ONCOGENIC ACTION OF SOME NONFIBROUS MINERAL DUSTS

V. N. Frash, N. N. Vanchugova, S. N. Rukoleeva, V. A. Zykova, S. A. Grebennikov, and S. V. Shcherbakov

UDC 615.277.4:622.367.6].015.4.07

KEY WORDS: mineral dusts; rats; mice; carcinogenic effect

Much research has established the oncogenic action of asbestos, glass fibers, and certain other mineral dusts (MD); it has been shown, moreover, that the oncogenicity of these substances is associated not with their chemical composition, but with their fibrous structure [10, 12, 15]. Fibers 6-20 μ long are most important, although the role of smaller fibers cannot be ruled out. Except in the case of quartz, the theoretically and practically important question of the oncogenic properties of nonfibrous MD has remained virtually unstudied [2, 6, 11].

EXPERIMENTAL METHOD

Oncogenic properties of nonfibrous dusts were studied in long-term experiments on rats and mice: antigorite (the complete chemical analog of chrysotile-asbestos), basalt (the original raw material for obtaining basalt fibers), cement (Mark 600 Portland Cement), zeolite-clinoptilolite, and γ-alumina. Fibrous dust of chrysotile-asbestos from the Bazhenovo Deposits of the Urals was used as the positive control. Dust samples were subjected to minerologic analysis and examined under light and electron microscopes. For electron microscopy the wet preparation method was used. The test samples, in the form of a suspension, were transferred to a grid with Formvar backing, and then dried and examined on the ÉVM-100B instrument at 75 kV. These dusts were injected intraperitoneally into noninbred albino rats and mice in doses corresponding to 25 mg for rats and 10 mg for mice, in 0.5 ml of sterile physiological saline, twice at intervals of one month. The first injection was given to the rats at the age of 2 months, and mice at the age of 1 month. Each group contained 100 animals, with a ratio of females to males of 1:1. Observations continued until the end of the animals' life and the material was subjected to standard histologic treatment.

EXPERIMENTAL RESULTS

In response to intraperitoneal injection of chrysotile-asbestos (CA) a high yield of abdominal mesotheliomas was observed: these tumors are characteristic of the action of asbestos and of other fibrous dusts on cells of the serous cavities [2, 7, 14]. In the present case CA induced mesotheliomas in 45% of experimental rats and in 35% of mice (Table 1): a sarcomalike type of these tumors was predominant (Fig. 1). Confirmation of the decisive role of the fibrous structure in the genesis of tumors of this type was given by their absence in response to injection of antigorite dust, which is identical in its chemical composition to CA but contains virtually no fibrous particles. Mesotheliomas likewise were not induced by cement dust, which also is distinguished by a low content of fibrous particles.

Research Center for Preventive Medicine and Protection of the Health of Industrial Workers, Ekaterinburg. (Presented by Academician of the Russian Academy of Medical Sciences B. T. Velichkovskii.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 114, No. 12, pp. 648-651. December, 1992. Original article submitted June 23, 1992.

 0007-4888/92/0012-1878$12.50

TABLE 1. Frequency of Abdominal Mesotheliomas in Rats and Mice Under the Influence of Various Fibrous and Nonfibrous Mineral Dusts

Dust injected	Species of animal	Fibrous particles		Number of rats*, mice*	Mesotheliomas	
		total, %	including 6-20 μ long		number	%
Chrysotile-asbestos	Rats	48.8	95	60	27	45.0
Antigorite	Rats	0.4	50	60	—	—
Basalt	Rats	0.5	0	45	4	8.9
Cement	Rats	2.5	28	60	—	—
Zeolite	Rats	1.4	100	98	6	6.1
Chrysotile-asbestos	Mice	20.0	70	60	21	35.0
γ-alumina	Mice	0	0	68	8	11.7

Legend. *) Effective number of animals given for groups with mesotheliomas, for the rest — number of rats surviving 6 months; data for frequency of tumors after injection of basalt, zeolite, and γ-alumina differ statistically significantly from background level ("φ" method, $p < 0.001$) and from data from chrysotile-asbestos ($p < 0.001$, Student's test).

The other nonfibrous dusts investigated, namely basalt, zeolite, and γ-alumina, caused the development of mesotheliomas, but in a much smaller percentage of cases than with CA (8.9 and 6.0% in rats and 11.8% in mice). Of the 16 mesotheliomas found, 14 were of the sarcomalike type. It will be recalled that the virtually complete absence of fibrous particles in specimens of basalt, zeolite, and γ-alumina was revealed under both light (Table 1) and electron (Fig. 2) microscopes. Incidentally, like other workers [7-9], we also did not observe spontaneous mesotheliomas during almost 600 autopsies on intact rats and 280 on mice, surviving until natural death. There was no difference between the groups in the frequency of tumors in other situations. It will also be recalled that we found no malignant tumors of the uterus in rats either in the control or in the experiment, in agreement with data in the literature on the low frequency of such tumors in this breed of animals obtained from Rappolovo [1, 5]. This remark is important, for malignant tumors of the uterus are found quite frequently in Wistar rats, and they usually metastasize into the abdominal organs. These metastases can be regarded as abdominal mesotheliomas [11].

The latent periods of tumors arising in response to the action of nonfibrous dusts (basalt and zeolite) was significantly longer than after injection of CA (19.3 ± 1.2 months for nonfibrous dusts, 10.2 ± 0.6 months for asbestos, data for rats).

The chemical composition and some biologically important physicochemical parameters of the nonfibrous dusts investigated are given in Table 2. No consistent differences with respect to these parameters could be found between dusts inducing and not inducing mesotheliomas. So far as carcinogenically active impurities are concerned, the content of benz(a)pyrene and of metals (lead, cadmium, arsenic, and so on) was not significant and could not explain the differences between the oncogenic effects of basalt, zeolite, and γ-alumina, on the one hand, and antigorite and cement, on the other hand.

Probably data obtained in recent years showing that they have mutagenic properties can probably be regarded as an indication of the potential carcinogenicity of basalt and the zeolites [2-4]. The first nonfibrous carcinogenic dust to have been discovered can evidently be considered to be crystalline silica (quartz) dust. Experts of the International Agency for the Study of Cancer assessed the existing information as "sufficient" to draw the conclusion that quartz is carcinogenic for animals [13]. Data on its oncogenicity, moreover, were obtained mainly after its injection into the

TABLE 2. Some Chemical and Physicochemical Parameters of Nonfibrous Dusts Studied

Substance	Parameters										
	ζ-potential mV	specific surface m /g	SiO_2, %	Al_2O_3, %	CaO, %	MgO, %	Fe, %	TiO_2, %	Na_2O, %	K_2O, %	H_2O, %
Antigorite	38,0±5,2	12,8	39,7	3,2	1,1	40,3	1,0	—	0,1	0,1	12,2
Basalt	23,7±5,5	4,2	50,0	15,0	8,9	4,8	14,8	1,35	—	—	—
Cement	17,5±6,3	1,0	60,0	5,0	25,5	5,0	3,3	—	0,8	—	—
Zeolite	35,0±2,3	67,0	70,9	11,5	1,2	0,37	0,81	0,17	2,7	4,6	—
γ-alumina	42,3±3,1	69,9	1,5	97,3	0,8	—	0,1	0,3	—	—	—

Legend. *) Effective number of animals given for groups with mesotheliomas, for the rest – number of rats surviving 6 months; data for frequency of tumors after injection of basalt, zeolite, and γ-alumina differ statistically significantly from background level ("φ" method, $p < 0.001$) and from data for chrysotileasbestos ($p < 0.001$, Student's test).

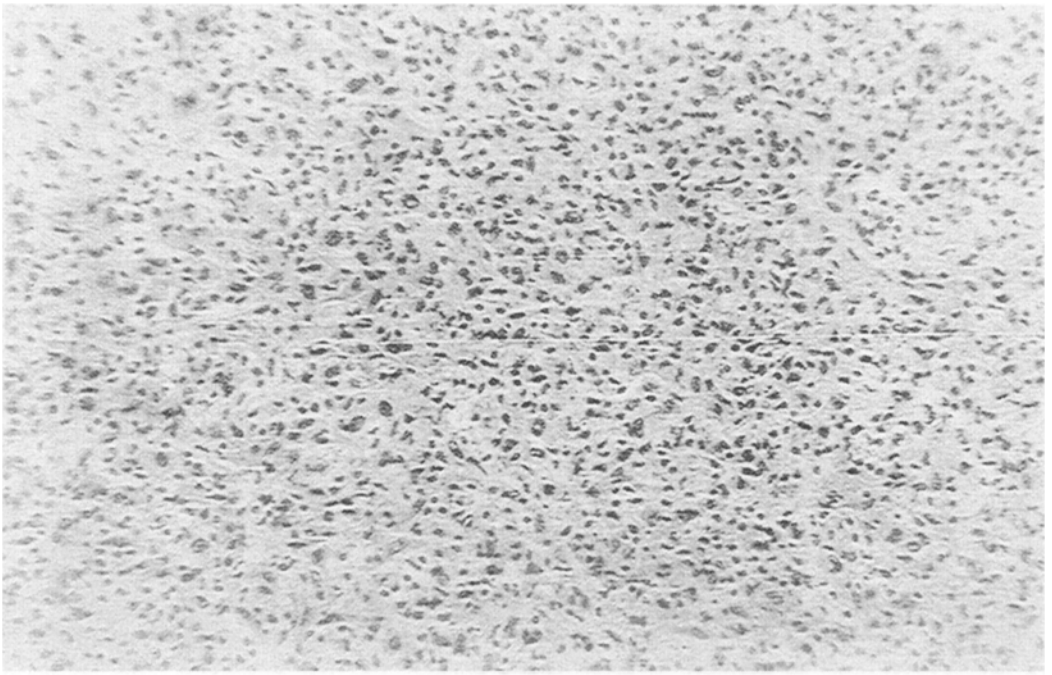

Fig. 1. Polymorphocellular sarcomalike mesothelioma (hematoxylin-eosin, 140×).

serous cavities. Considering that amorphous silica is evidently noncarcinogenic [13], it can be assumed that here, just as in the case of asbestos, structural or physicochemical features are more important than chemical composition.

The data given in this paper indicate a carcinogenic action of three other types of nonfibrous dusts, namely basalt, zeolite, and γ-alumina. The natural suggestion that in the case of the latter a small quantity of fibrous impurities, invariably present in natural MD, may play a role, is disproved by the data in Table 1: cement and antigorite dusts contain a percentage of fibrous particles which was not less than that in basalt and zeolite (up to 2.5% for cement compared with 1.4% for zeolite), but nevertheless, tumors were not observed to develop after injection of antigorite and cement.

Thus besides quartz, there are at least three other types of oncogenically active nonfibrous dusts, namely basalt, zeolite, and γ-alumina. The precise properties of the mineral skeleton with which this effect is connected could be important both for the theory of carcinogenesis and for the prediction of potential carcinogenicity of agents of this type for man, and for the development of preventive measures.

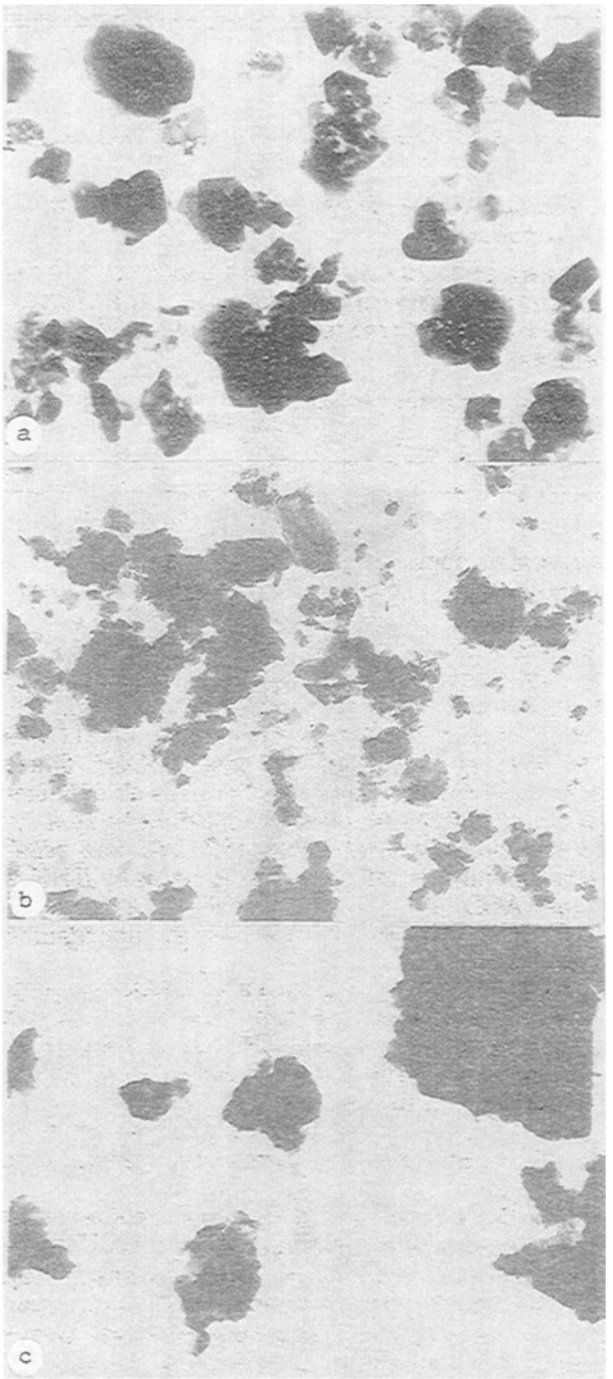

Fig. 2. Electron microscopy of basalt (a – 13,000×), zeolite-clinoptilolite (b – 13,200×), and γ-alumina (c – 15,600×) dust.

REFERENCES

1. V. N. Anisimov, V. A. Aleksandrov, and V. F. Klimashevskii, Vopr. Onkol., No. 1, 64 (1978).

2. N. N. Vanchugova, A. V. Karaulov, and V. N. Frash, Epidemiology, Prophylaxis, and Early Diagnosis of Malignant Tumors [in Russian], Tomsk (1987), pp. 105-107.
3. B. T. Velichkovskii, L. G. Korkina, and T. B. Suslova, Theoretical and Applied Problems of Introduction of Natural Zeolites in the National Economy of the RSFSR [in Russian], Kemerovo (1988), pp. 90-91.
4. S. G. Domnin, S. V. Shcherbakov, A. S. Fomina, et al., Natural Zeolites in the National Economy [in Russian], Novosibirsk (1990), pp. 174-176.
5. E. A. Ird, I. O. Smirnova, and V. S. Turusov, Éksp. Onkol., No. 4, 17 (1983).
6. L. N. Pylev, R. G. Bostashvili, and T. F. Kulagina, Gig. Truda, No. 5, 29 (1986).
7. L. N. Pylev, T. F. Kulagina, and E. P. Grankina, Gig. San., No. 8, 7 (1989).
8. D. L. Coffin, L. D. Palekar, and P. M. Cook, Toxicol. Lett., **13**, 143 (1981).
9. W. C. Heuper, J. Nat. Cancer Inst., **33**, No. 6, 1005 (1964).
10. F. Pott, Biological Effects of Mineral Fibres, Lyon (1980), pp. 261-272.
11. F. Pott, M. Roller, and U. Liem, Non-Occupational Exposure to Mineral Fibers, Lyon (1989), pp. 173-179.
12. M. F. Stenton, M. Layard, and A. Tegeris, J. Nat. Cancer Inst., **58**, 587 (1977).
13. Silica and Some Silicates (IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans), Vol. 42, Lyon (1987).
14. J. C. Wagner, Ann. N.Y. Acad. Sci., **132**, 1, 505 (1965).
15. J. C. Wagner, G. Berry, and F. D. Pooley, Brit. Med. Bull., **36**, No. 1, 53 (1980).