fibers of asbestos and other fibers (< 5 μm) in chronic studies in rats by inhalation (*14,15*) or intracavitary injection (*2,3*).

Fiber biopersistence may also be an important determinant of fiber toxicity and carcinogenicity. The concept of biopersistence arose from the observation that different natural and synthetic fibers have different lung retention characteristics; some persisting over long periods, others being less persistent. It has been hypothesized that a fiber with critical dimensions will be carcinogenic if it is sufficiently durable to remain chemically and physically intact in lung tissue in close contact with the target cells (*3*). Although more durable fibers appear to be more carcinogenic than more soluble fibers e.g., refractory ceramic fiber (RCF) versus glass fiber, neither the influence of biopersistence on fibrogenesis and carcinogenesis nor the length of time required for a fiber to remain in the lung to exert a pathogenic effect has been adequately defined. For instance, chrysotile asbestos fiber is significantly less biopersistent than amphibole asbestos, yet the fiber is clearly carcinogenic and fibrogenic in humans. In view of the many different mechanisms by which fibers might influence the carcinogenic process, it is difficult to determine the degree of biopersistence necessary for fiber carcinogenicity. In addition, available models of fiber solubility or durability in physiological systems, as well as fiber biopersistence in the lung, remain to be validated. Nevertheless, it is generally believed that fibers capable of biopersistence in the lung are of greater concern.

Other fiber characteristics such as surface area, chemistry, and chemical leaching are also likely to play a role in fiber-induced toxicity and carcinogenicity, although these are much less well understood. For example, acid-leached chrysotile fibers are less carcinogenic than native fibers (*16*).

Definition of Fibers of Concern

A major issue for the U.S. EPA is to define the category of fiber of concern. As discussed above, it is recognized that there are a number of fiber properties e.g., fiber size, chemical composition, biopersistence, and surface chemistry that are likely to exert an influence on the pulmonary toxicity and carcinogenicity of inhaled fibers. However, it is the presence of a long thin fibrous shape that appears to be the most important determinant of fiber-induced pathogenicity. Still, it is not known whether there is any single cutoff of fiber length or diameter that implies human safety. Moreover, the conventional definition of a fiber used for industrial hygiene purposes continues to be a practical index for risk assessment. Consequently, fibrous particles of respirable sizes are considered potentially hazardous unless there are available data to demonstrate otherwise.

For regulatory purposes, the U.S. EPA defines fiber as a particle of length > 5 μm with an aspect ratio (ratio of fiber length to fiber diameter) of at least 3:1 (*4*). This definition has been widely adopted by other organizations (*17,18*). Fibers with aerodynamic diameters of 10 to 12 μm or less, or actual fiber diameter of about 3.0 to 3.5 μm or less, are generally considered respirable for humans (*19*). The upper limit of fiber length for human respirability is about 200 μm (*20*). This definition applies to any particle that fulfills these criteria regardless of chemical composition or mineralogic characteristics.

Exposure Characterization

Given that fiber exposure characteristics greatly influence the nature of the hazard, it is essential that human exposures to fibers are measured to the extent feasible and fully characterized (e.g., airborne fiber dimensions and physicochemical characteristics, fiber concentrations per unit air volume, frequency and duration of exposure) to permit a more reliable characterization of potential human risk. Available data on human exposures to fibers, however, are often limited. Furthermore, standard analytical methods to characterize and monitor fiber exposures have been confined to only a few fiber types such as asbestos and man-made vitreous fibers. Improved techniques for characterizing human and animal exposure to other types of fibers are needed.

It is also important to note that fibers specified by the same name are used in numerous applications or products that may have varying physicochemical characteristics. Each fiber type, therefore, may pose different degrees of health hazard and should not be treated as a single entity. Moreover, fibers released into ambient air throughout the product cycle of the fiber can also vary greatly in size and characteristics. For example, a fiber may undergo breakage across the fiber axis, as in glass fibers, or may generate fibrils due to splitting longitudinally e.g., chrysotile. Fibrils

may also be peeled off from a core fiber e.g., *p*-aramid. A fiber may undergo structural changes during its use. For example, RCF may partially transform from an amorphous form into crystalline silica after use under high-temperature conditions. Thus, each fiber type may pose a different nature and magnitude of health risk under different exposure conditions e.g., workplace, user environments.

Hazard Evaluation

The question of fiber fibrogenicity and carcinogenicity in humans should be answered within the framework of all available evidence. Judgment about the WOE involves consideration of the quality, adequacy, and consistency of responses induced by the fiber in question. The questions to be asked may include: *a*) Can the fiber be inhaled and deposited in the human lung? *b*) What is known about its deposition pattern, clearance rate, retention, and translocation pathways? *c*) Does the deposited fiber have certain physical and chemical characteristics that are critical determinants of toxicity and carcinogenicity? *d*) What is the degree of evidence for a causal relationship between chronic respiratory effects in humans and fiber exposure? *e*) Is the fiber toxic to target cells? *f*) Does the fiber induce chronic inflammation and/or pathological lesions in the exposed animals after prolonged exposure to the fiber? *g*) What do we know about the toxicity and carcinogenicity potential of closely related fibrous particles?

Human data, when available, are given first priority in establishing the presence of an adverse effect in exposed human populations and a quantitative relationship between environmental exposure and adverse effects. For most fibers, there is insufficient information on effects in humans. In such cases, hazard evaluation relies primarily on animal studies, most often in the rat, on the fiber itself or on closely related fibrous particles. Information on fiber disposition (deposition, translocation, clearance), dissolution, biopersistence, *in vitro* biological activity, and mechanistic data can provide additional insights into possible toxicity and carcinogenicity of a fiber.

It should be pointed out that considerable uncertainties exist when extrapolating experimental findings to hazard assessment in humans. When making such extrapolations, one must recognize that the qualitative and quantitative aspects of fiber deposition, retention, and clearance in rodents are considerably different from those in humans due to differences in the anatomy and physiology of the respiratory tract (*21,22*). First, the respirability of rats is different from respirability in humans. Fibers with aerodynamic diameters > 3 μm are not respirable by the rat but more than 20% of these fibers can be deposited in the human lung. Second, fibrous particles are preferentially deposited at the alveolar duct bifurcations in rats, whereas they are deposited mainly at the bronchiolar bifurcations in humans. These differences may contribute to the different pattern of lesions among species. For example, asbestos causes bronchogenic carcinomas in humans; asbestos and other mineral fibers induce peripheral lung tumors in rats. Hamsters, on the other hand, seem to be more susceptible to the development of fiber-induced mesothelioma than lung tumors. The overall consequence is that inhalation studies in rodents may not necessarily be predictive of human toxicity and carcinogenicity. Interpretations of animal study results should be put into perspective with regard to potential human hazard and risk.

There has been considerable debate concerning the relevance of various routes of exposure to cancer hazard assessment of fibers in humans. The advantages and limitations of each route of administration are well recognized (*23,24*). Because inhalation is the major route of human exposure, positive results of an inhalation study in animals might have significant implications for hazard and dose–response assessment in humans. This finding would be bolstered by positive results from studies using nonphysiological routes of administration such as intratracheal instillation (IT), intrapleural inoculation or implantation, and ip injection.

On the other hand, lack of tumorigenic responses in an inhalation study does not necessarily mean that the fiber is nonhazardous to humans, because of species differences in the respirability and susceptibility between humans and rodents as discussed above. Such a finding, however, would strongly indicate that the fiber does not exhibit carcinogenic potential in humans if it was demonstrated that the target tissues (i.e., the lung) were exposed to sufficient quantities of critical-size fibers compared with a positive control (e.g., asbestos). Evidence for the absence of carcinogenic potential of the fiber in humans must be corroborated by consistent lack of biological and toxicological effects from other studies.

Studies using instillation or injection methods of administration are of considerable value for the evaluation of the potential human hazard of fibers. Positive results in instillation or injection studies would suggest a potential hazard to humans, but further investigation would be needed for a firm evaluation of the inhalation hazard for humans. However, a negative result in such studies would suggest that the fiber probably is of low human hazard potential and the need for additional inhalation testing would be mitigated. An exception to this would be for fibers that have the ability to agglomerate (certain organic fibers such as *p*-aramid) and tend to reduce the actual number of single fibers at target tissues.

Dose–Response Extrapolation

To more accurately predict and characterize human health risks from inhaled fibers, it is necessary to understand the mechanistic linkage between fiber exposure and biologically effective dose and between the biologically effective dose and response. Currently, validated biologically based models and mathematical models describing fiber exposure/dose–response relationships for fiber-induced toxicity and carcinogenicity in quantitative terms are not yet available. There is still a lack of information on the disposition of inhaled fibers both in laboratory animals and humans. Moreover, the knowledge of how fibers cause biological and pathological effects is still incomplete, and the question of how long a fiber has to persist in the target tissue to induce a biologic and pathologic response has yet to be fully investigated. Given the incomplete knowledge of fiber toxicology, the U.S. EPA often uses fiber exposure concentration as a surrogate for dose for risk assessment purposes.

There are other uncertainties associated with performing fiber exposure/response assessments when animal data are used. A number of scientific judgment and science policy choices must be made concerning the relevance of the animal model to humans and the appropriateness of extrapolating results from high experimental exposure to relatively low occupational and environmental exposures. The rat inhalation model is generally accepted as suitable for establishing the exposure/response relationship, in spite of known limitations. An exception to this would be cases where available data indicate that other animal species may be more sensitive (e.g., the hamster is more susceptible to RCF-induced carcinogenicity of the pleura than the rat). This policy

position is considered reasonable because it is assumed that humans are at least as innately sensitive as the most sensitive species tested. Furthermore, there is evidence that the rat inhalation model may underestimate the risk in humans, especially for mesotheliomas (*3*).

Dose–response assessment for fiber-induced respiratory noncancer toxicity utilizes the uncertainty factor approach. This approach assumes that a safe exposure level exists, i.e., at exposures below the threshold, clinical manifestations of pulmonary fibrosis or pleural changes are unlikely. It involves the identification of the highest fiber exposure concentration at which there are no statistically or biologically significant increases in the frequency or severity of adverse effects between the exposed population and its appropriate control, and is known as the no observed adverse effect level (NOAEL). To conclude that a particular effect is adverse requires sound professional judgment and a clear articulation of the scientific rationale. Because a fiber may elicit more than one end point, the critical end point used in the dose–response assessment is the effect with the lowest NOAEL.

With regard to dose–response assessment for carcinogenic effects of inhaled fibers, a linear, nonthreshold dose–response approach is generally used. This assumption is based on the current knowledge that asbestos fibers can influence the carcinogenic process at either early or late stages by both genetic and epigenetic mechanisms (*25*). However, a nonlinear threshold approach may be appropriate if there is sufficient evidence to support the mode of action of certain fibrous particles having a threshold, e.g., if the fiber-induced carcinogenesis is a secondary effect of fibrosis/scarring, which itself is a threshold phenomenon.

Risk Assessment of New Fibrous Substances under TSCA

Section 5 of TSCA requires anyone who intends to manufacture or import into the United States a chemical substance not on the TSCA inventory and not exempted from TSCA, to submit a formal notice known as the premanufactured notice (PMN) to the U.S. EPA. The U.S. EPA is required to review each PMN and make a decision within 90 days about potential risk to human health and environment of allowing the manufacture, import, processing, distribution, use, and disposal of that chemical.

Risk assessment of new fibers is generally hampered by lack of information submitted in the PMN, as the submitter is not required to generate toxicologic information on the new fibrous substance. As a result, the U.S. EPA/OPPT relies on the hazard and exposure information submitted (if any) and on readily available toxicologic and epidemiologic data on related fibrous substances to make a scientific judgment of whether the new fiber may present significant risk to human health or the environment. Thus, risk assessments of new fibers may be based almost entirely on current scientific knowledge about critical determinants of fiber toxicity and carcinogenicity, surrogate dose response and exposure data, and policy assumptions.

A regulatory decision is subsequently made either to drop the case from further consideration or take control action to protect against that risk. If it is determined that the fiber is of concern but there are insufficient data to assess the potential health effects of the fiber, control action may be imposed until additional information is obtained. As more information becomes available, the risk assessment is updated and risk management action is adjusted if deemed necessary. Screening-level testing may be imposed on a new fiber of low health concern if it is to be produced in large quantities and widely used in commercial products, which could result in substantial human exposure. Testing requirements are considered necessary to ensure that the new fiber does not pose significant risk to exposed humans. For fibers determined to be potentially hazardous, the agency may issue a significant new use rule (SNUR) to prevent the fibers from reentering commerce without U.S. EPA notification.

Hazard Identification

Key factors that are generally considered in predicting the health hazard potential of inhaled fibers are: *a*) the ability of the fiber to generate airborne respirable particles; *b*) the fiber size distribution of the airborne fibers; *c*) the morphologic and chemical characteristics of the fiber; *d*) the *in vitro* solubility of the fiber; *e*) the biopersistence of the fiber in the lung; *f*) the ability of the fiber to cause cytoxicity, cell proliferation, chromosomal damage, and other biological endpoints in *in vitro* and *in vivo* assays; *g*) the ability of the fiber to cause pathological changes in short term or lifetime studies in laboratory animals by inhalation, IT, and/or ip injection; and *h*) the toxicity and carcinogenicity profiles of chemically and structurally related fibrous particles.

In the absence of any toxicologic information, a new fibrous material is presumed to pose a fibrogenic hazard if it is respirable. If the new fiber also contains a significant proportion of particles with a long, thin, fibrous shape (fiber diameter ≤ 1 μm and fiber length ≥ 10 μm), it is considered potentially fibrogenic and carcinogenic. This science policy position is justified, as fiber dimension is an important determinant of fiber toxicity and carcinogenicity. Health concerns about potential carcinogenic and fibrogenic effects of a fiber increase if available information indicates that it is relatively insoluble in physiological systems and biopersists in the lung. The concern is heightened if chemically and structurally related fibrous substances are known to cause *in vitro* and *in vivo* toxicity in short-term studies and/or carcinogenicity in long-term studies.

A fiber is not considered a significant hazard to human health if available information indicates that the fiber is nonrespirable or has a low degree of respirability. A respirable fiber may be of low health concern if the fiber is relatively short, does not biopersist in the lung, is relatively soluble, exhibits low biological and toxicologic effects in *in vitro* and *in vivo* short-term studies, and/or demonstrates a lack of fibrogenic and carcinogenic effect in long-term animal studies. Some short fibers may be fibrogenic at high exposure levels but may not be carcinogenic. On the other hand, a carcinogenic fiber is also likely to be fibrogenic.

The minimum data set required by the agency for a screening-level determination of potential health hazards of a new fiber should include a complete physical and chemical characterization of the fiber and the results from a well-designed and well conducted 90-day subchronic inhalation study in the rat. Other toxicologic information such as *in vitro* solubility, *in vitro* cellular assays (e.g., cytotoxicity, genotoxicity, cell proliferation, or generation of ROS), and lifetime IT or ip carcinogenicity studies, are considered highly relevant and desirable in the evaluation of the potential hazard of the fiber. However, at the present time, these studies are not part of the regulatory testing requirement for new fibers. The U.S. EPA is in the process of developing fiber toxicity and carcinogenicity testing guidelines for new and existing fibers (*24*).

Dose–Response Assessment

For new fibers, it is preferable to conduct dose–response assessments using data from well-conducted lifetime inhalation studies in laboratory rodents. However, toxicologic information on new fibers is often lacking. Dose–response risk assessments for chronic respiratory noncancer toxicity of new fibers are generally based on animal data from the most closely related fibrous particles. Cancer risk assessment of new fibers, on the other hand, is based primarily on unit risk estimates derived from epidemiologic studies of asbestos workers. This approach is considered valid only if the fibers under evaluation do not differ greatly from those of asbestos in terms of fiber morphology, dimensions, and biopersistence. However, because most fibers differ widely in their physical and chemical characteristics, this approach may overestimate or underestimate the cancer risk of the fibers under evaluation. This uncertainty is taken into consideration in the risk characterization step of the risk assessment process. Therefore, these types of assessments are considered screening level and often only qualitative in nature.

Exposure Assessment

The first step in exposure assessment is the evaluation of the life cycle of the fiber (how the fiber is manufactured, processed, used, removed, and disposed of) and the identification of any points in the product life cycle that may result in human exposure by inhalation in the occupational setting, as an end user, or from environmental releases. This is followed by the estimation of the population, frequency, and magnitude of exposure for each potential exposure scenario, and an evaluation of any alterations in the physical and chemical characteristics of the fiber throughout its life cycle. This is important because the physicochemical properties of the fiber are major determinants of toxicity and carcinogenicity.

A major source of uncertainty in the assessment of anticipated human exposure to new fibers is the absence of monitoring data on fiber exposure in the workplace, during use, and from environmental release. As a result, compliance with the permissible exposure limit for respirable nuisance dust (5 mg/m^3 as an 8-hr time-weighted average, set by the Occupational Safety and Health Administration) is generally assumed. Considerable uncertainties also exist for the conversion of gravimetric concentration into fiber concentration.

Risk Characterization

Risk characterization includes an integrative analysis of hazard, dose response, and exposure assessments to characterize the risk posed by a fiber throughout its expected product life cycle. Major results of the risk assessment are presented in a risk characterization summary. The summary generally includes *a*) the qualitative WOE conclusions as to the likelihood that the new fiber may pose a hazard to human health; *b*) a discussion of the dose–response information considered in the assessment of risk from chronic respiratory toxicity and carcinogenicity; *c*) estimates of the nature and extent of the exposure, and the number and types of people exposed; *d*) a conclusion with regard to the nature and extent of the risk; and *e*) a discussion of the overall confidence and uncertainty in the analysis, including the major assumptions made, the scientific judgments employed, and the degree of conservatism involved.

In the integrated analysis for noncancer respiratory effects, a margin of exposure (MOE) analysis is derived to determine the likelihood of a health risk. MOE is defined as the ratio of the NOAEL divided by the estimated human exposure of interest. When MOE is equal to or greater than the product of uncertainty factors (UFs) and a modifying factor (MF), the need for regulatory concern is likely to be small. UFs are used to account for interspecies variation in sensitivity and intraspecies extrapolation, and an MF is used to account for the completeness of the data base. With regard to cancer risk assessment of inhaled fibers, an excess lifetime cancer risk of > 1 in 10,000 is generally considered of low regulatory concern.

Risk Assessment for Existing Fibrous Substances under TSCA

Few risk assessments have been conducted to date on existing fibrous substances listed on the TSCA inventory. The scope and depth of the risk assessments vary depending on the regulatory purposes. Testing action, significant new use rulemaking, identification of potential candidates for risk reduction action, or priority setting may be included.

Assessment in Support of Testing Action

Section 4 of TSCA gives the U.S. EPA the authority to gather information about toxicity of existing chemicals and the extent to which humans are exposed to them if the agency determines that insufficient data exist to evaluate risks to human health or the environment. Testing action can be triggered if the fiber is produced in substantial quantities and if one of the following applies: *a*) the fiber enters the environment in substantial quantities, *b*) there is substantial human exposure (number of people exposed), or *c*) there is significant human exposure (magnitude of exposure). Testing action can also be supported if there is evidence to indicate that the chemical may present an unreasonable risk to human health or the environment.

U.S. EPA investigators believe that there are sufficient reasons, based on hazard information, to suspect possible health effects from long-term inhalation exposure to respirable fibers. Therefore, the agency has added a respirable fibers category as a priority substance for hazard and exposure testing on the U.S. EPA's Master Testing List (*26*).

To date, the agency has taken testing action on only one class of fibers. The agency has concluded that RCF is likely to be carcinogenic and fibrogenic, but exposure data are inadequate to determine if RCF poses an unreasonable risk to workers (*27*). Consequently, the U.S. EPA and the manufacturers of RCF developed an exposure monitoring program pursuant to an enforceable consent order to obtain additional worker data (*28*). The agency is presently developing guidelines for chronic toxicity and carcinogenicity testing for fibrous particles (*24*).

The objective of risk assessment in support of testing action is to determine if the available data indicate a potential health hazard and the extent of human exposure, and if the information is sufficient to perform a quantitative risk assessment to justify risk reduction actions. Thus, risk assessment in support of testing action generally includes only two components: a hazard assessment and an exposure assessment.

The hazard assessment involves an in-depth review and evaluation of health effects data available in the open literature and/or directed to the U.S. EPA via TSCA submissions. The questions to be asked are: *a*) On the basis of available information, what can be concluded about the carcinogenic and fibrogenic potential of the fiber under review? *b*) Are the available data adequate for hazard characterization and dose–response assessment? The types of scientific information used in the hazard

evaluation are similar to those discussed in the section on new fibers. The evaluation includes a qualitative WOE conclusion as to the likelihood that the fiber may pose a hazard to human health, identification of data gap, if any, and recommendations for tests to fill the data gap.

The purpose of the exposure assessment is to estimate the nature and extent of human exposure to the fiber of interest and to determine whether the available exposure information is adequate for assessing potential health risk. The exposure assessment includes consideration of the product cycle for the fiber, estimates of the size and nature of the populations exposed to the fiber, and the source, magnitude, frequency, and duration of inhalation exposure to the fiber, based on available monitoring or modeling results. A discussion of the confidence and uncertainties of the analysis is included.

Assessment in Support of a Significant New Use Rule

The technical support for a SNUR involves an in-depth hazard assessment similar to that used in support of testing actions. The U.S. EPA has promulgated a SNUR under section 5(e) of TSCA for erionite (*29*) and issued a proposed SNUR for RCF (*28*) on the basis that these fibers are hazardous to human health, and any use of these fibers may result in significant human exposure. The SNUR would allow the U.S. EPA to evaluate the intended new use and, if necessary, to prohibit or restrict that activity if such use would pose an unreasonable risk to human health.

Assessment for Priority Setting

The U.S. EPA is developing a screening assessment to identify fibers of high concern for control action. The assessment entails a review of readily available hazard and exposure data from reliable sources to make a qualitative judgment regarding the nature and magnitude of possible health risk. The scope and depth of the assessment is comparable to the assessment for new fibers. The assessment may be based on surrogate dose response and exposure data and on policy assumptions. Outcomes of the review may include withdrawal from the review process because of low hazard concern and/or limited exposure potential, recommendation for additional information, and a need for more in-depth review for risk reduction action.

Assessment for Risk Reduction Action

A comprehensive risk assessment is considered necessary to support an unreasonable risk finding before any risk reduction action is enacted under section 6 of TSCA. To date, the U.S. EPA/OPPT has conducted no comprehensive risk assessments on any existing fibers except asbestos. A comprehensive assessment of a fiber such as asbestos entails a critical analysis of all relevant hazard, dose response, and environmental exposure data, and an assessment of quantitative expression of cancer risk (*4*).

Conclusions

Risk assessment is the starting point for risk management consideration and the foundation for regulatory decisionmaking. Risk assessment approaches used by the U.S. EPA to support regulatory decisions under TSCA for naturally occurring and synthetic fibers differ, depending on whether the fiber in question is an existing or a new fiber. This is due to differences in the purpose of the assessment, the availability of data, time, and resources, and the intended nature of regulatory action.

Risk assessments of new and existing fibers are prone to uncertainties because health hazard and human exposure information is incomplete for most fibers. Furthermore, how fibers cause diseases and what specific determinants are critical to fiber-induced toxicity and carcinogenicity are still not completely understood. Of necessity, many default assumptions bridge both data and knowledge gaps. Further research to improve our knowledge base in fiber toxicology and additional toxicity and exposure data gathering are needed to more accurately characterize the health risks from exposure to inhaled fibers.

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