Metal Interactions in Carcinogenesis: Enhancement, Inhibition

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Metals constitute a fundamentally important part of the total human environment. Since human exposure often involves complex mixtures of metal compounds and, possibly, organic compounds which may be carcinogenic per se, interactions between these compounds may add significantly to human cancer risk. Our present knowledge about these kinds of interactions is very limited. The best investigated area is benzo(a)pyrene (BP)-metal oxide particle interactions in respiratory carcinogenesis in the hamster. Metal oxide particles were also shown to modify the carcinogenic effect of nitrosamines. Several reports describe experiments in which selenium compounds exerted a generally anticarcinogenic and antimutagenic activity. Inorganic arsenic compounds, which are accepted to be carcinogenic in man, have so far been negative in animal experiments except for one recent suggested report. Several authors have, however, suggested that these compounds may act as cocarcinogens due to their inhibition of DNA repair, although animal experiments to demonstrate a cocarcinogenic effect of arsenic compounds have been negative so far, except for one preliminary report. The concentration of zinc in the diet seemed to influence both transplanted tumor growth and the carcinogenicity of several organic compounds, and the possibility of a correlation between dietary zinc and certain cancer forms in man has been suggested. Protection against development of Leydigiomas usually induced by cadmium injection was afforded by simultaneous injection of zinc salts. Nickel carcinogenesis has been reported to be antagonized by manganese, and synergism between Ni and organic carcinogens, e.g. BP, has been demonstrated. There is no firm evidence that lead may be a cocarcinogen, although some limited experimental evidence is available. Oxidizing agents have been demonstrated to increase, and reducing agents to antagonize, the mutagenic effect of chromium compounds in vitro. The content of carcinogenic and other metals in asbestos has been suggested to modify the carcinogenic properties of asbestos. Since much of the information availabel at present is suggestive, further research on these interactions as well as other possible interactions in metal carcinogenesis is needed. Studies should be made both in well defined in vitro systems and in relevant animal models.

Introduction

About 80 of the 104 identified members of the periodical table of the elements are usually considered metals. They comprise a fundamentally important part of our natural environment. Considerable addition to natural human metal exposures may occur both from work and from general environmental pollution. Emissions from automobiles, from combustion of coal and oil, as well as from mining and other industrial activities contain complex mixtures of metals and some incompletely combusted organic materials. Interactions between these compounds may take place and increase the risk of adverse health effects. In some populations exposed to such complex mixtures, increased incidence rates of human cancer have been detected in epidemiological studies. However, exposure to only one agent has often been studied and statistically correlated with increased incidence of malignancy. In the general environment humans are always exposed to complex mixtures of substances in relatively low concentrations. The work environment is sometimes believed to present more clear-cut exposures to single metal compounds. However, this is probably more an exception than a rule, and workers may be exposed to very complex

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mixtures of metallic compounds.

A good example of this is the environment at some metal smelters and refineries. Workers in this environment have recently been shown to retain increased lung burdens of a number of elements such as As, Sb, Pb, Cd, Cr, Co, and La even several years after retirement (1,2). An increased incidence of lung cancer among such smelter workers has been statistically associated with exposure to arsenic (3). However, it cannot be excluded that the other metals found may also be involved in development of malignant lung disease (P. O. Wester, D. Brune, and G. F. Nordberg, Arsenic and selenium in tissues of smelter workers in relation to diagnosis, to be published). Interactions among metals have previously been reviewed in relation to noncarcinogenic effects (4) and in relation to carcinogenesis (5,6). This review will focus on the role of metals as factors enhancing or inhibiting carcinogenesis and mutagenesis in experimental systems in relation to experience from human epidemiological studies and will try to identify pertinent research needs.

Arsenic

Human exposures to inorganic arsenic compounds have been associated with an increased incidence of cancer. Occupational exposure in the smelting and refining of copper ore and in the manufacturing of arsenic containing insecticides has given rise to lung cancer. The medicinal use of trivalent inorganic arsenic compounds has been associated with the development of skin cancer. This form of cancer is also more commonly found in populations exposed to arsenic through drinking water. Angiosarcoma of the liver and malignancies of lymphatic tissues have also been reported to be associated with exposure to arsenic, but the evidence is not conclusive.

Carcinogenic effects of arsenic has recently been reviewed (7,8).

Although human exposures to arsenic often involve simultaneous exposure to a number of other agents, interactions have not been clearly demonstrated. A possible interaction with SO_2 was examined by Lee and Fraumeni (9), who reported a significant increase in lung cancer mortality among arsenic exposed workers. When dividing the studied population according to exposure levels at different working areas into heavy, medium and light exposure to arsenic, 6.7, 4.8, and 2.4 times the expected mortality from respiratory cancer was found. Workers were also exposed to SO_2, and similar division according to exposure to SO_2 gave 6.0 to 2.6 times the mortality expected. Working

areas with a heavy exposure to arsenic were also medium SO_2-exposed, and heavy SO_2 exposure areas were medium arsenic-exposed. The authors concluded that the worker with the highest risk of respiratory cancer had a heavy exposure to arsenic and a medium exposure to SO_2. Pershagen et al. (3) noted a significant increase in mortality (2-3 times) from respiratory cancer in a population around a metal smelter emitting arsenic and several other metals. The increased mortality was no longer significant when employees at the plant were excluded.

Chromosomal anomalies have been induced in mammalian cells after arsenite and arsenate exposure *in vitro* (10,11) and have been observed in cultured human lymphocytes after *in vivo* exposure to arsenic compounds due to medical use (12,13) or occupational exposure (14,15).

It was claimed (16) that arsenic compounds are mutagenic in bacteria, but reinvestigation by others (17,18) showed that both in bacteria (*E. coli* and *Salmonella*) and mammalian cells (Chinese hamster V79) arsenite was not mutagenic. Due to inhibition of error-prone DNA repair, arsenite lowered the rate of UV-induced mutations in *E. coli* (19). It has been suggested that arsenic may substitute for phosphorus in the phosphorylation of nucleotides (12,13,20), although evidence for this has not been presented. Jung et al. (21) found that arsenic enhanced the UV sensitivity of human epidermal fibroblasts. Several reports describe inhibiting effects of arsenic on enzymes, especially those containing SH-groups necessary for activity.

Beckman et al. (14) and Nordenson et al. (15), who noted an excess of chromosome aberrations in workers exposed to arsenic, stressed that the individual with the highest rate of aberrations had also been exposed to lead and selenium and that the correlation between arsenic exposure and frequency of breaks was rather poor. Their data also indicated that arsenic exposure in combination with smoking caused more breaks than smoking or arsenic exposure alone.

Published animal experiments concerning carcinogenesis of arsenic compounds do not allow a definite conclusion that arsenic is a carcinogen in experimental animals (7) in spite of the fact that there is sufficient epidemiological evidence to declare arsenic as a carcinogen in man. In light of the previously mentioned effects of arsenic on DNA-synthesis, it is possible that arsenic is a cocarcinogen, inhibiting repair of DNA lesions produced by other carcinogens. Some studies designed to examine this possibility have been negative. Boutwell (22) found no initiating effect of potassium arsenite followed by croton oil in induction of skin cancer in mice.

Potassium arsenite was not cocarcinogenic after DMBA[7,12-dimethylbenz(a)anthracene] application in the same study. Initiation with DMBA followed by promotion with croton oil was not influenced by additional application of arsenite. Barone et al. (23), testing the same substances, also concluded that arsenate was not cocarcinogenic. Kroes et al. (24) found no synergism between diethylnitrosamine and arsenate with regard to tumors in rats.

When discussing possible interactions involving arsenic, two recent preliminary studies are of interest. Ishinishi et al. (25) reported that intratracheal instillation of arsenic trioxide, arsenic containing copper ore, and flue dust from metal refining might act as cocarcinogens on benzo(a)pyrene (BP)-induced lung cancer in rats. Different groups of rats received 15 weekly intratracheal instillations of BP alone or in combination with copper ore, flue dust, or pure As_2O_3. Control groups received the same amounts of copper ore, flue dust, pure As_2O_3, or the instillation vehicle, 0.9% NaCl. The groups (7-10 rats/group) were too small to yield significant differences: Numbers of malignant lung tumor (squamous cell carcinoma + adenocarcinoma)-bearing animals were: 1/7 in the BP group (14.3%) and the sum 8/27 in the three groups receiving BP plus arsenic (ore/dust/As_2O_3) (29.6%). Adenocarcinoma (1/7) was found in the group receiving flue dust without BP, and in the other control groups no malignant tumors were found. An evaluation of this study is difficult because of the small number of animals used in the various groups and, therefore, an enhancement of BP-carcinogenesis by arsenic cannot be regarded as established. Ivankovic et al. (26) gave a single intratracheal instillation of calcium arsenate together with copper sulfate and calcium oxide. In 15 rats surviving the treatment, nine lung tumors developed. Controls given saline had no tumors.

Other studies suggest an inhibiting effect of arsenic compounds in tumorigenesis. Schrauzer and Ishmael (27) found that arsenite (10 ppm in drinking water) significantly reduced the incidence rate of spontaneous mammary cancer after 15 months in virgin female C3H/St mice to 27% compared with 82% in controls, although tumor growth was significantly enhanced. Arsenic-treated mice gained 15% less weight during the experiment than did control mice and an unspecific effect related to food consumption might have been of importance.

Kanisawa and Schroeder (28) fed mice on a diet low in trace elements in an environment where external metal contamination was avoided and added different metal salts to the drinking water. In a group given 5 µg/ml of arsenite, 11.9% of the mice died with tumors compared to 34.5% in the control group. The largest part of the difference was for benign tumors; for malignant tumors the numbers were 10.6% for the control group and 7.2% for the arsenic-exposed group.

Milner (29) investigated the effect of arsenic trioxide (0.01% in drinking water) on methylcholanthrene (MC)-induced cutaneous tumors in three strains of mice. Application of 10% MC in paraffin discs to shaven skin was used for tumor initiation. Promotion was achieved by grafting to syngeneic recipients after 2-3 weeks. In different subexperiments arsenic drinking water was given either during initiation, during promotion or during both initiation and promotion for DBA and Balb/C mice, but only during initiation and promotion for CxC3H. CxC3H mice drank arsenic water during 8 weeks, DBA mice during 4 weeks, and Balb/C mice during 2 weeks prior to MC treatment. Recipients drank arsenic water only during 8 weeks of observation after grafting. In Balb/C mice arsenic had neither cocarcinogenic nor anticarcinogenic effect, but in CxC3H mice arsenic produced a significant reduction in MC induced carcinogenesis. In DBA mice a nonsignificant increase in carcinogenesis was observed. The differences in arsenic treatment of the different mouse strains makes it difficult to evaluate this study.

For a long time arsenic has been known to possess an antagonistic effect against general toxicity and also against teratogenic effects of selenium and vice versa (30). No reports are found concerning antagonistic effects between arsenic and selenium with regard to carcinogenicity or mutagenicity.

The possibility of such an effect, however, was suggested by recent studies of metal concentrations in lungs from smelter workers. Workers that died with malignancies had higher As/Se ratios than those from the same environment who died from other causes. Concentrations of arsenic were the same in these groups (Wester, unpublished).

Walker and Bradley (31) reported synergistic effects of sodium arsenate and selenocysteine on chromosomal crossing over in *Drosophila melanogaster*, which they tentatively ascribed to incorporation of arsenate into DNA and selenocysteine into chromosomal protein. Moutschen and Degraeve (32) found synergistic effects between the organic arsenical *m*-diamino-*p*-dioxyarsenobenzene methylene sulfoxylic acid and ethyl methanesulfonate in induction of chromosome anomalies in barley. Škrám and Bencko (33) reported that arsenic significantly increased the yield of dominant lethal mutations in F_3 of mice after treatment with TEPA [tris (1-aziridinyl) phosphine oxide] and suggested that the enhancing effect of arsenic was due to blocking of SH-groups in enzymes involved in DNA repair (34).

Conclusions on Arsenic

In many cases human exposure to arsenic and its compounds occurs in combination with other metals, SO_2 or organic carcinogens. However, conclusive evidence is not yet available concerning enhancing or antagonistic effects of arsenic compounds in combination with other metals or carcinogens. One reason for the difficulties in studying interactions involving the carcinogenic effects of arsenic is the absence of a suitable animal model. Interestingly two recent studies employing combinations of arsenic compounds and other substances furnish suggestive evidence of a carcinogenic effect in animals. Since arsenic compounds might act as cocarcinogens, further studies *in vivo* and *in vitro* with arsenic compounds and other carcinogenic compounds in combination should be carried out. In particular combinations of agents which occur in human exposure situations should be examined. These include combinations of arsenic compounds with BP, SO_2, selenium, cadmium, copper, zinc, lead, and several other metals that occur in emissions from mining operations, oil and coal burning.

Selenium

Selenium is an essential trace element, which is highly toxic in higher concentrations. It was originally thought to be a carcinogen (35,36), but extensive reinvestigation did not support this (37,38). A review on carcinogenesis experiments with selenium in animals has been given in an IARC publication (39). Some evidence actually suggests selenium to possess antitumorigenic activities: Schrauzer and Ishmael (27) demonstrated that 2 ppm selenite in drinking water for 15 months lowered the incidence of spontaneous mammary cancers in female virgin C3H/St mice down to 10% compared with 82% in controls. Selenium also inhibited the growth rate of spontaneous tumors. A later report (40) described that $ZnCl_2$ abolishes the cancer-protecting effect of selenite. In tumor induction experiments with several organic carcinogens dietary selenite significantly reduced the number of tumors (Table 1).

In addition to the dietary experiments summarized in Table 1, some nondietary experiments have been reported. Shamberger and Rudolph (46) dem-

Table 1. Anticarcinogenic effects of selenium compounds.

Animal	Carcinogen	Selenium treatment	Result	Reference
Female OSU brown Rats (20 per group)	N-2-Fluorenyl acetamide, 150 ppm in food	Selenite, 2.5 ppm in food	80% tumors (320 days)	(41)
		0	100% tumors (320 days)	
Male Sprague-Dawley rats	3-Methyl-4-dimethyl-aminoazobenzene, 0.05%, in food	Selenite, 6 ppm in in food	9/14 animals with liver tumors (12 weeks)	(42)
		Selenite, 6 ppm in water	7/15 animals with liver tumors (12 weeks)	
		0	11/12 animals with liver tumors (12 weeks)	
Male Sprague-Dawley rats	1,2-Dimethyl hydrazine, inj. 20 mg/kg, 1 × 18 weeks	Selenite, 4 ppm in water	6/15 animals with colon tumors	(43)
		0	13/15 animals with colon tumors	
Male Sprague-Dawley rats	Methylazoxymethanol acetate, inj. 20 mg/kg, 1 × 18 weeks	Selenite, 4 ppm in water	14/15 animals with colon tumors (total 42 tumors)	(43)
		0	14/14 animals with colon tumors (total 73 tumors)	
Rats (unspecified)	m-Methyl-p-dimethyl-aminoazobenzene, 0.064%, 2 × 4 weeks, in food	Selenite, 5 ppm in food, 4 weeks between weeks with carcinogen	7/15 animals with liver tumors	(44)
		0	4/13 animals with liver tumors	
Female albino ICR swiss mice (36 animals per group)	DMBA-croton oil (skin painting)	Selenite, 0.1 ppm	60% animals with tumors after 20 weeks	(45)
		Selenite, 0.1 ppm in food	78% animals with tumors after 20 weeks	
		Selenite, 1.0 ppm in food	35% animals with tumors after 20 weeks	
		0	72% animals with tumors after 20 weeks	
Female albino ICR swiss mice (36 animals per group)	Benzopyrene (skin painting)	Selenite, 0.1 ppm	18/35 animals with tumors after 22 weeks	(46)
		Selenite, 0.1 ppm in food	26/36 animals with tumors after 22 weeks	
		Selenite, 1.0 ppm in food	16/36 animals with tumors after 22 weeks	
		0	31/36 animals with tumors after 22 weeks	

onstrated that sodium selenide, when painted together with croton oil on the skin of mice which had been initiated with dimethylbenzanthracene, reduced the total number of skin tumors observed from 132 in 39 control animals only treated with croton oil down to 9 in 30 animals treated with both croton oil and selenide. This finding was confirmed by Riley (47), using the same compounds. Shamberger (45) reported that selenide also decreased the carcinogenic effect of 3-methylcholanthrene in mice. Both compounds were applied by skin painting. Exon et al. (48) investigated the effect of dietary selenium on tumor induction by the oncogenic Rauscher leukemia virus, and found no protective effect.

Several studies describe lower serum selenium values in cancer patients than in persons not suffering from a malignant disease (49-52). Therapy elevated serum selenium levels in cancer patients (50). It cannot be concluded whether these effects had any relationship to the proposed anticarcinogenic effects of selenium compounds.

It has been reported in demographic investigations that cancer mortality may be inversely related to bioavailability of selenium (27,53-55); however, because of several problems in these studies, including difficulties in the geographical correlation of Se intakes with cancer mortality, these studies cannot be regarded as conclusive. In smelter workers exposed to arsenic and other metals, tissue selenium concentrations were lower in workers dying from malignancies (Wester, unpublished data) compared with those dying from other causes.

Selenium compounds are weak mutagens in bacteria (56,57) and cause chromosome aberrations (56,58) and elevated SCE (sister chromatic exchange) rate in human cells (59). But some other reports describe antimutagenic effects of selenium compounds in vitro: selenite decreased the mutagenicity of 2-acetylaminofluorene, N-hydroxyaminofluorene, and N-hydroxy-2-acetylaminofluorene in the Ames test (60). Na_2SeO_3 significantly lowered the chromosome breakage in human lymphocytes treated in vitro with DMBA (61).

Conclusions on Selenium

Possible carcinogenic properties of selenium are not completely ruled out, especially since selenium compounds have been shown to be weakly mutagenic in bacteria and cause chromosome anomalies in mammalian cells. Several reports describe antitumorigenic activity of selenium in experimental animals. Human data are presently inconclusive, but suggest the possibility of an anticarcinogenic effect of high dietary selenium. Further research is needed, employing adequate epidemiological methods in population groups exposed to carcinogens. Experiments with known mutagenic metals and selenium in combination should be carried out both in vitro and in animal models. Further studies of the role of dietary selenium at concentrations relevant for the human situation would also be of value.

Zinc

Zinc is an essential trace element. It is incorporated into several metalloenzymes and is necessary for DNA, RNA, and protein synthesis in mammalian cells. Zinc accelerates wound healing, is involved in membrane stabilization, and is mitogenic to T-lymphocytes. Zinc deficiency leads to impairment of cell mediated immunity. In animal experiments, the only carcinogenic effect of zinc reported is induction of testes tumors after intratesticular injection (62). There are no indications that occupational exposure to zinc leads to increased cancer risk. Zinc protects experimental animals against the necrotizing activity in the testes, of injected cadmium, and also against cadmium induced Leydigioma after total testes atrophy. This will be discussed in detail in the section about cadmium.

In the following, experiments investigating the effect of dietary zinc supplementation on tumor growth and chemical carcinogenesis will be reviewed.

Petering et al. (63) investigated the effect of dietary zinc on the growth of Walker 256 carcinosarcoma in the rat and found a linear positive relationship between tumor growth and dietary zinc between 40 and 640 μg zinc/day per animal. This has been confirmed by several other groups. The experiments are summarized in Table 2. In these experiments, the control groups of rats or mice received either 50-80 μg/g zinc in the food or a zinc-free diet and 50-60 μg/ml zinc in water. This is more than the amount needed for optimal growth.

Several reports describe that dietary zinc restriction decreases the growth of a range of transplanted tumors in rats and mice (Table 2).

Barr and Harris (68) grew the P 388 leukemia as an ascites tumor in male DBA/2 mice fed a zinc-deficient diet (0.8 ppm zinc). They found a significant reduction in tumor cell growth when animals were given zinc-free water compared with animals given water containing 670 ppm zinc. Since a zinc-adequate group was not included, evaluation of this study is difficult.

Intraperitoneal injection of 3 × 0.5 mg zinc acetate at 1, 3, and 5 days after IP injection of L1210 leukemia cells into BDF mice reduced the

mortality due to tumor development from 100% in the control group not receiving zinc injections down to 30%. In a similar experiment, where BW5147 lymphatic leukemia cells were injected into AKR/J mice, repeated zinc injections gave only a marginal increase in survival time without affecting the mortality (69).

A single report describes that very high dietary zinc inhibits transplanted tumor growth (Table 2). The effect of dietary zinc supplementation on chemical carcinogenesis has been investigated in several reports with a number of chemical carcinogens. The experiments are summarized in Table 3.

Epidemiological evidence relating to the role of zinc in carcinogenesis is very limited and difficult to interpret. In some reports concerning demographic data, it has been suggested that high dietary zinc may increase the incidence of gastric cancer (76,77).

Schrauzer et al. (78) used data from their own studies and from those of Kubota et al. (79) and calculated correlation coefficients between concentrations of zinc in whole blood and female breast cancer mortalities in several states and major cities in the U.S. In these studies the authors claimed to have found an association between high zinc intake or high blood zinc and a high incidence of breast cancer. However, these macroepidemiological studies suffer from the weaknesses usually encountered in such studies. The difficulties in obtaining a true geographical congruence between the zinc data and the mortality data should be appreciated as well as the difficulties in finding appropriate mathematical-statistical means of treating the data which were not collected particularly for the purpose of this study (78). It may well be that dietary zinc intake is of importance for the development of human can-

Table 2. Effect of dietary zinc on transplanted tumor growth in relation to control animals given "normal" zinc (not shown).

Animal	Dietary zinc status	Transplanted tumor type	Result[a]	Reference
Female Wistar rats	500 mg/g food 0.4 µg/g food	Hepatoma induced by 3'-methyl- 4-dimethylaminoazobenzene	i i	(64)
Male Sprague- Dawley rats	Zinc-free 500 µg/g water	Walker 256 carcinosarcoma	i	(65)
Male Sprague- Dawley rats	Zinc-free	Walker 256 carcinosarcoma	i	(66)
Male CDF mice	Zinc-free	L5178yt leukemia L1210 leukemia P388 leukemia	i (i) –	(67)
Male C57BL/6	Zinc-free	Lewis lung carcinoma	i	(67)

[a] i = inhibition; – = not statistically different from control.

Table 3. Effect of dietary zinc on local chemical carcinogenesis in relation to controls with "normal" zinc intake (not shown).

Animal	Dietary zinc status	Carcinogen	Application	Result[a]	Reference
Male Charles River rats	7 µg/g food	Methylbenzylnitrosamine	Gavage (esophagus)	e	(70)
Female Swiss mice	0.4 µg/g food > 500 µg/g food	3-Methylcholanthracene	Skin painting	i i	(71)
Sprague-Dawley rats	0.23 mmole/kg food[b] 3,06 mmole/kg food[b]	4-Nitroquinoline N-oxide	Painting of palatal mucosa	r a	(72)
Syrian golden hamsters	21.9 µg/g zinc in food + 100 µg/g zinc in water[c]	Dimethylbenzanthracene	Painting of cheek pouch	i	(73)
Syrian golden hamsters	22.1 µg/g zinc in food + 100 µg/g in water[c]	Dimethylbenzanthracene	Painting of cheek pouch	i	(74)
Wistar rats	250 µg/g water	Dimethylbenzanthracene	Implant in submandibular gland	r	(75)

[a] Results: e = enhancement i = inhibition; a = acceleration; r = retardation.
[b] Drinking water contained 0.1 µM zinc.
[c] Control animals received the same amount of zinc in food + zinc-free water.

cer, but presently available data can by no means be regarded as conclusive evidence.

Conclusions on Zinc

Dietary zinc deficiency in the rat (7 μg/g or less in the diet) leads to suppression of transplanted tumor growth and possibly to reduced chemical carcinogenesis. Dietary zinc supplementation (> 200 μg/g) leads to equivocal changes in transplanted tumor growth and in carcinogenic response. The significance of higher or lower dietary zinc in relation to human cancer remains unresolved. Injected zinc offers protection against cadmium-induced testicular tumors in mice and rats. Further epidemiological research concerning the role of dietary zinc in carcinogenesis is recommended, since the human dietary zinc intake shows great variations. Further animal studies including marginally adequate zinc intakes would be of interest since most of the animal experiments reported so far used control concentrations higher than necessary.

Such studies should always include untreated control groups given the same dietary zinc concentrations as carcinogen-treated animals, and the serum and liver concentrations of zinc and also of copper should be measured in all groups during the experimental period.

Nickel

Slightly soluble nickel compounds are carcinogenic in animal experiments. Occupational exposure to nickel compounds have led to nasal, laryngeal and lung cancer in humans. Reviews on nickel carcinogenesis have been published by Sunderman (62,80) and the National Academy of Sciences (81). The carcinogenic properties of nickel compounds were recognized many years ago, and a considerable amount of information including experimental work concerning nickel carcinogenesis is available also in relation to other compounds.

Maenza et al. (82) observed a synergistic action between Ni_3S_2 and BP after im application, since the time lag for induction of sarcomas was significantly shortened by simultaneous application of both carcinogens, a result which could not be obtained by increasing the dose of one of the carcinogens in single applications. They injected either 10 mg of Ni_3S_2, 5 mg of BP, or both, deep into both thighs of the rats. These (high) doses caused sarcomas in all animals in all groups, but the mean latency time before initial palpation of tumors was 18 ± 3 weeks for the group receiving both carcinogens compared with 26 ± 5 weeks for the group receiving Ni_3S_2, and 31 ± 10 weeks for the group receiving BP. Also

the mean survival time was significantly lowered in the group receiving both carcinogens.

Kasprzak et al. (83) found increased incidence of premalignant changes in lungs of rats receiving intratracheal injections with a mixture of BP and Ni_3S_2 compared with groups receiving one carcinogen at a time: 0 of 13 animals receiving 5 mg of Ni_3S_2 developed bronchial squamous metaplasia, which was found in 4 of 13 animals receiving 2 mg of BP and in 8 of 13 animals receiving both 5 mg of Ni_3S_2 and 2 mg of BP. Evaluation took place after 15 months. Toda (84) found that NiO increased the incidence of lung tumors in rats induced by 20-methylcholanthrene.

The synergistic effect reported between organic carcinogens and Ni-compounds has been suggested to be related to the inhibitory effect of Ni compounds on lung and liver microsomal mixed function oxygenase systems, which was shown with nickel carbonyl by Sunderman (85,86). The activity of BP-hydroxylase *in vitro* was not inhibited by nickel carbonyl (81). It was suggested by Sunderman (85) that the synergism between nickel and BP is due to slower metabolism of BP and longer tissue retention of BP when nickel is present. This received experimental support by the findings of Sunderman and Roszel (87) that exposure to nickel carbonyl inhibited mobilization from lung and liver of BP in rats after IV injection of BP. The inhibition lasted 48 hr.

Nickel carbonyl also inhibits rat hepatic nuclear RNA polymerase activity both *in vivo* and *in vitro* (88,89), furnishing a possible explanation for the inhibitory effect of nickel on BP hydroxylase induction observed *in vivo*.

Manganese was shown to antagonize the tumorigenic effect of Ni_3S_2 (90,91). Aluminum, copper, and chromium had no effect in the same experimental set up (90). Rats were given single im injections of 2.5 mg of Ni_3S_2 alone or in combination with metal dust. When 2.1 mg of manganese dust was given with Ni_3S_2, 15/24 rats developed sarcomas at the injection site, compared with the control group, receiving only Ni_3S_2, where 39/40 rats developed sarcomas. Observation time was 2 years. Sunderman et al. (91) showed that neither the excretion of Ni nor the retention at the injection site were altered by Mn, while the concentration of ^{63}Ni in supernatants from ultracentrifugations of homogenates of injection sites was 5.8 ± 0.7 (SD) ng/ml 20-24 weeks after injection of 1.2 mg of $^{63}Ni_3S_2$ and 2.0 mg of Mn dust compared with 8.4 ± 3.2 (SD) ng/ml in animals receiving 1.2 mg of $^{63}Ni_3S_2$ alone. *In vitro* experints showed that the solubility of Ni was significantly lowered in serum and water by Mn^0. Sunderman (90) suggested that Mn antagonized the

inhibition effect of Ni on RNA polymerase. *In vitro* Mn^0 has also been shown to antagonize the effect of Ni_3S_2, since transformation of Syrian hamster fetal cells by Ni_3S_2 could be almost totally inhibited by addition of Mn dust (*92*).

There are some indications from epidemiological studies (*93,94*) that tobacco smoking may be synergistic to nickel compounds in induction of lung cancer, as was suggested by Doll et al. (*95*). See also (*78*). Animal experiments in hamsters with life time exposure to NiO and cigarette smoke did not confirm this (*96*).

Conclusions on Nickel

Nickel compounds are strong human and experimental carcinogens. Synergism between the environmental carcinogen BP and nickel in experimental tumor induction has been documented. Synergism between nickel exposure and cigarette smoking in man has been suggested but not confirmed in animal experiments.

Manganese antagonizes muscle tumorigenesis and *in vitro* transformation induced by Ni_3S_2. Further research on the combined effect of nickel compounds and especially other metals or carcinogens (e.g., cadmium, hexavalent chromium and BP) found together with nickel in industrial exposure should be carried out.

Lead

Epidemiological investigations give no conclusive evidence that lead is a human carcinogen (*7,97,98*). Renal adenomas and carcinomas could regularly be induced in animals by soluble lead salts after different routes of application. Reviews of animal experiments with lead-induced cancer has been published by Sunderman (*62*) and IARC (*7*). The latter reference also includes data on mutagenesis. The data by Cooper and Gaffey (*99*), partly reanalyzed by Kang et al. (*100*), indicated increased mortality from malignant neoplasms of the digestive organs and respiratory system in lead-exposed workers in the USA. Cooper (*101*) stressed that these workers had also been exposed to many other substances and concluded that lead cannot be ruled out as a cocarcinogen.

Kobayashi and Okamoto (*102*) suggested a cocarcinogenic effect of PbO on BP-induced lung tumors in hamsters after repeated intratracheal instillations since the incidence of premalignant metaplasias was increased in animals receiving both PbO and BP compared with groups receiving either compound alone. Groups of 30 hamsters were given 10 weekly intratracheal instillations; one group given 1 mg PbO had some metaplastic

changes in alveoli, another group given 1 mg BP also had metaplasia but no tumors. A third group given both substances had 9 adenomas and 1 adenocarcinoma. In groups given the vehicle (0.5% carboxymethylcellulose in 0.9% NaCl) or left untreated no pathological lesions were found. The time of observation was 60 weeks.

Beek and Obe (*103*) found no effect of lead acetate on x-ray-induced chromosome breaks in human lymphocytes *in vitro*, but Skreb and Habazin-Novak (*104*) found that the rate of ^{3}H-thymidine uptake by HeLa cells is inhibited both by UV irradiation and by addition of lead chloride in single application, and that the effects of irradiation and lead chloride were additive in combined application, suggesting that lead ions may affect DNA repair.

Whether lead exposure alone can cause severe chromosome aberrations in man is still questioned. The conflicting results present up to 1977 were cited by Deknudt et al. (*105*). Several cytogenetic studies of lead-exposed workers did not show an increased rate of chromosome aberrations (*106-108*). Also, *in vitro* exposure of human cells and Chinese hamster cells to lead salts failed to yield an increase in chromosome anomalies (*108,109*).

In some other studies in which combined exposure to lead and other metals occurred increased rates of chromosome anomalies were found: Deknudt and collaborators (*110,111*) found an increased incidence of chromosomal aberrations among workers exposed to high concentrations of both lead and cadmium. Bauchinger et al. (*112*) also investigated workers exposed to both lead and cadmium and suggested that these two heavy metals might act synergistically to each other in inducing chromosome anomalies. Nordenson et al. (*113*) investigated lead exposed workers from the Rönnskär smelter. A characteristic feature of this working place is that a number of different potentially hazardous agents are present. Thus, the positive findings of Nordenson et al. (*113*) might be due to a combined exposure. Deknudt et al. (*105*) exposed Cynomolgus monkeys to lead in drinking water. Two monkeys kept on a diet low in calcium had significantly more chromosome anomalies than two monkeys kept on a calcium-sufficient diet. This finding is in accord with the fact that a low calcium diet increases the gastrointestinal absorption of lead. It is likely that other factors that increase gastrointestinal absorption of Pb, i.e., deficiency of Fe, Vitamin D (*114*) could also increase the chromosome breaking effect of lead.

Conclusions on Lead

There is no firm evidence that lead compounds are carcinogenic or cocarcinogenic in man. Consis-

tent data regarding the effect of lead on the carcinogenic effects of other metals and carcinogens are lacking. Due to the heavy environmental pollution with lead which is taking place, further experiments investigating carcinogenic (or cocarcinogenic) effects of inorganic and organic lead compounds particularly in combination with other agents deserve high priority. Further epidemiological investigations are needed concerning cancer incidence in populations exposed to lead in combination with other agents.

Chromium

Epidemiological investigations indicate that some chromium compounds are carcinogenic for humans, lung cancer having been found in excess among workers in the chromate producing and utilizing industry.

A few recent epidemiological investigations associate chromium exposure with an increase in gastric cancer (115). In animal experiments, local sarcomas were induced in different species after several routes of application of chromium compounds. Several reviews on chromium carcinogenesis are available (7,62,115-117). Many experiments indicate that the mutagenic and, most likely, also carcinogenic properties of chromium are exerted by hexavalent compounds; reports that describe the effect of changing the oxidation state of chromium are of special interest in this context. Hexavalent chromium ions can easily pass the cell and nuclear membrane, but trivalent chromium ions cannot. Thus, intracellular reduction captures Cr(III) inside the cell.

Tsuda and Kato (118,119) treated Syrian hamster embryo cells growing *in vitro* with $K_2Cr_2O_7$. At 0.5 μg/ml, a significant increase in chromosomal aberrations was found (33% abnormal metaphases), compared with untreated cultures (3-4% abnormal metaphases). When 0.645 μg/ml of Na_2SO_3 was added together with 0.5 μg/ml of $K_2Cr_2O_7$, the rate of chromosome anomalies returned to nearly normal values (6% abnormal metaphases). Petrilli and DeFlora (120) demonstrated that several hexavalent chromium compounds were active mutagens when evaluated by the Ames test. By using several mutants deficient in repair, they obtained evidence that chromate induces both frame shifts and base pair substitutions in Salmonella DNA. Addition of S9-mix completely destroyed the mutagenic activity of chromate, if enough S9 was added. This is in agreement with the report by Gruber and Jennette (121) that rat liver microsomes reduce hexavalent chromium *in vitro*. Mutagenicity disappeared when several reducing agents were included in the assay

mix in the studies of Petrilli and DeFlora (122). The reducing effect could be abolished by $KMnO_4$ which restored the mutagenic effect of hexavalent chromium abolished by liver microsomes. Also human erythrocyte lysate reduced the mutagenicity of hexavalent chromium. Petrilli and DeFlora (122) also demonstrated that trivalent chromium applied alone was inefficient as a mutagen in the Ames test, but that the addition of the oxidizing agent $KMnO_4$, which was inactive when applied alone, gave rise to a high reversion rate.

These studies do agree well with the report by Nakamuro et al. (123). Trivalent chromium compounds were found to be weak inducers of chromosomal aberrations in human lymphocytes *in vitro*, and to be weakly mutagenic in the rec-assay with *E. coli* Hs30R, while hexavalent chromium compounds were strongly active in inducing chromosome anomalies and mutations. The effects of hexavalent impurities in the trivalent chromium compounds used in the studies mentioned may account for the slight mutagenic effect observed. In fact, Petrilli and DeFlora (122) demonstrated that the addition of ascorbic acid to an industrial sample of chromite, which was weakly mutagenic reduced this mutagenicity.

Lane and Mass (124) tested chromium carbonyl (CC) as a carcinogen and as a cocarcinogen with BP. Tracheal grafts implanted subcutaneously on syngeneic rats were filled, either with 2.5 mg of CC in agar, with 2.5 mg of BP, or with both carcinogens. Control grafts received the vehicle agar alone. BP yielded eight squamous cell carcinomas in 22 grafts, CC yielded two carcinomas in 22 grafts, but BP + CC gave ten neoplasms, of which three metastasized within 9 months in 24 grafts. The authors suggested that CC might act as a cocarcinogen with BP.

Conclusion on Chromium

Since hexavalent chromium is accepted as the mutagenic and carcinogenic form of chromium and since oxidative/reductive processes involving other compounds have been demonstrated *in vitro* to control the mutagenic effect of chromium, there is need for further studies of the metabolic activation/deactivation of chromium compounds in whole animals: In man, exposure to hexavalent chromium compounds has been reported only to induce lung cancer, and possibly gastric cancer. The most likely explanation as to why cancer does not occur at other sites is the reduction of hexavalent chromium to the trivalent state immediately after absorption. In animal experiments hexavalent chromium compounds induce local sarcomas.

Cadmium

Some cadmium compounds are probably carcinogenic in man following occupational exposure (7) as respiratory and prostatic cancer have been found in excess frequency among cadmium workers. The carcinogenic properties of cadmium compounds have also found some support in animal experiments where local sarcomata at the site of injection and remote tumors in the testes have been demonstrated. A detailed review of the role of cadmium in the etiology of prostatic cancer is given by Piscator (125).

Although combined exposures to cadmium and other agents as in tobacco smoking or occurring simultaneously in situations of occupational exposure are very common, only the influence of simultaneous zinc exposure has been demonstrated. Gunn et al. (126,127) reported that a combined treatment with Zn gave a lower incidence of Cd-induced testicular tumors (Leydigomas) in Wistar rats and albino mice. A single subcutaneous injection of $CdCl_2$ (0.03 mmole/kg) was given and after 10 months, 21 out of 25 rats (88%) had tumors. In another group, a total of 3 mmole/kg of Zn acetate was given by injection in addition to the same subcutaneous Cd dose as in the first group, but only 2/17 developed testicular tumors. An effect of the zinc treatment on the incidence of pleomorphic sarcomas at the site of Cd-injections was reported as well: 9/22 Cd-injected rats had such tumors but only 2/17 Cd + Zn-injected and 0/18 in the control-group. In another experiment 20/26 mice given 0.03 mmole/kg of Cd developed tumors after 14 months but 0/25 mice, given 3.0 mmole/kg of Zn in addition to the Cd, developed tumors. It was further demonstrated that the content of ICSH-stimulating hormone in the pituitary was higher in Cd-treated animals than in the control group, showing that the interstitial cells of the testis were not functioning normally in these animals although they regenerated after initial damage immediately following a Cd injection. A hormonal mechanism of Leydigoma-induction was thus indicated and the zinc treatment probably interfered with this inductional mechanism. There are also other agents in addition to zinc, which protect the testicles of experimental animals against the necrotizing action of injected cadmium, i.e. selenium (128,129) and cobaltous chloride (130) or even pretreatment with a smaller dose of cadmium itself (131-133).

Deknudt and Leonard (110) found a higher frequency of severe chromosome anomalies in workers exposed to a combination of lead and cadmium compared with workers exposed mainly to zinc (but with a low exposure to lead and cadmium). Bauchinger et al. (112) found an increased number of chromosome aberrations in workers exposed to lead, cadmium and zinc compared with the control group. O'Riordan et al. (134) found no statistically significant increase in the number of chromosome aberrations in 40 men exposed to cadmium only (in the form of Cd pigments) and speculated that effects reported by other authors might be due to combined effects of Cd and other metals.

Unger and Clausen (135) demonstrated that injected cadmium salt gave rise to a diminished P-450 activity in the liver of mice. This effect does not occur in long-term repeated exposure due to the protective effect of induced metallothionein (136) and, although an effect of cadmium on mixed-function oxygenase would be of interest in relation to the carcinogenicity of many organic compounds, the fact that it occurs only in acute exposures makes it of limited practical importance with regard to the situation in liver tissue.

Conclusions on Cadmium

Exposure to cadmium compounds has been shown to contribute to the development of prostatic cancer in workers exposed to high concentrations. In animals injection of cadmium compounds give rise to testicular atrophy and subsequent development of Leydig cell tumors. These effects can be prevented by injection of large doses of zinc. It has been demonstrated in animals that hormonal factors are of importance for the development of the Leydig cell tumors. Hormonal factors may well be of importance also in the case of human prostatic cancer and factors influencing the male sex hormones may deserve further study.

Further research on possible interactions between cadmium and e.g. BP, arsenic and selenium would be of interest. In exposure at work, cadmium is found together with nickel, zinc, copper, and lead. Combination experiments involving these metals and their compounds are needed.

Metal Interactions in BP, Nitrosamine, and Asbestos Carcinogenesis

BP and other PAH (polycyclic aromatic hydrocarbons) present in oil products or produced by incomplete combustion of organic material are considered as potent human carcinogens partially responsible for the increase in lung cancer observed. Saffiotti et al. (137) reviewed evidence that BP (which after skin application leads to skin tumors) is only weakly carcinogenic in the respiratory system

of the hamster after intratracheal instillation. They presented experimental evidence that BP is a strong respiratory carcinogen when administered in combination with Fe_2O_3 in mixtures prepared by grinding. Feron (138) and Feron et al. (139) showed that high doses of BP and long observation times are required (36 × 1 mg/week or more) to obtain a high tumor yield. The carcinogenic effect of BP-Fe_2O_3 mixtures was further investigated by Saffiotti et al. (140,141), who examined the response after different dose levels and different number of instillations. When hamsters were given 30 weekly instillations of 1:1 mixtures of BP and Fe_2O_3 in 0.9% NaCl at doses of 0.25, 0.50, 1.0, and 2.0 mg/week of each compound, a correlation between dose and response could be seen. In other experiments the tumor incidence was compared among groups of animals receiving the same total dose in one instillation or several instillations. The effect of dose fractionation was evident. When 3 mg of BP was given with 3 mg of Fe_2O_3 weekly for 5, 10, and 15 weeks, a clear effect of repeated instillation was found: The group receiving 15 instillations had 105 respiratory tract tumors in 94 animals, the group receiving 10 instillations had 53 respiratory tumors in 121 animals, and the group receiving 5 instillations had 20 respiratory tumors. A group of animals receiving one single instillation of 37.5 mg BP + 12.5 mg Fe_2O_3 had 10 respiratory tumors in 60 animals. In these studies control animals received either Fe_2O_3 at different doses and number of instillations or were instilled with 0.9% NaCl. No respiratory tract tumors were found in control animals.

In a later study by Henry et al. (142) a control group receiving only BP was included. Syrian golden hamsters were given 30 weekly instillations in gelatin (total dose of BP 26.1-27.4 mg). In one group given BP-Fe_2O_3 prepared by low temperature precipitation of BP on Fe_2O_3, 73% developed tumors. BP-Fe_2O_3 prepared by grinding yielded 84% tumor-bearing animals. In group 3, given BP-Fe_2O_3 prepared by mixing together the two components in the instillation vehicle (gelatin), 12% developed tumors. In group 4, receiving BP alone in gelatin, 17% had tumors. Group 5, receiving gelatin alone, had no tumors. Development of tumors was much faster in groups receiving Fe_2O_3 and BP prepared by grinding or low temperature precipitation than in groups receiving BP alone or mixed with Fe_2O_3, demonstrating further the importance of the physical properties of metal oxide-BP-mixtures.

As had been noted in studies by Saffiotti and co-workers (143) the lung clearance of BP is dependent on the character of the instillation mixture. BP-Fe_2O_3 mixtures prepared by grinding were cleared much more slowly than BP instilled alone, or mixed with Fe_2O_3 without physical attachment.

Stenbäck et al. (144,145) compared other metal oxides with Fe_2O_3 as carrier dust in BP-induced lung carcinogenesis in Syrian golden hamsters. They found that MgO was as effective as Fe_2O_3. In a group receiving 20 weekly instillations of 2 mg of BP + 1 mg of MgO there were 72% respiratory cancer-bearing animals. In a group receiving 15 weekly instillations of 3 mg of BP + 3 mg of Fe_2O_3, 70% tumor-bearing animals were found.

In another experiment, different groups of animals received 15 weekly instillations of TiO_2, Al_2O_3, carbon, or Fe_2O_3, alone or in combination with BP. One group received BP and one group was untreated. The authors do not state how large were the doses that the individual groups received. Evaluation of the results is therefore difficult. The authors concluded that Al_2O_3 and carbon are inefficient as carrier dusts, but that TiO_2 is as efficient as Fe_2O_3. BP alone yielded few respiratory tumors.

Montesano et al. (146) found a modifying effect of Fe_2O_3 on DEN (diethylnitrosamine) carcinogenesis. A group of hamsters received a total dose of 30 mg of BP + 30 mg of Fe_2O_3 in 15 installations every second week, followed by a total dose of 12 mg DEN administered subcutaneously in 12 weekly injections. Other groups received the same dose of BP + Fe_2O_3 without DEN, and the same dose of DEN without BP + Fe_2O_3. One group received 30 mg of Fe_2O_3 without BP, and 12 mg of DEN. All groups receiving DEN showed a high yield of total tumors not significantly different between groups. The group receiving BP + Fe_2O_3 had less than 1/3 of the tumor yield observed in other groups. The authors concluded that BP-Fe_2O_3 acted synergistically with DEN, since the group receiving both carcinogenic treatments developed many tumors below the nasal cavity. In that group, the rate of squamous cell carcinomas of the tracheobronchial tract was 31% compared with 0% in the 3 other groups.

The latency time for the development of respiratory tract tumors excluding nasal cavity was much shorter when animals received both DEN and BP-Fe_2O_3, suggesting a synergistic effect.

The group receiving DEN and Fe_2O_3 yielded slightly more tumors than the group receiving only DEN, suggesting an enhancing effect. Stenbäck et al. (147) also noted an enhancing effect when 12 weekly SC injections of 1 mg of DEN were combined with intratracheal instillations of different dusts. Although the total tumor yield did not vary between the groups, a high yield of lung tumors was only observed in animals receiving intratracheal

instillations. The dusts used were MgO, Al_2O_3, and carbon. In all groups the instillation vehicle was 0.9% $NaCl$. In the group receiving DEN but no instillations, only one lung tumor was observed. In groups receiving dust instillations without DEN, no lung tumors were seen. In a group receiving DEN and instillations of 0.9% $NaCl$, the lung tumor yield was as high as in the groups receiving dust; the question is whether a mechanical effect of the instillation process influences DEN carcinogenesis.

Nettesheim et al. (148) noted an enhancing effect of Fe_2O_3 on DEN induced lung carcinogenesis. They gave groups of hamsters 12 weekly SC injections of 0.25 mg of DEN and exposed the different groups to different inhalation schedules for life time. In 131 animals receiving only DEN were found 18 nasal, 140 larynx plus trachea, and 17 lung plus bronical tumors (175 in total). In 133 animals receiving DEN plus Fe_2O_3, 40 mg/m^3 during 6 hr, 5 days/week there were 6 nasal, 114 larynx plus trachea, and 46 lung plus bronchial tumors (166 in total). In 132 animals exposed to Fe_2O_3 alone, no respiratory tract tumors were found. Although the total tumor yield did not vary much, the localization of tumors was significantly different. The latency time, both for development of lung tumors and for deaths from lung tumors due to DEN-application, was shortened significantly by Fe_2O_3 exposure.

Studies in the rat demonstrated that metal ions enhanced the carcinogenic and toxic action of ENU (N-ethyl-N-nitrosourea) (149,150). $CuSO_4$, $NiSO_4$, and especially $CoCl_2$ increased the tumor yield after SC injection of ENU. Also $FeCl_2$ and $MnCl_2$ increased the number of local sarcomas and decreased the latency time for tumor induction when compared with animals receiving ENU alone (151). On the other hand, $CuSO_4$ and $CoCl_2$ did not influence carcinogenesis induced by DEN in rats (152).

The present belief is that the carcinogenicity of asbestos fibers is closely related to fiber structure and size. This will not be further discussed in this text. However, asbestos fibers may be a carrier dust for other carcinogens, e.g., metals and BP. Several investigations have shown that small amounts of metals are associated with asbestos fibers, both in elementary form and as salts, especially those of nickel, chromium, manganese and iron. Smaller amounts of vanadium, zinc, copper and cobalt may be found.

Cralley (153) suggested that electromotive properties of metals in asbestos fibers might influence the carcinogenic properties. Especially the content of nickel and manganese was discussed. He argued that the standard reduction potentials for the individual metals associated with asbestos fibers determined both the rate and order in which the metals would be solubilized in ionic form, and which electrolytes would be reduced to elementary metals, and suggested that this may modify asbestos carcinogenesis. Since relationships between carcinogenicity and tissue concentration of specific metal species are not completely known it is difficult to evaluate the plausibility of these theories concerning the role of metals in asbestos carcinogenicity.

Thomson et al. (154,155) investigated the effect of asbestos-associated metal ions on the metabolism of BP by rat liver microsomes and on the binding of BP to macromolecules in vitro. They found that Mn^{2+} stimulated the metabolism of BP in vitro, while Cu^{2+}, Zn^{2+}, Pb^{2+}, Ni^{2+}, Cr^{3+}, Fe^{3+}, Mg^{2+} all inhibited BP metabolism (with falling efficiency). Cu^{2+}, Cr^{3+}, Zn^{2+}, Cd^{2+}, Mn^{2+}, and Ni^{2+} all inhibited the binding of BP to macromolecules (with falling efficiency). Mg^{2+} did not affect binding, while Fe^{3+} increased the binding up to 10 μmole Fe^{3+}/assay. At higher concentrations, Fe^{3+} inhibited BP binding.

Conclusions

BP, nitrosamines and asbestos are all regarded as human carcinogens. They all appear in combination with metals in human exposure media. As far as interactions between BP and metal oxides are concerned a considerable body of knowledge is available, demonstrating that Fe_2O_3, MgO, TiO_2 and possibly other dusts strongly potentiated the carcinogenic activity of BP when instilled intratracheally in combination. The reason for this is probably an increased retention time for BP in the respiratory tract when BP is associated with carrier dust. For nitrosamines, results suggest that tumor localization can be significantly changed and the latency time shortened by metal oxide exposures. The underlying mechanism remains unclear. For asbestos carcinogenesis, an effect of asbestos-associated metal ions in relation to the carcinogenic process has been suggested, but further research is needed before the plausibility of this hypothesis can be evaluated.

Concluding Remarks

It was stressed that human exposures often involve complex mixtures of potentially hazardous metal compounds. Such mixtures occur both in the occupational and general environment, but so far, only few of the important combinations existing have been investigated in experimental systems. Interactions that have been demonstrated are sum-

marized after each section in the main text of this review and this section will only deal with a few aspects of general interest. In several cases, the mechanism behind enhancement or inhibition of carcinogenesis is unclear, but a few examples of interactions taking place at different levels in the metabolism of carcinogens may be mentioned. The following categories of interaction can be identified:

(1) Change in absorption and retention of carcinogens (e.g., BP-metal oxide particle interactions).

(2) Effect on biochemical metabolism (e.g., inhibition of microsomal drug metabolizing enzymes by metals such as Cd, Pb, etc.).

(3) Change of valency state of a metal carcinogen (redox effects). Examples are the role of oxidizing and reducing agents on the mutagenic activity of chromium compounds, the effect of Mn^0 on Ni_3S_2 carcinogenesis and the antioxidant effect of selenium reducing the carcinogenic effect of several organic carcinogens.

(4) Effects of metals and other agents on DNA synthesis and repair (e.g., the combined effect of UV light and arsenic compounds).

(5) Modification of hormonal regulation (e.g., the protective effects of zinc against ICSH-induced Leydigomas after cadmium injection).

It is evidently useful, particularly when trying to relate experimental observations to human exposure situations, to have an indication of the mechanism through which interactions take place. Further research aiming at the identification of additional interactions of the type listed would, therefore, be of great value. Experiments utilizing established *in vitro* systems such as the Ames test, induction of high sister chromatid exchange rate in cultured lymphocytes, and either direct or virus-mediated cell transformation, as well as neoplastic transformation in tissue culture may be used to investigate possible interactions as well as long-term tests in laboratory animals. An important area of research is the testing of complex mixtures of metal-containing pollutants that occur in working environments, ambient air, food or drinking water. These assays should be related to effects of the pure constituents (individually and in combination) in parallel.

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