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Contribution of Environmental Fibers to Respiratory Cancer

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This article reviews studies of the carcinogenicity of mineral fibers, notably asbestos, and presents seven major recommendations for further research. Mineral fibers represent the greatest cause—after cigarette smoke—of respiratory cancer due to air pollutants. Past asbestos exposure may currently account for 2000 mesothelioma deaths per year and 4000 to 6000 lung cancer deaths per year. All major commercial types of asbestos (crocidolite, amosite, and chrysotile) can cause each of the major asbestos-related respiratory diseases. Lung cancers in asbestos-exposed individuals probably do not have a different distribution of histological types from that of non-asbestos-related lung cancers. Nonoccupational exposures are likely to be associated with malignant disease outcomes qualitatively similar to those associated with occupational exposures. Further investigations of fibers are needed to characterize the relationships among physicochemical properties, patterns of migration and clearance, dose, and adverse health effects. Transmission electron microscopy has been found to be the preferred method of analysis of environmental fibers. Relations among time factors (e.g., age at first exposure), dose, and risk for adverse health effects require analyses of existing and new epidemiologic studies of exposed cohorts. Concomitant exposures, behavioral factors, and host factors affecting susceptibility to asbestos should be identified.

Exposures during production and use of mineral fibers, notably asbestos fibers, represent the greatest cause—after cigarette smoke—of respiratory cancer due to air pollutants. Asbestos acts directly to cause mesotheliomas of the pleura and peritoneum and acts directly and especially synergistically with cigarette smoking to cause bronchogenic carcinomas. It is estimated that past asbestos exposures may currently account for approximately 2000 mesothelioma deaths per year and 4000 to 6000 lung cancer deaths per year (*1*). Current exposures are much lower because of alternative materials and occupational exposure controls.

Because the size, shape, and persistence of asbestos and related fibers seem to be critical properties for carcinogenicity, it is likely that other chemically diverse fibers that share these critical attributes may be similarly carcinogenic. A scheme for classification of environmental fibers is presented in Figure 1. Such fibers—natural and synthetic—are coming into widespread use, both as replacements for asbestos and in technological innovations requiring materials with high tensile strength. Thus, the development and validation of *in vitro* screening tests and animal bioassays for these fibers will be increasingly important, as will well-planned epidemiologic surveillance of workers. It would be better to identify potentially hazardous substances before there is widespread human exposure than to learn only later from epidemiologic and clinical studies that considerable disease has been caused.

Human Health Effects

Recent major reports to the governments of the United States, Great Britain, and Canada have reviewed the health effects of asbestiform fibers in detail (*2–4*). Thus, a full recapitulation here is unnecessary.

These reports are in essential agreement about the major malignant and nonmalignant asbestos-related sequelae of exposure and about the dose-response relationship for occupational asbestos exposures. However, there are large uncertainties about the dose-response

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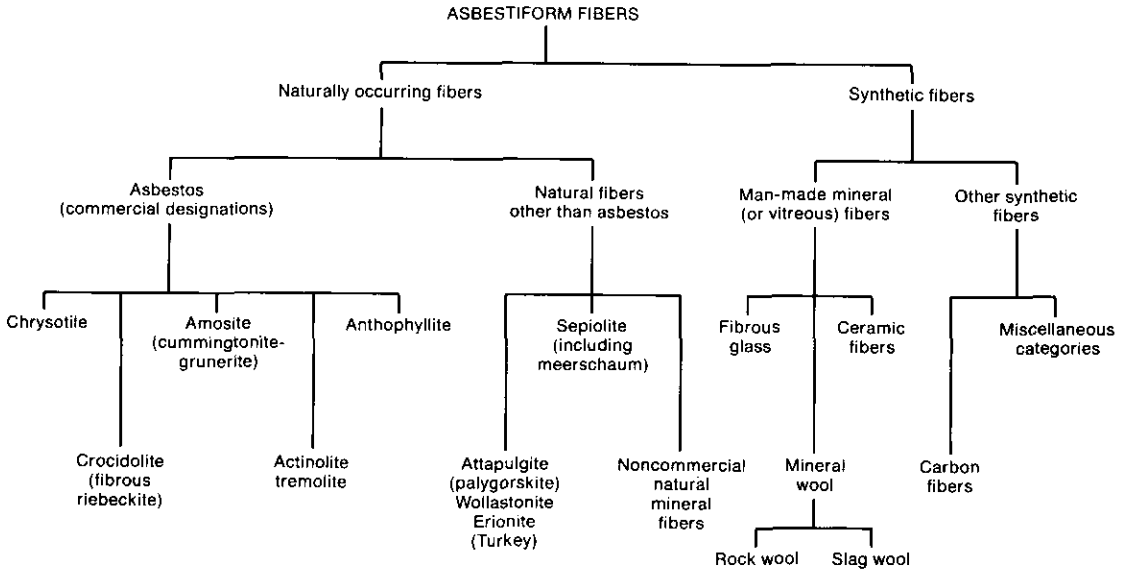

FIGURE 1. Asbestiform fibers (*1*).

Table 1. Pulmonary manifestations of asbestos exposure.

Effect	Dose-response relationships: Strength of data	Comments	Relation to smoking
Malignant			
Lung cancer	+ + + +	Linear, cumulative (relative risk model)	Yes (multiplicative)
Mesothelioma	+	Cumulative (absolute risk model)	No
Nonmalignant			
Parenchymal fibrosis	+ + +	Linear, cumulative with duration and intensity	No (uncertain)
Pleural thickening	+ +	Cumulative; strong relation to time from first exposure	No
Pleural effusions	+		No
Small airway disease	−		Yes (?additive)

relationships for much lower exposures in nonoccupational settings. In addition, there are controversies about possible differential effects of the major types of asbestos fibers and about the significance of inconsistent observations of increased risk for gastrointestinal cancer.

Table 1 summarizes the recognized adverse pulmonary effects of asbestos exposure, the knowledge of their relation to exposure dose, and the extent and nature of their relation to cigarette smoking. In general, the natural history of nonmalignant respiratory disease and its relation to the risk for cancer needs further elucidation. Specifically, independent of dose, does the presence of nonmalignant sequelae (particularly parenchymal fibrosis but also discrete or generalized pleural thickening and small airways disease) confer a greater risk for either bronchogenic carcinoma or mesothelioma?

Key conclusions from reports and studies are the following:

The major commercial types of asbestos (crocidolite, amosite, and chrysotile) all can cause each of the major asbestos-related diseases of the respiratory system. Chrysotile, the form most widely used in the United States, may be less likely than the others to cause pleural mesotheliomas and seems not to be associated with peritoneal mesothelioma.

Lung cancers in asbestos-exposed individuals probably do not have a different distribution of histological types from that of non-asbestos-related lung cancer. There has been a temporal increase in the histologic diagnosis of adenocarcinoma in both groups.

Nonoccupational asbestos exposures are likely to be associated with malignant disease outcomes qualitatively similar to those associated with occupational exposures.

The absence of recorded cases of asbestosis caused by low-level, nonoccupational exposures and the fact that asbestosis is a progressive, generalized condition would be consistent with a threshold below which fibrosis may not occur.

Major economic, legal, and social issues are intertwined with analyses of causation and attributable risk from past occupational asbestos exposures. These dimensions are beyond the scope of this discussion.

Research Agenda

The pathogenesis of all asbestos-related sequelae remains unknown. Despite the available experimental evi-

dence duplicating the major observed effects on human health, further investigations of fibers are needed to characterize the relationships among physicochemical properties (size, shape, and charge), patterns of migration and clearance, dose, and adverse health effects. Relations among time factors (age at first exposure, time since first exposure, duration, and calendar time), dose, and risk for adverse health effects will require detailed analysis of existing and new epidemiologic studies of exposed cohorts. These studies need to identify concomitant exposures, behavioral factors, and host factors affecting susceptibility to asbestos and development of specific clinical endpoints. In addition, asbestos-exposed workers, particularly smokers, are an excellent high-risk population to study mechanisms and risk reduction strategies in carcinogenesis.

Recommendation 1: More epidemiologic studies are warranted. Particular attention should be given to time factors, nonmalignant sequelae as potential predictors of cancer risk, biological markers, immunologic dysfunction, and dietary factors.

Recommendation 2: Strategies to prevent respiratory cancer in high-risk asbestos-exposed cohorts deserve priority. These strategies include elimination of asbestos exposures, cessation of cigarette smoking, and chemoprevention with agents such as retinoids. There should be systematic surveillance of asbestiform fiber exposures, lung cancer, and mesothelioma, seeking to document the expected declines due to control measures.

Recommendation 3: Instillation and inhalation studies in animals should be continued. These studies remain the preferred means for investigating translocation, clearance, and retention of fibers and the relationship of physicochemical and physiological parameters to pulmonary effects.

Recommendation 4: *In vitro* predictive tests need to be developed and validated. With many new or modified fibrous materials being introduced in industry, screening tests for cytotoxicity, fibrogenicity, or malignant transformation would have great value. Such tests may provide clues to underlying mechanisms as well.

Measurement of Exposure

The detection, identification, and enumeration of asbestiform fibers in air, water, foods, beverages, pharmaceutical products, body fluids, and tissues are complicated issues of considerable importance. The most critical step is sampling. How often should a site be sampled? What volume of air, water, or tissue should be taken? Available instrumentation encompasses light microscopy, transmission electron microscopy (TEM), scanning electron microscopy (SEM), automated counting devices using television camera/computer techniques, light scattering (Tyndallometry), and magnetic alignment devices. What is the most appropriate form of microscopy to use? What are the limits of detection?

Measurement of the amount of asbestos collected on a sample filter can be determined in terms of mass or number of fibers. Total mass is inappropriate, because small numbers of large fibers that are not respirable influence the determination disproportionately. Methods of counting fibers by phase-contrast optical microscopy are unable to resolve fibers less than 0.2 μm in diameter and suffer considerable interlaboratory variability. The transmission electron microscope with high-resolution, selected-area electron diffraction and energy-dispersive X-ray analysis can resolve the finest fibrils and provide positive mineralogical identification in the majority of cases. Because these procedures are time-consuming and demand a high degree of expertise, development of image analysis methods for the TEM could be useful.

At present, there are three levels of resolution available for enumerating and sizing mineral fibers: 0.2 μm by phase-contrast microscopy (PCM), 50 Å by SEM, and 5 Å by TEM. Assuming a deposition of fibers on a membrane filter (of, e.g., 47 mm diameter), the maximum area of filter that can be examined in one preparation is potentially 100% by PCM, 8% by SEM, and 0.4% by TEM. Lack of uniformity in distribution of the fibers will lead to an increase in error by use of SEM and even more so by TEM unless multiple sampling of a filter is undertaken. Nevertheless, with careful sampling procedures and appropriate controls, TEM is the best method available. Counting of fibers is an exercise in probability theory.

Reported concentrations of chrysotile asbestos in the ambient air of U.S. cities range from 1 ng/m^3 to 100 ng/m^3, with a geometric mean concentration estimated to be about 1.5 ng/m^3 (3.5 ng/m^3 for large urban areas). An exposure of 1.5 ng/m^3 is equivalent to about 0.00006 fibers > 5.0 μm long/cm^3. Not surprisingly, high ambient exceptions do occur; for example, regions 6 miles distant from the mining site in Asbestos, Quebec, are subjected to ambient air concentrations of asbestos fibers that are sometimes as high as those found in areas bordering the mines.

Recommendation 5: Transmission electron microscopy (TEM) is the preferred method of analysis for environmental fibers. Concentrations should be expressed in fibers/cm^3, and size distributions should be described.

Recommendation 6: A standardized method for TEM analysis should be adopted by EPA. Reference laboratories for these types of analyses are desirable. EPA and the National Bureau of Standards (NBS) should work out an acceptable arrangement. Standard reference samples of asbestiform fibers are needed to allow reasonable standardization among research and testing protocols. These samples should be well characterized in terms of physical, morphological, and chemical properties.

Quantitative Risk Estimation

Data are available from several studies of workers occupationally exposed to chrysotile, amosite, or mix-

tures of chrysotile, amosite, and/or crocidolite. These data allow a model of the dose, age, and time dependence of asbestos-related lung cancer to be developed. The data suggest a relative risk model in which the asbestos-related risk of lung cancer t years from onset of exposure is independent of age and proportional to the cumulative exposure to asbestos at time $(t - 10)$ years, multiplied by the age, sex, and calendar year risk of lung cancer in the absence of exposure. The incidence can be expressed formally by:

$$I_L\,(a,y,s,t,d,f) = I_E\,(a,s,y)\,[1 + Kfd\,(t - 10)]$$

Here $I_L\,(a,y,s,t,d,f)$ is the lung cancer incidence observed or projected in a population of age a, observed in calendar year y, at t years from onset of an asbestos exposure of duration d, and at average intensity f. $I_E\,(a,s,y)$ is the age, sex, and calendar year lung cancer incidence expected in the absence of exposure. If data are available, I_L and I_E can also be smoking-specific.

Evaluation of the dose-response relationships in 11 studies of workers exposed to asbestos in textile production, asbestos product manufacturing, and insulation application suggests an average value of K_L of 0.01. Figure 2 gives a summary of all studies for which dose-response data are available. Those studies for which data exist at various doses are displayed in Figure 3. This value, or a similar value, has been estimated in major studies sponsored in the United States, Great Britain, Canada, and Europe. Dose-response data in chrysotile mining suggest a significantly lower value of K_L (one-tenth). The difference between the unit exposure risk of lung cancer in chrysotile mining and milling and chrysotile textile production or asbestos product manufacturing or use may lie in different size distributions present in the different work circumstances. Although no data exist that provide a unit exposure risk estimate for pure crocidolite exposures, the existing data do not indicate any substantial differences in K_L attributable to fiber type.

It is clear from Figure 2 that there is great uncertainty in estimates of K_L. Some of the contributing factors are uncertainties in exposure estimates, statistical uncertainties associated with limited numbers of deaths in epidemiologic studies, biases in these studies, and differences in response associated with differing fiber-size distributions or fiber type. Additional uncertainties exist in the extrapolation of risk from occupational ex-

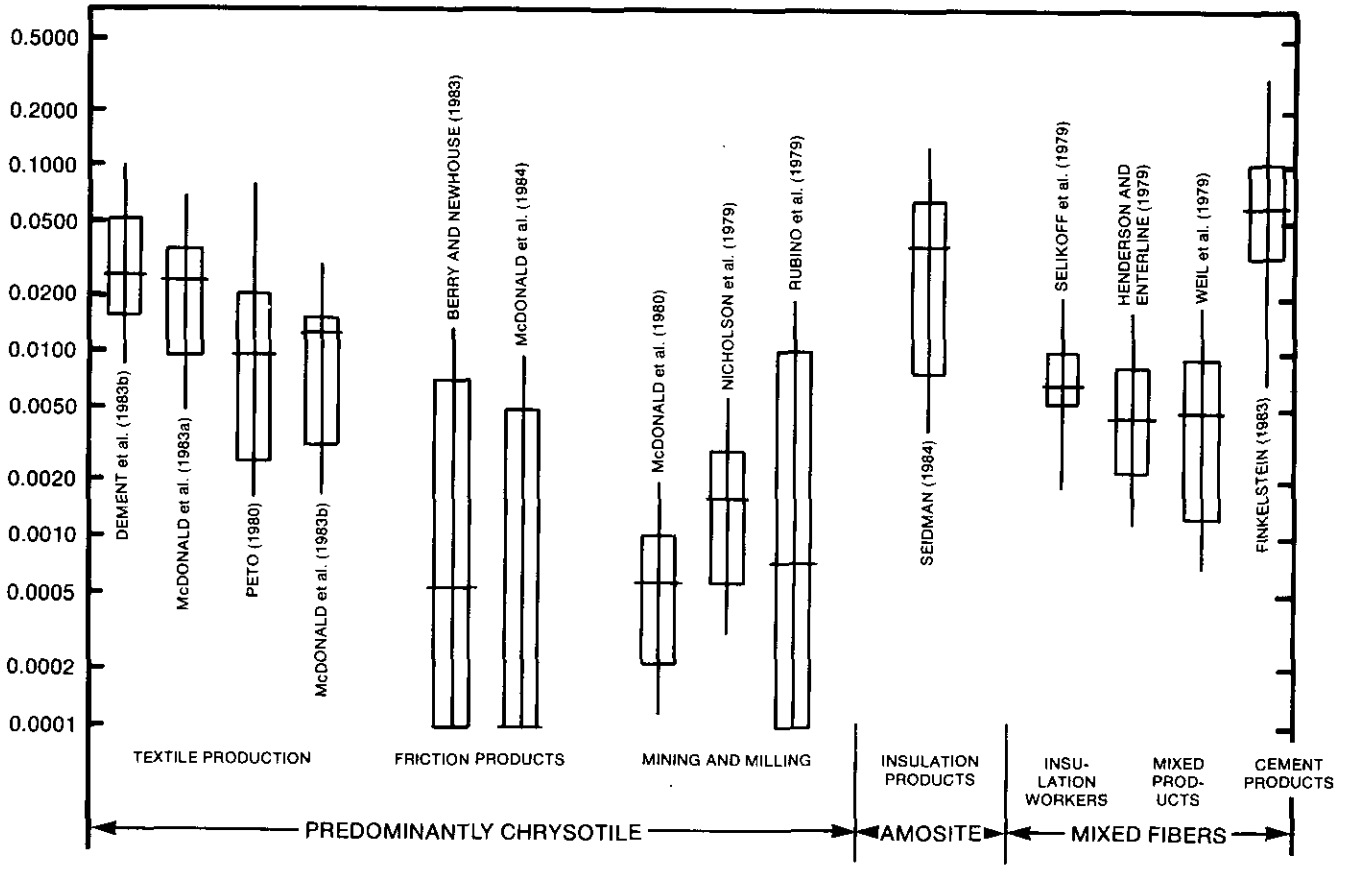

FIGURE 2. Values of K_L, the fractional increase in lung cancer per fibers/mL-y of exposure in 14 asbestos-exposed cohorts. The open bar reflects the estimated 95% confidence limits associated with measures of response. The line represents the uncertainties associated with measures of exposure, generally ± a factor of 2. (Data of W. J. Nicholson, unpublished.)

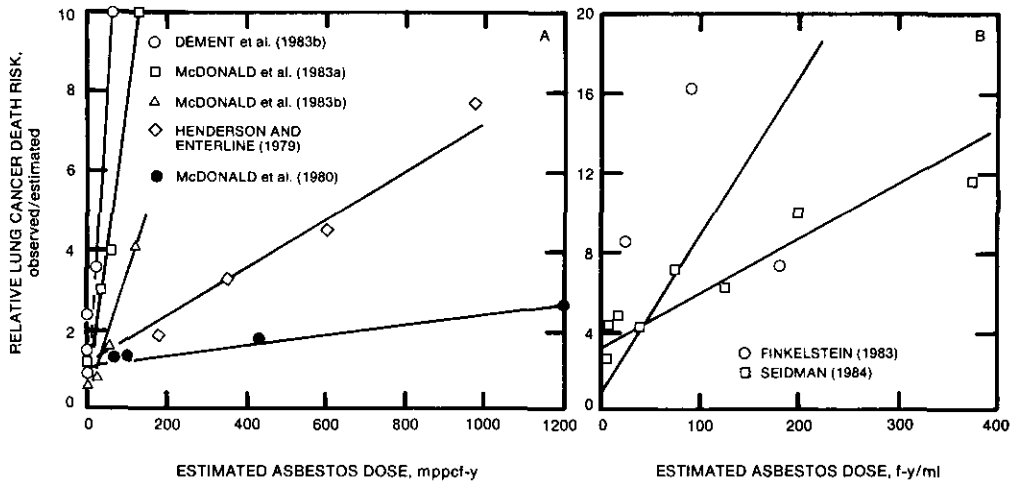

FIGURE 3. Exposure-response relationships for lung cancer observed in seven studies. Cumulative exposures are measured in terms of millions of particles per cubic foot-years (mppcf-y) or fibers per milliliter-years (f-y/mL). (Data of W. J. Nicholson, unpublished.)

posures to environmental exposures two or three orders of magnitude lower. These result from the need to convert exposures measured in fibers longer than 5 μm by using phase-contrast microscopy to fibers counted by TEM, and by the uncertainty of the appropriateness of a linear dose-response model over the range of extrapolation.

In contrast to lung cancer, mesothelioma is described by an absolute risk model. Here, it is found that risk of death per person-year increases as about the fourth power of time from onset of exposure in continuous exposure circumstances and is independent of the age of exposure. A delay may be incorporated in the model, in which case a lower exponent would apply. Far fewer data are available on the dose-response relationship, but they are consistent with a linear response with dose and with duration of employment. Estimates of mesothelioma potency on a unit exposure basis suggest that the ratio of pleural mesothelioma risk to excess lung cancer risk is roughly similar in most exposure circumstances. However, this ratio may be two to three times greater in pure crocidolite exposures. Peritoneal mesothelioma has rarely been associated with chrysotile exposure. The model for mesothelioma incidence and data on the risk relative to lung cancer allow estimates to be made of mesothelioma mortality in various exposure circumstances. However, the risk estimates, particularly at low exposures and for long periods of time, are more uncertain than those for lung cancer.

Animal data support the epidemiologic data in terms of the relative carcinogenicity of different fiber types. Injection studies (into the peritoneum) and implantation studies (onto the pleura) demonstrate that mesothelioma (and presumably lung cancer) risk is strongly related to fiber size. Fibers thinner than 0.3 μm and longer than 10 μm appear to be the most carcinogenic; thicker fibers and fibers shorter than 5 μm also demonstrate carcinogenicity, but to a lesser degree. Various other mineral fibers are carcinogenic in the above models, with length and diameter rather than surface chemistry or mineral structure as the most important factors in carcinogenic potency.

Asbestos Fibers in Ambient Air and in Buildings

Measurements of asbestos fiber concentrations in ambient atmospheres have been conducted worldwide, but comparisons are extremely difficult because of differences in methods of collection, analysis, and interpretation.

Limited measurements of concentrations in buildings with damaged asbestos surfacing materials indicate that some buildings may have 6- to 8-hr concentrations exceeding 100 times background. However, the average concentrations in the vast majority of buildings with asbestos as surfacing material do not differ significantly from background. Evidence of damage in many buildings suggests past episodic concentrations that may have exceeded 1 fiber/cm^3 for short periods of time. As asbestos concentrations in the ambient atmosphere and in buildings are usually much less than 0.001 fiber/cm^3, the concentration can be measured only by TEM fiber counts; optical microscope counts include many nonasbestos fibers, and TEM mass measurements may be dominated by particles and nonrespirable fibers that are not carcinogenic at all. It is generally agreed that the lower limit of quantitation of the membrane filter method is between 0.1 and 0.5 fibers > 5 μm in length/cm^3 for air measurements.

In 1983, the U.S. EPA Office of Toxic Substances conducted a study on airborne asbestos levels in 25 schools (116 samples). The principal conclusions were that airborne asbestos levels in school buildings with asbestos were significantly higher (about 0.009 fiber/

cm^3) than outdoor ambient levels (about 0.0003 fiber/cm^3) and that, within a school building, asbestos fibers are transported from rooms having asbestos-containing materials to rooms without these materials.

The use of the model for lung cancer risk with a value of $K_L = 0.01$ suggests that fewer than 100 lung cancers and 100 mesotheliomas per year develop in the general population from the ambient exposures that existed in previous years. The contribution of building exposures to current or future lung cancer incidence is impossible to estimate without more data on the distribution of air concentrations in a wide variety of buildings with asbestos surfacing materials.

Recommendation 7: A systematic survey of average TEM counts of airborne asbestos fibers in a random sample of schools and other buildings containing asbestos, and in buildings from which asbestos has been removed, should be done. Limited surveys of TEM fiber counts in Britain and Canada indicate that average levels in such buildings rarely exceed 0.001 fiber/cm^3, but TEM fiber counts in the United States and France suggest that substantially higher levels may sometimes occur. It is not clear whether this difference is due to the selection of buildings sampled or to differences between the methods of sampling or analysis. Collaborative analytical studies now being conducted jointly by the EPA and the British government should lead to more uniform TEM techniques. When these have been completed and more extensive surveys have been carried out, an international consensus on the significance of asbestos in buildings will probably be achieved.

There is considerable public concern over the possible dangers of asbestos in buildings, particularly schools. These data are needed to confirm or refute the suggestion that an extensive asbestos removal program is not necessary (*1,2*). When asbestos is seriously damaged or deteriorating, asbestos removal should proceed. Asbestos removal is difficult to control, however, and in buildings in which average levels are low, the exposure to both workers and occupants caused by asbestos removal may actually increase the health hazard.

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