NR 2000:22

Scientific Basis for Swedish Occupational Standards XXI

Criteria Group for Occupational Standards
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ARBETE OCH HÄLSA | VETENSKAPLIG SKRIFTSERIE
ISBN 91-7045-582-1 ISSN 0346-7821 http://www.niwl.se/ah/

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National Institute for Working Life

The National Institute for Working Life is Sweden's national centre for work life research, development and training.

The labour market, occupational safety and health, and work organisation are our main fields of activity. The creation and use of knowledge through learning, information and documentation are important to the Institute, as is international co-operation. The Institute is collaborating with interested parties in various development projects.

The areas in which the Institute is active include:

- labour market and labour law,
- work organisation,
- musculoskeletal disorders,
- chemical substances and allergens, noise and electromagnetic fields,
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ARBETE OCH HÄLSA

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ISBN 91–7045–582–1
ISSN 0346–7821
http://www.niwl.se/ah/
Printed at CM Gruppen

Preface

The Criteria Group of the Swedish National Institute for Working Life (NIWL) has the task of gathering and evaluating data which can be used as a scientific basis for the proposal of occupational exposure limits given by the National Board of Occupational Safety and Health (NBOSH). In most cases a scientific basis is written on request from the NBOSH. The Criteria Group shall not propose a numerical occupational exposure limit value but, as far as possible, give a dose-response/dose-effect relationship and the critical effect of occupational exposure.

In searching of the literature several data bases are used, such as RTECS, Toxline, Medline, Cancerlit, Nioshtic and Riskline. Also information in existing criteria documents is used, e.g. documents from WHO, EU, US NIOSH, the Dutch Expert Committee for Occupational Standards (DECOS) and the Nordic Expert Group. In some cases criteria documents are produced within the Criteria Group, often in collaboration with DECOS or US NIOSH.

Evaluations are made of all relevant published original papers found in the searches. In some cases information from handbooks and reports from e.g. US NIOSH and US EPA is used. A draft consensus report is written by the secretariat or by a scientist appointed by the secretariat. The author of the draft is indicated under Contents. A qualified evaluation is made of the information in the references. In some cases the information can be omitted if some criteria are not fulfilled. In some cases such information is included in the report but with a comment why the data are not included in the evaluation. After discussion in the Criteria Group the drafts are approved and accepted as a consensus report from the group. They are sent to NBOSH.

This is the 21st volume which is published and it contains consensus reports approved by the Criteria Group during the period July 1999 to August 2000. These and previously published consensus reports are listed in the Appendix (p 79). Technical editing for printing was made by Karin Sundström.

Johan Högberg
Chairman

Johan Montelius
Secretary

The Criteria Group has the following membership (as of August, 2000)

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Contents

Consensus Report for Antimony and Antimony Compounds

December 8, 1999

This report is based primarily on a criteria document from the Nordic Expert Group (6).

Chemical and physical data

Substance, Formula	CAS No.	Mol. weight	Melting point °C	Boiling point °C	Solubility (cold water)
Antimony, Sb	7440-36-0	121.75	630.5	1750	none
Antimony trisulfide, Sb_2S_3	1345-04-6	339.68			
as antimony orange	1345-04-6	339.68	550	ca 1150	none
as stibnite	1317-86-8; 7446-32-4	339.68	550	ca 1150	none
Antimony pentasulfide, Sb_2S_5	1315-04-4	403.80	75 (disint.)	–	none
Antimony trioxide, Sb_2O_3	1309-64-4	291.50			
as senarmontite	12412-52-1	291.52	656	1550 (subl.)	very low
as valentinite	1317-98-2	291.52	656	1550	very low
Antimony tetroxide, Sb_2O_4	1332-81-6	307.52			
as cervantite			930	–	very low
Antimony pentoxide, Sb_2O_5, Sb_4O_{10}	1314-60-9	323.50	380, 930	– –	very low
Antimony selenide, Sb_2Se_3	1315-05-5	480.40	611	–	very low
Antimony triiodide, SbI_3	7790-44-5	502.47	170	401	(disint.)
Antimony tribromide, $SbBr_3$	7789-61-9	361.48	96.6	280	(disint.)
Antimony trichloride, $SbCl_3$	10025-91-9	228.11	73.4	283	very high
Antimony pentachloride, $SbCl_5$	7647-18-9	299.00	2.8	79	(disint.)
Antimony trifluoride, SbF_3	7783-56-4	178.75	292	319 (subl.)	very high
Antimony pentafluoride, SbF_5	7783-70-2	216.75	7	149.5	high
Antimony hydride, SbH_3 (stibine)	7803-52-3	124.78	-88	-17.1	low
Antimony potassium tartrate, $K_2[Sb_2(C_4H_2O_6)_2]x3H_2O$	28300-74-5	667.87	–	–	high

(subl.)=sublimates; (disint.)=disintegrates; ca=circa. Data in the table are from References 6, 8, 33, 35, 44 and 46.

Antimony is a silver-white, brittle, hard, metallic element that is easily powdered (53, 70). It occurs naturally in several minerals, including stibnite (53). It occurs in valences of -3, 0, +3 and +5 (53). Pentavalent antimony has a tendency to become trivalent antimony in acidic environments, and thus functions as an oxidant (70). Antimony oxidizes slowly in damp air, forming a dark gray mixture of antimony and antimony oxide (70). Oxidation may be more rapid if the metal is in the form of airborne particles (51). When metallic antimony is burned in air, it forms a white vapor – antimony trioxide – that smells like garlic. Antimony hydride (stibine) at room temperature is a colorless gas with an unpleasant odor (70).

Occurrence, use

Antimony is widely used in alloys of lead, tin and copper to increase hardness (4, 6). Metals containing antimony are used in automobile batteries, solder, cable sheathing, electrodes, printing type and ammunition. Antimony with a high degree of purity is used in semiconductors, in thermoelectric equipment and in the glass industry. Antimony trioxide is used, for example, as a catalyst, a white pigment in paint, and in the pharmaceutical industry for production of organic antimony salts. Antimony trioxide combined with a halide is widely used as a fire retardant, especially in textiles. Antimony trisulfide and/or antimony pentasulfide are used as pigments, in fireworks, in matches and in vulcanizing rubber. Antimony trichloride can be used in textile dyeing and in the chemical process industry. Organic antimony salts are used medically to treat parasite infections (4, 6, 46, 49).

Uptake, biotransformation, excretion

Antimony and its compounds can be taken up from the digestive tract (2, 6, 15, 25, 43), but uptake of the inorganic antimony compounds with low solubility is probably quite limited (3, 9, 27). Lung retention data from animal experiments indicate that the more readily soluble antimony compounds are much more readily taken up by the lungs (16, 20, 28, 51). In two studies with rodents, the portion of the total body burden of antimony in the lungs was calculated with the help of isotope-labeled antimony. It was found that <1% was in the lungs 2 hours after inhalation exposure to an aerosol of trivalent or pentavalent antimony tartrate, whereas 35-50% of the antimony was still in the lungs two days after inhalation exposure to antimony trichloride (16, 20).

In vitro experiments with human blood have shown that trivalent antimony binds to red blood cells much more readily than pentavalent antimony (66). Antimony accumulated in the red blood cells of rats repeatedly exposed to antimony potassium tartrate via drinking water; concentrations of antimony measured in organs were much lower (spleen, liver >kidneys >brain, fat) (55). Localization in the red blood cells and distribution to liver, spleen and kidneys are also reported in an inhalation study in which animals were exposed to stibine (62). Accumulation of antimony in thyroid was observed in rats after long-term oral exposure to antimony trioxide (27). It has also been demonstrated in animal experiments that soluble antimony salts are

secreted in milk, and can pass the placental barrier (25). Data on distribution of antimony after uptake from occupational exposure are sparse. A study of smelter and refinery workers in Sweden reports antimony levels in femurs that may indicate some deposition of antimony in bone tissue (45). After oral intake of a water-soluble antimony salt (a case of poisoning) the largest concentrations of antimony were reported to be in liver, bile/gall bladder, and mucous membranes of the digestive tract (43).

In man, the main excretion pathway for antimony is reported to be via the kidneys (21), but antimony can also be excreted in feces, and an enterohepatic cycle has been demonstrated (2). Animal data indicate that antimony (antimony trichloride) is excreted in bile in the form of glutathione conjugate and in urine in inorganic form (2). Rapid excretion of antimony in urine is described in a case report of acute poisoning by antimony trichloride smoke (65). In another study, slow excretion was observed in a worker with antimony pneumoconiosis: elevated antimony levels could be detected in urine several years after termination of exposure (47). In a study of battery production workers occupationally exposed to low concentrations (up to 0.04 mg Sb/m^3, personal monitors) of antimony trioxide or antimony trioxide and stibine, it was calculated that the half time for excretion in urine was about 4 days (39). There was a significant correlation between Sb concentrations in air and in blood/urine, and by linear extrapolation a rough estimate of biological exposure equivalents was made: an air concentration of 0.1 mg Sb/m^3 (as Sb in total dust) should thus correspond to a urine concentration of 60 µg Sb/g creatinine and a blood concentration of 50 µg Sb/liter (39). In another work, in which antimony in urine and in the breathing zones (personal monitors) of workers producing inorganic penta-valent antimony compounds was monitored, it is calculated that with 8 hours of exposure to air concentrations around 500 µg Sb/m^3 the Sb concentration in urine increases by an average 35 µg/g creatinine (2).

Toxic effects

Animal data

The acute toxicity of the various antimony compounds varies considerably. The LD_{50} for antimony trioxide given orally to rats is reported in an older study (63) to be >20 g/kg. The reported LD_{50}'s for oral administration of antimony pentachloride and antimony trichloride (rats) are 1115 and 675 mg/kg respectively (1). One study (32) reports deaths in mice 4-8 hours after 15 minutes of exposure to 30–50 ppm (155–259 mg/m^3) stibine. Stibine can damage red blood cells and cause hemolysis. Guinea pigs exposed to 65 ppm (337 mg/m^3) stibine for 1 hour had changes in blood composition, hemoglobin in urine, anemia and oliguria (67). Lung damage and edema (but not hemoglobinuria) were observed in dogs and cats after one hour of exposure to 40-45 ppm (207-233 mg/m^3) stibine (67).

Inhalation exposure to sparingly soluble inorganic antimony compounds has caused changes in lung tissue – probably due to the irritating qualities of the dust – and effects on the heart and eyes: higher doses have resulted in effects on the liver and spleen (see Table 1). Slight changes in the lungs (including focal hemorrhages)

are reported in a study in which rats were intermittently exposed to 3.1 mg/m^3 antimony trisulfide over a period of six weeks. In the same study, ECG changes and histopathological changes in the heart were observed after six to ten weeks of exposure to 3.1-5.6 mg/m^3 (7). In a long-term experiment in which rats were exposed to 0.06, 0.5 or 4.5 mg/m^3 antimony trioxide (99.7% pure), inflammatory changes (interstitial and granulomatous inflammation) and fibrosis were observed in lungs of the high-exposure group 6 to 12 months after termination of exposure (51). This study also reports indications of an increased incidence of lens clouding in all dose groups (especially among the females), although no clear dose-response relationship could be identified and the significance of this observation is unclear. In an unpublished study (Watt, 1983; cited in References 3 and 35) it is reported that lung changes (including focal fibrosis, hyperplasia, increased lung weight, inflammatory changes) were observed in female rats exposed by inhalation to 1.9 or 5 mg/m^3 antimony trioxide for one year.

Changes in spleen and liver were observed after repeated exposure to 45 mg/m^3 antimony trioxide (14). Rats given repeated intraperitoneal injections of antimony potassium tartrate for three months developed liver damage (inflammation, fibrosis) at dose levels of 3 mg/kg body weight or above (15). Another study reports mild, reversible histological changes in the livers of rats given drinking water containing 5 ppm antimony in the form of antimony potassium tartrate (equivalent to about 0.6 mg/kg body weight/day) for 3 months (55).

Human data

Antimony is extremely irritating to the digestive tract. Acute symptoms of poisoning after oral intake include stomach cramps, nausea, vomiting and diarrhea (43). Liver and kidney damage have been noted in severe cases (43). Symptoms of less severe poisoning (metallic taste in the mouth, slight stomach pain, difficulty swallowing) are reported after ingestion of an unknown amount of antimony trisulfide. The subject's blood level in this case was 5.1 µg Sb/l a few hours after the intake (2).

Disturbances in the digestive system, chemical burns/irritation of skin and eyes, and irritation of upper respiratory passages are reported in a study of some workers who were briefly exposed (precise times not reported) to smoke/spray or vapor from a leak in a closed processing system containing a solution of 98% antimony trichloride in anhydrous hydrochloric acid (65). The concentrations of antimony measured in urine of a few persons with stomach symptoms 1-2 days after the exposure were 1-5 mg/liter. Air concentrations were estimated to have been up to 73 mg Sb/m^3 and 146 mg HCl/m^3.

Symptoms/effects on 69 of 78 smelter workers who were exposed to smoke containing antimony oxide are reported in an older study (57). Nosebleeds/sores in the nose and inflammatory changes in respiratory passages were common, and some workers who became ill 2 to 12 hours after exposure to "high" air concentrations were diagnosed with pneumonia. There were also a few cases of dermatitis. Several of the most highly exposed workers also reported symptoms involving the digestive tract and nervous system (dizziness, headache, "tingling") and one worker, who had large amounts of antimony in urine (600 mg/l), had indications of kidney damage

(albuminuria). Muscle pain was reported in a few cases. Measured air concentrations of antimony varied considerably. Concentrations ranging from 0.9 to 71 mg/m^3 in the breathing zone, and from 0.4 to 23 mg/m^3 around stationary monitors, were reported. The average concentration was reported to be 10-12 mg/m^3. The workers were also exposed to arsenic (up to 5 mg/m^3 in the breathing zone) and in some cases to sodium hydroxide as well, and this may have contributed to the observed effects.

Irritation of respiratory passages from exposure to antimony has been reported in several other studies. Some severe cases of pulmonary edema and chemical burns were reported after exposure to antimony pentachloride during a production disturbance (no exposure data given) (12). Two studies report nasal irritation and recurring nosebleeds in a few persons who were exposed to dust of metallic antimony and dust/smoke of antimony trioxide, but exposure to other substances may have contributed to these effects (11, 68). One of the studies (68) reports the antimony concentrations in the breathing zone of a worker who had antimony dermatitis and nosebleeds. His job involved crushing high-purity (99.86%) metallic antimony and heating it together with other metals. The average antimony content in the breathing zone (8 hours) was calculated to be 0.39 mg/m^3. The average concentration for a 250-minute period was 0.67 mg Sb/m^3. It is stated, however, that air concentrations were probably much higher for brief periods (68).

Long-term exposure to dust of inorganic antimony compounds (especially antimony trioxide) has been reported to cause pneumoconiosis (antimoniosis). It is similar both clinically and roentgenologically to other types of pneumoconiosis, such as miner's lung (26, 47, 48, 56). One study reports pneumoconiosis (verified by X-rays) in 44 of 244 process workers at an antimony smelter (48). A later study (49) reports that measurements made during the 1980s showed air concentrations of around 0.5 mg Sb/m^3 (time-weighted average), and states that they had previously been much higher (49). This statement is supported by a work published in 1963 (47), which reports that air concentrations of antimony (average values) measured at different places in the smelter were usually in the range 0.5-5.3 mg/m^3. The composition of the dust is not described, but the antimony was probably mostly in the form of oxide. In another study (56) it is reported that pneumoconiosis (verified by X-rays) was diagnosed in 51 smelter workers exposed for 9 years or more to antimony trioxide (39-89%) and antimony pentoxide (2-8%) along with small amounts of other substances including free silicon dioxide and arsenic trioxide (0.2-6%). Measured dust concentrations were reported to range from 17 to 86 mg/m^3. Exposed persons experienced coughing and breathlessness, and some of them had emphysema and inflammatory changes in lungs (chronic bronchitis, inflammation in upper respiratory passages). More than one in four had conjunctivitis. The influence of smoking on these symptoms is not taken up.

Medicines containing antimony can have toxic effects on the heart, and deaths have been reported (5, 7, 49, 59, 70). It is not clear whether occupational exposure to antimony can affect the heart. One study (7) concerns 125 workers who made polishing discs, and were exposed to dust containing antimony trisulfide for periods ranging from 8 months to 2 years. There were six sudden deaths in the group, all but

one of which were ascribed to heart problems. The study reports ECG changes in 37 of 75 examined workers. In the 16 years before antimony was introduced there had been only one death in that department (heart infarct). After the use of antimony trisulfide was discontinued, no new deaths due to heart disease and no abnormal increase in heart/circulatory problems were reported in the department, although the ECG changes persisted in 12 workers. Air concentrations of antimony were reported to range from 0.6 to 5.5 mg/m^3, usually above 3 mg/m^3. Whether the dust contained arsenic or other substances is not mentioned. It is not possible to determine from this study whether there is a cause-effect relationship between exposure to antimony trisulfide and effects on the heart. In another study (9) of a few persons exposed to extremely high concentrations (42-52 mg/m^3) of high-purity antimony trisulfide dust (<0.07% arsenic, <0.18% lead), it is reported that very little of the dust was absorbed and that the exposed subjects had no symptoms of poisoning.

It is also impossible to draw any definite conclusions from the published epidemiological studies of antimony smelter workers (37, 49, 60), since they were probably exposed to arsenic, lead and other substances as well. One study (60) reports the Standardized Rate Ratio (SRR) and 90% confidence interval (CI) for mortality due to ischemic heart disease for smelter workers in comparisons with three different control groups: 1.49 (90% CI=0.84-2.63), 1.22 (90% CI=0.78-1.89) and 0.91 (90% CI=0.84-1.09). Another study reports that the number of deaths due to ischemic heart disease was lower than predicted. A report of the results published in 1994 (37) gives 49 deaths vs. 60.5 predicted. (References 37 and 49 report different results.)

There are several reports of contact eczema due to occupational exposure to antimony, particularly antimony trioxide (6, 47, 49, 56, 64, 68). The skin symptoms, usually intense itching and a characteristic rash called “antimony spots,” develop on exposed skin – especially sweaty skin in warm, damp surroundings. They usually clear up rapidly after exposure is stopped (47, 56, 64, 68). Antimony trioxide can also be skin sensitizing (13, 50).

Mutagenicity

Antimony trioxide, antimony pentoxide, antimony trichloride and antimony pentachloride were negative in mutagenicity assays with *E. coli* and *Salmonella* (18, 38, 41), but two of four other *in vitro* studies (38, 41, 42, 52) report that antimony trioxide, antimony trichloride and antimony pentachloride were genotoxic in tests with bacteria. One work (10) reports that antimony triacetate increased viral transformation of mammalian cells *in vitro.* In another *in vitro* test with mammalian cells, antimony trioxide showed no mutagenic activity (18). A significant increase of sister chromatid exchanges was observed in human lymphocytes and mammalian cells exposed *in vitro* to antimony trioxide and antimony trichloride, but not antimony pentoxide or antimony pentachloride (24, 41). Antimony trichloride was also shown to induce micronuclei in tests with mammalian and human cells *in vitro* (22, 23, 34). In another *in vitro* study with antimony trichloride, indications of DNA strand breaks (but not DNA-protein crosslinking) were observed in mammalian cells (23). Antimony trioxide induced chromosome aberrations in human lymphocytes *in*

vitro (18). A significant increase in the number of cells with chromatid breaks was observed in human leucocytes exposed *in vitro* to sodium antimony tartrate (54).

There are few *in vivo* studies. One study reports no significant increase of chromosome deviations in bone marrow cells of mice given antimony trioxide in single oral doses of 400-1000 mg/kg body weight (29). However, the same authors report a dose-related increase in the incidence of chromosome deviations in bone marrow cells – but no significant effects on gametes (sperm head abnormalities) – in mice given antimony trioxide by gavage in doses of 400-1000 mg/kg/day for one to three weeks. Animals in the highest dose group died after three weeks of exposure. The daily doses of antimony were calculated to be 1/50, 1/30 and 1/20 of the LD_{50} (31). Neither of these reports (29, 31) contains information on the purity of the substance. In a later study with similar doses, no indication of chromosome damage (as micronuclei in bone marrow erythrocytes) was seen (18). The antimony used in this study was 99.9% pure, and the mice were given either a single oral dose of 5 g/kg or daily doses of 400-1000 mg/kg for up to three weeks (18). The mice showed no clinical indications of toxicity, but in the females given the single large dose there was a transient reduction in the proportion of immature erythrocytes (18). No indication of increased DNA repair was seen in hepatic cells of rats given antimony trioxide in single oral doses of up to 5 g/kg (18).

DNA strand breaks were seen in the spleens of mice after oral administration of 1500 mg antimony trichloride/kg body weight (Ashry et al, 1988; cited in Reference 6). In another study, dose-dependent chromosome aberrations were seen in the bone marrow cells of mice given antimony trichloride (purity not reported) in single oral doses of 70-233 mg/kg body weight. The doses were calculated to be 1/10, 1/5 and 1/3 of the LD_{50} (30).

Potassium antimony tartrate (purity not given) was also tested *in vivo* for cyto-genetic effects (19). Doses of 2, 8.4 or 14.8 mg/kg (the highest dose = maximum tolerable dose, or LD_5) were given to rats by intraperitoneal injection, either all at once or spread over 5 days. There were significant increases of chromosome aberrations at all dose levels and with both the acute (linear increase with dose) and sub-acute (maximum effect at intermediate dose) exposures.

Carcinogenicity

No increase in the occurrence of tumors was seen in mice given drinking water containing 5 ppm potassium antimony tartrate throughout their lives (61).

In one study (28), male and female rats (90 animals per group) were exposed to either 45-46 mg/m^3 antimony trioxide (0.004% arsenic) or 36-40 mg/m^3 antimony ore (mostly antimony trisulfide; 0.08% arsenic) 7 hours/day, 5 days/week for up to one year, and killed at intervals up to five months after exposure was terminated. For exposed females (both substances) there was an elevated incidence ($p < 0.001$) of various types of lung tumors. The lung tumors were observed after 41 to 72 weeks in 19/70 (antimony trioxide) and 17/68 (antimony ore) animals. No lung tumors were found in the exposed males or in controls of either sex. The tumor incidences in other organs were not significantly elevated in any group (28). A high incidence of lung

tumors in female rats exposed to antimony trioxide was also reported in another study (Watt, 1983; cited in Reference 35). The animals (females only – about 50 per group) were exposed to either 5 mg/m^3 (4.2 mg Sb/m^3) or 1.9 mg/m^3 (1.6 mg Sb/m^3) antimony trioxide (0.02% arsenic) 6 hours/day, 5 days/week for 13 months, and killed up to 1 year after termination of exposure. Lung tumors were observed after two years in 14/18 animals in the high-dose group, 1/17 in the low-dose group and 0/13 in controls. Lung tumors had also been observed in animals killed earlier: 6/16 in the high-dose group and 1/6 in controls. In 1988, the IARC concluded from these studies that there is "sufficient evidence" that antimony trioxide is carcinogenic to experimental animals and "limited evidence" that antimony trisulfide is carcinogenic to experimental animals (35).

Another cancer study with laboratory animals has since been made. In this study (51), rats (both sexes, 65 per group) were exposed to antimony trioxide concentrations of 0.06, 0.5 or 4.5 mg/m^3, 6 hours/day, 5 days/week for up to 12 months, and then observed for up to a year. No elevation in tumor incidence was seen. A possible explanation for the discrepancy between this study and the Watt study is that the exposure levels in the Watt study were probably higher than reported (51).

There are very little reliable carcinogenicity data on humans. In 1988 the IARC concluded that it could not be definitely determined whether antimony trioxide and antimony trisulfide are carcinogenic to humans (35). In its overall assessment, antimony trioxide was classified as "possibly carcinogenic to humans" (Group 2B), whereas antimony trisulfide was "not classifiable" as to its carcinogenicity to humans (Group 3).

Several epidemiological studies have since been published. In a British study which followed its cohort from 1961 to 1992, there was an elevated incidence of lung cancer in antimony process workers hired prior to 1961: 32 deaths due to lung cancer vs. 14.7 predicted ($p < 0.001$). For workers recruited after 1960, however, there was no over-frequency of lung cancer: 5 deaths vs. 9.2 predicted (17, 37, 49). An article published in 1963 (47) reports that average air concentrations of antimony at the smelter were usually between 0.5 and 5.3 mg/m^3 (rising to 37 mg Sb/m^3 at one location for short periods only). An American cohort study of smelter workers hired between 1937 and 1971 (60) reports a trend to an elevated incidence of lung cancer (Standardized Mortality Ratio (SMR) 1.39; 90% CI=1.01-1.88) and a significant positive trend with longer time on the job. In this study it is reported that the air concentrations of antimony at the smelter were between 0.1 and 2 mg/m^3 ("8-hour area samples") when they were measured in 1975. An elevated risk of cancer in the large intestine was identified in a Swedish study of workers in art glass production. The workers had been exposed to inorganic antimony (no air concentrations given) and several other substances (69). No definite conclusions on whether there is a risk of cancer from antimony exposure can be drawn from these studies, since the results may have been affected by numerous other factors including the presence of arsenic (3, 6).

Teratogenicity, effects on reproduction

No effects were seen in the fetuses of sheep given potassium antimony tartrate orally in doses of 2 mg/kg body weight/day during gestation (36). In another reproduction study (58), antimony trichloride was given in drinking water (0.1 or 1 mg/dl) to female rats during gestation and for three weeks afterward, and to the pups from 22 to 60 days of age. The mothers in both dose groups had somewhat lower weight gain, but no effects were seen on either litter size or length of gestation, and no malformations were seen in macroscopic examination of the pups. Vasomotor reactivity was tested in the pups at the ages of 1 and 2 months, and it was noted that there was a dose-dependent reduction in the response triggered by *l*-noradrenaline, *l*-isoprenaline and acetylcholine on day 60. The pups in the high-dose group also weighed significantly less from 10 days of age.

There is a Russian study (Belyaeva, 1967; cited in Reference 6) of pregnancy outcome and menstrual irregularities. The quality of the study has been questioned, however, so no definite conclusions can be drawn from it (3, 6).

Dose-effect/dose-response relationships

There are few reliable workplace measurements of air concentrations of antimony, and it is thus difficult to establish a direct dose-response relationship for occupational exposure. There is also the problem of mixed exposures – especially arsenic – which makes it difficult to isolate the effects of antimony. Several studies, however, have reported pneumoconiosis and skin rashes (antimony spots) in persons occupationally exposed to antimony dust/smoke. One work (49) reports that the proportion of smelter workers with pneumoconiosis dropped below 4% when the work environment in the antimony smelter was improved, and that antimony spots also became less common. The air concentration of antimony (8-hour average) at the smelter had earlier been above 0.5 g/m^3, and had been brought down to that level only a few years previously. Another work (68) describes dermatitis in three workers which could probably be ascribed to exposure to antimony trioxide smoke. Two of the three also had recurring nosebleeds, but it is not clear whether they were due to the antimony exposure. Their job involved work with metallic antimony of very high purity (99.86%). The antimony exposure (8-hour averages, breathing zone) was calculated for one worker to be 0.39 mg/m^3. The average concentration for 250 minutes was 0.67 mg Sb/m^3. It is also reported, however, that extremely high peaks probably occurred (68). The dose-effect relationships observed in laboratory animals exposed to antimony are summarized in Table 1.

Table 1. Exposure-effect relationships observed in experimental animals exposed by inhalation to sparingly soluble antimony compounds

Exposure	Substance	Species	Effect	Ref.
45-46 mg/m^3, 7 hours/day, 5 days/week, up to 1 year + up to 20 weeks observation	Sb_2O_3	Rat	Lung tumors (females), lung changes (including fibrosis, metaplasia)(both sexes), slightly reduced weight gain (males)	28
45 mg/m^3, 2-3 hours/day, 7 days/week, 16 days-30 weeks	Sb_2O_3	Guinea pig	Lungs: inflammatory changes, hemorrhages, increased weight. Liver: fatty degeneration, increased weight. Spleen: increase in hemoglobin, hyperplasia in lymph follicles.	14
36-40 mg/m^3, 7 hours/day, 5 days/week, up to 1 year + up to 20 weeks observation	Antimony ore – mainly Sb_2S_3	Rat	Lung tumors (females), lung changes (including fibrosis, metaplasia)(both sexes), slightly reduced weight gain (females)	28
32 mg/m^3, 90 minutes	Metallic antimony	Rat	Lung changes, including pinhead hemorrhages, somewhat higher lung weight.	40
28 mg/m^3, 5 days	Sb_2S_3	Rabbit	ECG changes, slight to moderate heart degeneration, inflammatory changes in lungs, sight degeneration in liver and kidneys.	7
24 mg/m^3, 6 hours/day, 5 days/week, up to 13 weeks + up to 27 weeks observation	Sb_2O_3	Rat	Lower weight gain (males), higher absolute and relative liver weights. Fibrosis and inflammatory changes in lungs during observation period.	51
5.6 mg/m^3, 7 hours/day, 5 days/week, 6 weeks	Sb_2S_3	Rabbit (males)	ECG indicated slight to moderate damage to heart muscles, degenerative changes in heart.	7
5.6 mg/m^3, 7 hours/day, 5 days/week, 10 weeks	Sb_2S_3	Dog (females)	ECG indicated some damage to heart muscles, possibly slight degenerative changes in heart.	7
5 mg/m^3, 6 hours/day, 5 days/week, 13 months + up to 12 months observation	Sb_2O_3	Rat (females)	Lung tumors, elevated lung weights, focal fibrosis, hyperplasia and inflammatory changes in lungs.	3, 35
4.5 mg/m^3, 6 hours/day, 5 days/week, up to 12 months + up to 12 months observation	Sb_2O_3	Rat	During observation period: fibrosis and inflammatory changes in lungs.	51

Table 1. Cont.

Exposure	Substance	Species	Effect	Ref.
3.1 mg/m^3, 7 hours/day, 5 days/week, 6 weeks	Sb_2S_3	Rat (males)	ECG changes in all exposed animals, degenerative and very slight inflammatory changes in heart, slight lung changes (including focal hemorrhages).	7
1.9 mg/m^3, 6 hours/day, 5 days/week, 13 months + up to 12 months observation	Sb_2O_3	Rat (females)	Lung changes: increased lung weight, focal fibrosis and hyperplasia, inflammatory changes.	3, 35

Conclusions

Judging from the available data on occupational exposure to antimony, the critical effect is its effect on the respiratory passages. Irritation of respiratory passages has been reported to occur with short-term exposure to antimony, and pneumoconiosis has been reported after long-term exposure to sparingly soluble antimony compounds. Antimony compounds can also irritate eyes and skin, and cause contact eczema. Epidemiological data indicate that there is an elevated risk of lung cancer for persons exposed to antimony dust in smelters, but many other factors, notably the presence of arsenic, may have contributed to the observed effect.

In experimental animals, the critical effect of antimony exposure is its effect on the respiratory passages. Lung tumors have been observed in female rats exposed to sparingly soluble antimony compounds (antimony trioxide, antimony trisulfide). Antimony compounds have been shown to be genotoxic *in vitro*, but there is no conclusive *in vivo* evidence of genotoxicity.

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Consensus Report for Potassium Hydroxide

March 15, 2000

Chemical and physical data. Occurrence

CAS No.:	1310-58-3
Synonyms:	caustic potash, potassium hydrate, potash lye, potassa, potassa caustica
Formula:	KOH
Molecular weight:	56.11
Boiling point:	1320°C
Melting point:	360°C
Vapor pressure:	1 torr at 719°C
Solubility in water:	1120 g/l at 20°C

Potassium hydroxide is produced by electrolysis of potassium chloride. It is a white, hygroscopic solid, usually in the form of clumps, sticks or pellets. On exposure to air, it absorbs water vapor and carbon dioxide and rapidly disintegrates to bicarbonate and carbonate. A 0.1 M solution has a pH of 13.

Potassium hydroxide is used in soap production, in paint removers and cleaners, in galvanizing, in the photographic industry, and in production of other potassium compounds (1). Potassium hydroxide may occur in air as either dust or aerosol. There are no data on air concentrations.

Uptake, biotransformation, excretion

No data were found on uptake, biotransformation or excretion of potassium hydroxide.

Toxic effects

Human data

There are several case reports of poisoning due to ingestion of household products containing about 30% caustic potash (liquid lye), which caused severe damage to the esophagus (8). Even one second of exposure to a very small amount of lye can be enough to initiate necrosis.

There is a study of eye injuries due to industrial accidents with alkali (7), all of them due to splashes. In nearly half the cases, the eye was hit by an alkali solution under pressure. Most of the injuries occurred in the construction and chemical industries.

Animal data

For rats, the LD_{50} with oral intake is 214 to 1890 mg/kg (3, 6, 13). A 5% solution of potassium hydroxide (0.1 ml) was applied to either intact or damaged skin of rabbits and allowed to remain for 24 hours (6). The treatment resulted in mild irritation of intact skin and severe irritation of damaged skin.

Rabbits and guinea pigs were used in another study (11): 0.25 ml of a 10% solution of potassium hydroxide was applied to intact or damaged skin and left for 4 hours. The treatment resulted in severe burns. In a later study (12), 0.5 ml of a 5% or 10% solution of potassium hydroxide was applied to the skin of rabbits. Both solutions were judged to be severely irritating and corrosive after 1 hour of treatment.

To study the effects of potassium hydroxide on the esophagus, a cat was anesthetized and the esophagus opened. An 8% solution was applied for 30 seconds and then thoroughly rinsed off. After 2 hours extreme redness and fluid formation were noted at the site of application. Underlying muscle was also damaged (2).

Potential for eye irritation was tested using potassium hydroxide solutions in the concentration range 0.1 to 5%: 0.1 ml of solution was applied beneath the eyelid of a rabbit and left for either 5 minutes or 24 hours, after which it was thoroughly rinsed off. Five minutes of exposure to the 5% solution was "corrosive", whereas 5 minutes or 24 hours of exposure to the 1% solution was "irritating". The 0.5% solution left for 24 hours caused only "marginal irritation", and the 0.1% solution had no effect (6).

Mutagenicity

In a test system with *E. coli* based on reverse mutation to streptomycin resistance, no mutagenic effects were observed at potassium hydroxide concentrations up to 0.019% (4).

Cultures of hamster ovarian cells were used to assess chromosome damage from alkali. In potassium hydoxide solutions without metabolic activation (S9 mix) there was no chromosome damage in the pH range 7.3 to 10.9 (9). In the presence of the S9 mix a few chromosomal aberrations appeared at pH 10.4 (12 mM potassium hydroxide), and the frequency of aberrations increased with the amount of S9 added. The proposed explanation was that chromosome-damaging substances were formed by the breakdown of the S9 at high pH.

Carcinogenicity

In a cancer study, 3% to 6% solutions of potassium hydroxide were applied to the backs of mice (29 males and 52 females). The treatment was repeated daily or every second day until the first damage appeared, and thereafter about twice a week for 4 to 6 weeks. The total treatment time was 25 to 46 weeks. Tumors developed in 14% of the males and 15% of the females. There were no controls (19). This study is discussed by Ingram and Grasso (5). If tumors appear after the formation of sores and epidermal necrosis, it is probable that they are not of genotoxic origin. Substances that cause severe and repetitive skin damage can cause cancer by a non-

genotoxic mechanism. It is unlikely that humans would repeatedly suffer skin damage by alkali. Further, human skin is less sensitive than mouse skin (12).

Dose-effect/dose-response relationships

There are no data from which to derive a dose-effect or dose-response relationship for occupational exposure to potassium hydroxide. Eye irritation has been studied in rabbits. A 5% solution was corrosive to the eye, and a 0.1% solution had no effect. When the substance was applied to the skin of laboratory rodents, a 5% solution was highly corrosive. No NOEL (no observed effect level) has been reported.

Conclusions

There are no data that would serve to define a critical effect for occupational exposure to potassium hydroxide. Since the substance is a strong base, the critical effect is assumed to be irritation of eyes, skin and mucous membranes.

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Consensus Report for Chromium and Chromium Compounds

May 24, 2000

This report is an update of the Consensus Report published in 1993 (71), and is based primarily on the 1993 criteria document (58) and subsequently published research. The Criteria Group also published a consensus report on chromium and chromium compounds in 1981 (104).

Chemical and physical data. Occurrence.

	chromium	*chromium trioxide*
CAS No.:	7440-47-3	1333-82-0
Synonyms:	metallic chromium	chromium(VI) oxide chromic acid anhydride
Formula:		$CrCrO_3$
Molecular weight:	51.00	99.99
Boiling point:	2482°C	230°C
Melting point:	1890°C	196°C

	zinc chromate	*potassium dichromate*
CAS No.:	13530-65-9	7778-50-9
Synonyms:	zinc chromium oxide	potassium bichromate potassium dichromate(VI)
Formula:	$ZnCrO_4$	$K_2Cr_2O_7$
Molecular weight:	181.37	294.18
Boiling point:	(no information)	500°C
Melting point:	(no information)	398°C

Chromium occurs naturally in the earth's crust in the form of chromite. Chromium(III) oxide accounts for 15 to 65% of its metallic oxide content. Reduction of chromite by the addition of carbon at high temperature results in the formation of ferrochrome(0) and slag. Ferrochrome is used in the production of stainless steel and other alloys. Heating the chromite with sodium carbonate and nitrate forms sodium chromate, and this is the substance from which chromium compounds are obtained. Chromium occurs in valences of –II to +VI. The hexavalent and trivalent forms are those usually of concern with occupational exposure. Divalent chromium is transformed to trivalent chromium on exposure to air or water. Quadrivalent and pentavalent chromium are unstable transitional forms occurring when hexavalent chromium is reduced to trivalent chromium (42).

Table 1. Some chromium compounds and their chemical and physical characteristics (from Reference 42)

Compound	CAS No.	Formula	Mol. weight	Solubility in water (g/l)
Hexavalent compounds				
Barium chromate	10294-40-3	$BaCrO_4$	253.33	0.0044 (28°C)
Lead chromate	7758-97-6	$PbCrO_4$	323.18	0.00058 (25°C)
Calcium chromate	13765-19-0	$CaCrO_4$	156.09	Low (no data)
Potassium chromate	7789-00-6	K_2CrO_4	194.20	629 (20°C)
Potassium dichromate	7778-50-9	$K_2Cr_2O_7$	294.19	49 (0°C)
Sodium chromate	7775-11-3	Na_2CrO_4	169.97	873 (30°C)
Sodium dichromate	10588-01-9	$Na_2Cr_2O_7$	262.00	2380 (0°C)
Strontium chromate	7789-06-2	$SrCrO_4$	203.61	1.2 (15°C) 30 (100°C)
Zinc chromate	13530-65-9	$ZnCrO_4$	181.37	Insoluble in cold water
Trivalent compounds				
Chromium chloride	10125-73-7	$CrCl_3$	158.36	Insoluble in cold water
Chromium nitrate	13548-38-4	CrN_3O_9	238.03	Dissolves in water

Chromium was discovered by Vauquelin in 1797. It is widely used in industry because of its strength and hardness and the high resistance to corrosion provided by the strong oxidizing nature of chromates. Chromium has been widely used in the production of fireproof materials, in the chemical industry (as a catalyst), and in the production of alloys, particularly stainless steel (e.g. 18:8 steel) and other special steels (e.g. acid-resistant steels). Chromium is used for surface coatings, both chrome plating, which results in a surface layer of metallic chromium, and chromating, which provides a protective coating of chromates with various valences and degrees of solubility. Hexavalent chromium compounds are used in many pigments and chemicals. Chromates are used in wood impregnation (with arsenic and copper), leather tanning and fireworks. Chromium trioxide was once used medicinally to treat nosebleeds. Chromium(IV) oxide is used in production of cassette tapes.

A list of the chromium compounds mentioned in this report, with their valences, CAS numbers, molecular weights and solubility, is presented in Table 1.

Hexavalent chromium. Hexavalent chromium is the substance of greatest concern in the context of occupational exposure. According to a report from the National Swedish Board of Occupational Safety and Health (1), occupational exposure to chromium in Sweden affects 1000 steelworkers, several thousand welders, about 1000 chrome platers, several hundred in the paint and pigment industry, and 50 working with wood impregnation. In addition, there are a large number of construction workers who are exposed via cement. It has long been known that chrome plating, pigment production and welding in stainless steel can be associated with high exposures to hexavalent chromium, both in aerosol form and as particles in dust and welding fumes. A summary made by the Swedish Board of Occupational Safety and Health reports that in Sweden (up to 1993) air concentrations registered by personal monitors were 1-8 $\mu g/m^3$ around plating and 20-800 $\mu g/m^3$ around mixing

and charging chromium pigments (1). With welding in stainless steel, the method used determines how high the exposure can be: manual metal arc welding (MMA) results in the highest air concentrations of both total chromium and hexavalent chromium. Earlier studies have shown air concentration of hexavalent chromium sometimes exceeding 100 µg/m^3 (58), and more recent studies have shown even higher air concentrations - above 600-800 µg/m^3 (73, 75, 98, 107). Elevated levels of hexavalent chromium have not been found in the air around tungsten-inert gas welding (TIG) (99), and there is no exposure to hexavalent chromium associated with welding in mild steel (carbon steel).

Non-occupational exposure to hexavalent chromium may occur in environments around textile dyeing, chrome plating and pigment industries, or around plants making ferrochrome and stainless steel (78), or around incinerators handling tannery waste (46). In New Jersey, slag containing hexavalent chromium has been used as landfill in both commercial and residential construction (26). Non-occupational exposure to hexavalent chromium can also occur via cement.

Trivalent chromium. Trivalent chromium is an essential trace element, and minute amounts occur naturally in water and food. It participates in the regulation of carbohydrate and fat metabolism, and is necessary for the proper functioning of insulin (105). Occupational exposure to trivalent chromium may occur around industrial processes in which hexavalent chromium is reduced to trivalent chromium. There are no studies of occupational exposure that treat trivalent chromium separately. Exposure to trivalent chromium may also occur via leather tanned with chromium.

Uptake, biotransformation, excretion

For occupational exposure to hexavalent chromium, uptake via respiratory passages is of greatest concern. Chromium compounds with high or moderate solubility are absorbed more easily than compounds with low or no solubility. Particle size also plays a role in chromium uptake by the body. Small particles of hexavalent chromium like those in welding fumes penetrate deep within the lungs to the alveoli, where they may be reduced to trivalent form in macrophages (74). Chromium that is not absorbed remains in the lungs for a long time. In autopsy studies made during the 1980s it was found that elevated levels of chromium remained in lung tissues for several years after occupational exposure had ceased.

Skin uptake of hexavalent chromium can also be relevant in occupational exposures, as evinced by several case reports of renal and other systemic effects in chrome platers following skin contact with chromic acid. In experiments designed to measure body uptake via skin (volunteers took a 3-hour soak in bathwater containing 22 mg/l potassium dichromate, equivalent to the worst conceivable environmental exposure) there were slight, transient elevations of chromium levels in plasma, erythrocytes and urine (16). According to the authors, this was the first study that showed systemic uptake *in vivo*, and the low chromium levels in blood and urine were regarded as an expression of an effective reduction system in the skin. In *in vitro* permeability tests in which human skin was exposed to various chromium

compounds in a diffusion chamber, hexavalent potassium dichromate was taken up more readily than the trivalent compounds chromium chloride and chromium nitrate (33). It was noted that the hexavalent chromium was reduced in the skin to trivalent chromium, but that the reduction capacity of skin *in vitro* was limited. The explanation then proposed for the low skin uptake of trivalent chromium was that trivalent chromium was bound to proteins in the dermis, forming stable complexes (4).

Hexavalent chromium is much more readily taken up from the digestive tract than the trivalent form, and uptake is of comparable magnitude in experimental animals and man (58). When water-soluble hexavalent chromium was taken orally by human subjects, absorption was in the range 1-24% (13), compared with 0.4% for inorganic trivalent chromium (chromium chloride) and 1.7-4.0% for organic trivalent chromium (chromium picolinate) (35). When subjects drank 0.1 to 10 mg hexavalent potassium dichromate in water, uptake in plasma and erythrocytes was seen in those given 5 and 10 mg and elevated (dose-related) urine levels were observed in all of them (27, 57). Hexavalent chromium can be reduced to trivalent form in the acid environment of the stomach, which reduces absorption. Inter-individual variation in reduction capacity has been noted in subjects given potassium dichromate (54). A drink of orange juice increased the reduction capacity, resulting in lower and slower absorption (53).

Hexavalent chromium has the same structure as the negative phosphate and sulfate ions, and can therefore exploit the transport systems of these ions to cross through the cell membrane into blood cells and other tissues. There are extra-cellular reduction systems (with ascorbic acid or glutathione, for example) in many tissues and in blood plasma, which serve to reduce uptake and thus function as a detoxification mechanism (15). Within the erythrocytes, the hexavalent chromium is rapidly reduced to trivalent form via instable intermediates (quadrivalent and pentavalent chromium) and bound to the globulin in hemoglobin (95-97%), other intracellular proteins, and glutathione. The heme group then undergoes oxidation (54). Uptake in the white blood cells follows a similar two-step pattern, and also involves a specific transport mechanism that can become saturated (19). Most of the chromium taken up in the hepatic cells is bound to glutathione in the cytosol, which protects the cell from toxic effects. DNA damage requires passage of hexavalent chromium into a nucleated cell and intra-cellular reduction via +V and +IV chromium to trivalent chromium, which then penetrates the cell nucleus. This may halt the replication process prematurely, or the cell may die, or it may become cancerous (62, 86, 100).

Trivalent chromium has no uptake mechanism in the cell. Uptake occurs slowly via passive diffusion, perhaps aided by other processes also dependent on the chemical structure of the ligands that may be bound to chromium (54). Trivalent chromium is transported in the blood bound to serum albumin, various ß-globulins, and other metal-transporting proteins such as transferrin.

Autopsy studies made in the 1980s showed not only high levels of chromium remaining in lungs after occupational exposure from chrome plating or work with chromates: high levels were also seen in lymph nodes, lung hilum, spleen, liver, kidneys and heart (19).

It has been demonstrated in animal studies that hexavalent chromium which is inhaled or given by intratracheal instillation, as well as trivalent chromium injected intravenously, is distributed by the blood to lungs, liver, kidneys, testes, spleen and intestines (58). The chromium level in the spleen (unlike that in other organs) rises as the blood cells containing chromium die and break down. Rats were given potassium chromate in drinking water (100 ppm), and after six weeks of exposure the chromium concentration was highest in the bones, spleen and kidneys, and lower in liver and blood (101). Hexavalent chromium given parenterally to pregnant rats passes through the placental barrier (42).

Inhaled hexavalent chromium is excreted primarily in urine. Chromium given orally, as well as chromium that is trapped in mucus and swallowed, is excreted primarily in feces. A small portion is excreted via skin and perspiration (13). Elevated levels of chromium have been measured in semen of welders who do metal arc welding of stainless steel (6).

Half times. It has been shown that chromium distribution in the body has several compartments, such as blood, with rapid turnover, liver and spleen with moderate turnover, and other more compact tissues (such as bone) with slow turnover (27, 68). The proposed half time for chromium in whole blood is 5.5 days, and the reported half time for chromium in plasma is 4 days (19). The calculated half time for hexavalent chromium in urine (after oral intake of 5 mg potassium dichromate) is 39 hours (53).

The calculated half time for trivalent chromium in urine (after oral intake of 5 mg chromium chloride) is 10 hours (53)

The half time for whole-body chromium in laboratory rats has been estimated to be about 80 days (101).

Chromium levels in biological samples

It is difficult to establish a relationship between exposures to hexavalent chromium and chromium levels in biological samples. The chromium level in whole blood is an uncertain measure of chromium exposure. The chromium that has penetrated into an erythrocyte remains there during the entire lifetime of the erythrocyte (115 days). In studies of welders, a good correlation was found between chromium levels in air and in erythrocytes (112, 113). Chromium levels in plasma reflect all types of chromium. They rise rapidly during exposure and then quickly drop, and within a few days after the exposure they have decreased to background levels (54). Blood is filtered in the kidneys and the chromium is then excreted in urine. The chromium level in urine can reflect exposure to both trivalent and hexavalent chromium, and has been used for many years as a measure of occupational exposure (66). During the filtering process in the kidneys, however, the chromium may be resorbed in the renal tubuli and re-enter the blood; thus the urine level may also reflect the accumulation of chromium in the body from previous exposures. The urine level is also affected by kidney function and by the individual's ability to reduce hexavalent chromium to trivalent form in plasma. A high extra-cellular reduction reduces uptake in the erythrocytes, resulting in higher excretion in urine (74). These differences can make it difficult to interpret measurements. Among metal arc welders exposed to chromium, smokers

have higher urine levels of chromium than non-smokers even when they use facemasks with air filters or Airstream helmets (98). Urine samples are used for screening large groups of chromium-exposed workers. To determine an individual worker's current exposure, however, urine samples must be taken before and after a work shift (66).

Toxic effects

Human data

General effects.

The health effects of exposure to chromium are correlated to its valence and solubility, and to the exposure pathway, exposure level, and particle size (17). It is the hexavalent chromium compounds that are considered the greatest toxicological hazard, although occupational exposure to trivalent chromium compounds may also affect health.

Acute exposure to high levels may result in damage to the mucous membranes in the digestive tract, vomiting and diarrhea, followed by liver and kidney failure. There are several reported cases of death following intake of one gram of potassium di-chromate, corresponding to about 350 mg hexavalent chromium (51, 97). Long-term occupational exposure may result in eczema, open sores (chrome sores or chrome ulcers), perforation of the nasal septum, chronic respiratory disease, kidney damage, cancer, and effects on the immune system.

Skin

Eczema. Hand eczema was recognized as an effect of working with cement early in the 1900s, and in 1925 Parkhurst identified the cause as contact with chromium salts in the cement. In the 1950s, the methods of cement production were changed and the amount of hexavalent chromium in cement increased. Jäeger and Pelloni identified this as the cause of the marked increase of hand eczema subsequently observed among cement workers (36). The chromium content of cement varies with the production method and the raw materials used. In the Nordic countries, as in Great Britain, cement has relatively high chromium content – up to 40 µg/g. In the United States and Canada, cement has much lower chromium content and allergic contact eczema is consequently much less prevalent among construction workers. A group of Swedish dermatologists discovered that if iron sulfate was added to the cement its chromate content was greatly reduced (32). Producers in Denmark began adding iron(II) sulfate to cement in the early 1980s. Iron(II) sulfate in cement reduces hexavalent chromium to trivalent chromium when water is added, and it brought the content of soluble hexavalent chromium in the cement below 2 µg/g. Allergic contact eczema due to chromate has since become much less prevalent among construction workers (3). Iron sulfate has also been added to cement in Finland since 1987 and in Sweden since 1989, with similar reductions in contact eczema due to chromate (83). In Singapore the prevalence of chromate allergy dropped from 6.8% in 1986 to 2.7% in 1992, after changes in the production process that reduced the chromium content in cement by 60%, to 7.1 µg/g (36). In Great Britain, where no measures have been

taken to reduce the chromate in cement, 17% of the construction workers employed on the Channel tunnel had contact allergy to chromate (43). Contact allergy to chromium can arise from occupational exposure not only to wet cement, but to chrome plating baths and protective gloves of chromium-tanned leather, and in production of pigments and dyes, printing, dry cleaning, leather tanning, and textile dyeing (4). Contact with chromates in matches, wood ash, rust preventives, galvanized steel, recording tapes, some green fabrics (e.g. military uniforms), and chromium-tanned leather in shoes can also cause allergic contact eczema. Allergic contact eczema due to chromate is widespread and often chronic (12, 31, 102, 109).

Allergic contact eczema due to chromate arises when soluble hexavalent chromium compounds, which are readily absorbed by the skin, are reduced in the skin to trivalent chromium which binds to proteins and activates the immune system, causing sensitization (33). Contact allergy to chromate is identified by patch tests (epicutaneous tests).

Many chromium compounds are sensitizing, and they can cause sensitization and eczema in people who already have allergies. The usual cause of sensitization is hexavalent chromium in cement. A person sensitized to hexavalent chromium also reacts to trivalent chromium. Trivalent chromium compounds are much less allergenic than the hexavalent ones because of their lower penetration, but in high concentrations they can probably trigger allergic reactions. Metallic chromium is not sensitizing because it has very low solubility and the chromate ions are therefore not accessible to the skin (29).

Irritation and ulceration. Skin irritation and ulceration have been reported at an average air concentration of 15 µg hexavalent chromium/m^3 (4-74 µg/m^3) (70) (Table 3). Chrome sores can range in size from small, painful and persistent sores to large, deep ulcers which with continued exposure pose a risk of increased chromium uptake and severe systemic effects. Chrome sores used to be common in chromate factories, particularly among new employees. The frequency has dropped with the years, as changes in production methods have reduced exposure to hexavalent chromium and hygienic routines have been improved (21).

Respiratory passage

Nose. Inhalation of chromate dust or vapor can cause nasal irritation, sores and perforation of the nasal septum. Nasal irritation has been documented in chrome platers exposed to chromic acid in air at levels of 1 µg/m^3 or higher (65) (Table 3). In the same study it was found that at average air levels of 2 to 20 µg/m^3 33% of the workers had nasal sores and 21% had perforated nasal septa. Later studies of chrome platers have reported 48% with sores and 10% with perforated nasal septa at average air concentrations (total chromium) of 11 µg/m^3, and 68% with sores and 35% with perforated septa at 28 µg/m^3 (64) (Table 3). The authors calculated that there was a 50% risk of perforated nasal septum after 2.2 years of chromium exposure as a plater, and 100% risk after 8.2 years, at air exposures of 50 µg Cr/m^3. Production processes were changed in the chromate production industry in Germany in the 1970s, and the chromic acid in the air was reduced to 12-73 µg/m^3 (annual averages). The prevalence of perforated nasal septa subsequently dropped from 30% to 4% (56).

Lungs. Temporary reductions in the lung function parameters FVC (forced vital capacity) and $FEV_{1.0}$ (forced expiratory volume during one second) have been observed among chrome platers exposed to average air concentrations of hexavalent chromium in the range 2-20 µg/m^3. A reduction of FVC was also seen among workers who had low chromium exposure but were also exposed to a mixture of acids and metals (65). Chromium-exposed platers who developed asthma have had positive reactions to a prick test with chromium sulfate (79). Asthmatic construction workers exposed to cement have had positive reactions to inhalation provocation with potassium dichromate vapor (but not cement dust), resulting in a 20% reduction of $FEV_{1.0}$ (61). Among chromate workers, elevated mortality due to chronic obstructive lung disease has been observed for those employed prior to the process changes introduced in the 1960s, but not for those hired later (21). Stainless steel welding with coated electrodes has been associated with development of asthma (55). Elevated frequencies of respiratory symptoms have been noted among welders exposed to hexavalent chromium while welding stainless steel or railroad tracks (88) (Table 3). The symptoms increased at chromium concentration above 20 µg/m^3 but were not correlated to particle concentration. Only one of the 46 controls (a smoker) had respiratory symptoms. Both elevated occurrences of respiratory symptoms and lowered lung function have been documented after 25 years of welding in stainless steel (91). Welders of mild steel and stainless steel (TIG and MIG methods), non-smokers as well as smokers, have elevated incidences of respiratory problems such as chronic bronchitis. No difference related to welding methods has been found, possibly because subjects are usually not grouped according to chromium exposure (10, 23, 28, 111).

Kidneys

Increased excretion of $ß_2$-microglobulin, an indication of damage to proximal renal tubuli, has been observed in chrome platers exposed to hexavalent chromium in average air concentrations of 4-8 µg/m^3 (67) (Table 3). Platers exposed to an average air concentration of 4 µg/m^3 (0.4-183 µg/m^3) total chromium, and with chromium levels of 2.4 µg/g creatinine in urine (0.1-21 µg/g creatinine) had higher excretion of $ß_2$-microglobulin as well as N-acetyl-ß-D-glucosaminidase (NAG), an indication of renal dysfunction (69) (Table 3). Renal effects in the form of elevated excretion of retinol-binding protein in urine at urine chromium levels exceeding 15 µg/g creatinine had been observed in earlier studies of men who had worked in chromate production for seven years (30). The authors suggested that this level in urine was probably the threshold for effects on renal tubules. Air monitoring showed chromium levels that were usually below 50 µg/m^3, though there were some peaks as high as 1000 µg/m^3 (Table 3). Elevated excretion of NAG and other enzymes was also noted in ferrochrome workers who had over 15 µg chromium /g creatinine in urine, leading the authors of this study also to propose a chromium level of 15 µg/g creatinine in urine as the threshold for toxic effects on kidneys (110). It was also concluded that ten years of exposure to hexavalent chromium causes kidney damage. No exposure data/air monitoring data are given in this study. There is a case report describing a plasma cutter in stainless steel with chronic interstitial nephropathy. The chromium

level in the patient's blood was 59.6 nmol/l (about 7 times higher than the reference value) and the urine level was a corresponding 13 µg/g creatinine. There was considered to be no explanation other than the chromium exposure (81). In a study of stainless steel welders, slightly elevated levels of $ß_2$-microglobulin were found in those exposed to air concentrations a bit over 50 µg Cr/m^3, resulting in a concentration of 30 µg chromium/g creatinine in urine. No other effects on kidneys were seen (107). In another study, welders in stainless steel were compared with welders in mild steel, with former welders and with controls. The study showed renal effects in the form of increased protein excretion in urine (albumin, immunoglobulin G, transferrin and orosomucoid, but not $ß_2$-microglobulin) in both groups of welders. No changes could be found in the controls. The former welders showed only a slightly elevated albumin excretion, suggesting the renal effects were at least partially reversible (9).

Liver

Effects of hexavalent chromium compounds on the liver have been observed only at extremely high exposures (97). There are no studies documenting effects on the liver from occupational exposure to hexavalent chromium.

Immunotoxicity

In *in vitro* studies using cells from human bronchial epithelium, chromium exposure has caused some activation of the immune system. Trivalent and hexavalent chromium were about equally effective, probably because of intracellular transformation of the chromium (84). Chromium added to lymphocytes resulted in inhibition of the cell-mediated immune response (37).

Animal data

Skin. Potassium dichromate was assessed in a Guinea Pig Maximization Test to determine its potential for inducing contact allergy (delayed skin hypersensitivity). The induction concentrations were 0.5% intradermal and 1% topical, the test concentration was 0.3%, and 8 of 15 animals were sensitized (63). In another study, potassium dichromate was tested in a Guinea Pig Maximization Test (GPMT), Cumulative Contact Enhancement Test (CCET) and Freund's Complete Adjuvant Test (FCAT) using a multi-dose-response protocol. The highest proportions of sensitized animals were 4 of 5 in the GPMT, 7 of 9 in the CCET, and 7 of 8 in the FCAT (108).

Kidneys. The NOAEL (no observed adverse effect level) for acute effects on the kidneys of rats after intraperitoneal injection was calculated to be 10 mg hexavalent chromium/kg body weight (94).

Liver. Effects of hexavalent chromium compounds have been seen on the liver only at extremely high exposures (103).

Immunotoxicity. Lung inflammation was observed in rats that were exposed by inhalation to soluble potassium dichromate or insoluble barium chromate (about 350 µg/m^3) 25 hours per week for 2 or 4 weeks. There were greater numbers of neutrophiles and monocytes in lavage fluid from the rats that had been exposed to the soluble chromium (14). The total number of macrophages was unchanged, but the

function of lung macrophages regarding IL-1 and TNF-α liberation was inhibited in the rats that had inhaled the soluble chromium compound. The formation of free radicals was increased in the rats that inhaled the insoluble chromium compound. The groups of rats that had been simultaneously exposed to ozone were not observably different.

Teratogenicity

Human data

In the late 1970s, Shmitova reported an elevated incidence of pregnancy and delivery complications in women who worked in chromate production. These results are difficult to assess, since no exposure data are given. No more recent studies of chromium-exposed women were found.

An elevated risk of spontaneous abortion was reported among women whose husbands were welders working with stainless steel: OR 1.99 for arc welding (95% CI 1.07-3.69), OR 1.71 for TIG welding (95% CI 0.84-3.39), and OR 1.1 for welding in mild steel (95% CI 0.5-2.4) (8). The exact times of these miscarriages were not given, which made the exposure data uncertain and left open the possibility of misclassification. A supplementary study was therefore made covering miscarriages in medical records of the wives of 1715 stainless steel welders during the 1977-87 period. No correlation was found between miscarriage and having a husband who was a welder. The possibility of early miscarriage, not requiring contact with medical services, could not be excluded (40).

Studies of male fertility have been focused on welders, and the results have been contradictory. Some studies report deterioration in semen quality, while in other studies no such effect was observed. It has been proposed that it is the heat itself that is behind the tendency to reduced fertility that has sometimes been seen in welders, regardless of which method they use. There is often no exposure data, which makes it impossible to determine whether there is a relationship between exposure to chromium and reduced male fertility. No correlation has been found between chromium in urine and semen quality, or between chromium levels in blood, semen quality and sex hormone level (7, 41). In two studies of welders (stainless steel or mild steel) and different welding methods (TIG, MIG/MAG, arc welding) no effects on sex hormones or semen quality were observed. The chromium levels in urine and blood were as low as those of controls not exposed to metals, and in both studies the authors concluded that the results might have been different if the chromium exposures had been higher (6, 41).

No elevation in the frequency of birth defects or cancer has been seen in the children of welders of stainless or mild steel (8).

Animal data

It has long been known from animal experiments that hexavalent chromium can pass through the placental barrier and exert toxic effects on the embryo or fetus – death, retarded growth and skeletal anomalies (42). Female rats given potassium dichromate in drinking water (250, 500 or 750 ppm) for three months before mating had lower

fertility and higher resorption of fetuses, and there were skin hemorrhages and skeletal defects in the young of the rats given 500 or 750 ppm. These doses also had a general effect on the mothers (50). When mice were given chromium in drinking water (250, 500 or 750 ppm) during gestation they had a higher frequency of abortions, and at the two higher doses there were effects on growth, hemorrhages and skeletal defects in the young (47). No general effects on the mothers were observed. Mice were given 1000 ppm potassium dichromate (hexavalent) or chromium chloride (trivalent) in drinking water during gestation and lactation, and the young of both groups had impaired reproductive function and fertility in adulthood (2).

It was shown in 1990 that hexavalent chromium has toxic effects on the reproductive systems of male rats: intraperitoneal injections of sodium chromate (1, 2, or 4 mg/kg) were given daily for 5 days (24), and two months later all the animals had dose-related changes in testes and lower sperm counts. No such effects were observed with chromium chloride (trivalent chromium). In a subsequent long-term study, rats were given 0.5 mg/kg sodium chromate intraperitoneally 5 days/week for 8 weeks. Effects of the treatment included reduced sperm motility and lower testosterone levels. The changes were reversible (25).

Mutagenicity and genotoxicity

In its 1990 monograph, the IARC concluded that many hexavalent chromium compounds with various degrees of solubility can cause mutations and DNA damage in bacteria and in mammalian and human cells. Trivalent chromium can also be genotoxic under certain conditions. The trivalent form, however, is considerably less active than the hexavelent form, probably due to its lower degree of absorption. Indications of chromosome damage were observed in an *in vitro* study in which Chinese hamster ovary cells were exposed to trivalent chromium in the form of chromium picolinate (95). It has been observed in several other *in vitro* studies that trivalent chromium can form bonds with DNA and interfere with replication (11, 87, 90). When hexavalent chromium was added to cell cultures it was transformed to trivalent chromium, forming in the process DNA adducts with mutagenic effects (106). The experimental conditions of an *in vitro* study play a large role in determining the reactivity of the intermediates, which probably explains why results are sometimes contradictory (96).

Studies of chromium-exposed workers have also reported contradictory results, with increases of chromosomal aberrations and sister chromatid exchanges in some studies that could not be confirmed in others. Several methods using biological samples to trace the mutagenic effects of chromium on the individual have been developed and tried in recent years. Blood samples have been used, since blood contains nucleated lymphocytes and cells from the target organs for chromosome damage are usually more difficult to obtain. Methods presently in use are based on detection of changes in DNA, usually in the form of DNA-protein cross-links, sister chromatid exchanges or DNA strand breaks, or on the formation of the oxidized deoxynucleoside 8-hydroxy-deoxyguanosine (8-OHdG) as an expression of oxidative stress (18, 74, 113). Lymphocytes from chromate workers exposed to hexavalent

chromium (<10 µg/m^3, with occasional peaks up to 55 µg/m^3) were examined in a pilot study. The chromium-exposed workers had higher levels of chromium in blood and urine than controls, but no increase in DNA strand breaks or 8-OHdG was seen (34). In 1990, when the IARC published its monograph on chromium, evidence of genotoxic effect on welders was still judged to be inconclusive. More recent studies of stainless-steel welders (arc welding) have shown a significant increase in the frequency of chromatid breaks at an average exposure of 35 µg hexavalent chromium/m^3 (0.6-252 µg/m^3) (44) (Table 3). Welders of stainless steel using other methods (TIG, MIG/MAG), whose average measured exposure to hexavalent chromium was 1.8 µg/m^3 (0.04 -12 µg/m^3) showed no increase in frequency of DNA damage (45). Welders exposed to chromium and nickel (urine levels corresponding to exposures of 70-80 µg CrO_3/m^3 and <100 µg Ni/m^3) showed a significant increase in the frequency of DNA-protein cross-linking but no indications of DNA strand breaks (82) (Table 3). In a later study of welders with higher exposure to chromium and nickel (levels in erythrocytes corresponding to exposures of about 100 µg CrO_3/m^3 and 300 µg Ni/m^3), a significant increase in frequency of DNA strand breaks was observed (112) (Table 3). In the first study, the frequency of sister chromatid exchanges was significantly lower in the welders than in controls, whereas in the second study it was significantly higher. Since inconsistent findings regarding chromatid exchanges had also been reported earlier, the authors discuss factors other than chromium exposure that might conceivably have affected the findings: nickel exposure, age, smoking and drinking habits etc. (112). They also discuss the saturation effect in DNA-protein cross-linking observed earlier (18) in lymphocytes at a blood content of 7-8 µg Cr/l (corresponding to exposure to 30 µg CrO_3/m^3 air). As a possible reason for the observation of more DNA-protein cross-linking with exposure to lower chromium levels and more DNA strand breaks at higher exposures (112), the authors suggest that if earlier theories are correct – that it is DNA-protein cross-linking that is the primary cause of cancer - exposures below 50 µg/m^3 may be more hazardous than higher ones (112). Another widely spread hypothesis is that high chromium levels are more harmful, since they afford the cell's repair system too little time to repair the breaks in DNA strands.

Carcinogenicity

Human data

Lung cancer

Chromium has been suspected of causing cancer for 100 years, and over the past century there have been numerous studies to clarify the connection. Both the valence and the solubility of the chromium compound are relevant to its carcinogenic effect. The IARC monograph on chromium published in 1990 (42) states that there is "sufficient evidence" that the hexavalent chromium compounds associated with chrome plating and production of chromates and chromate pigments are carcinogenic to humans, and "limited evidence" of carcinogenicity for the chromium compounds present in welding fumes and gases, but welding fumes were judged to be "probably carcinogenic." Metallic and trivalent chromium were not classified as carcinogenic,

since there was no proof of their carcinogenicity to humans. A problem with many studies is that they contain inadequate exposure data for chromium and asbestos and no information on smoking habits, which makes any derived estimates of risk uncertain. There are also problems with extrapolating data from animal experiments. A review article published in 1993 (59) concludes that inhalation of hexavalent chromium can cause cancer. Zinc chromate was considered especially potent, but calcium chromate was also regarded as carcinogenic.

Chromate production. In the 1950s, it was noticed in the United States, Great Britain, Japan, Germany and Italy that chromate workers had a greater than average risk of developing cancer in the lungs or nose, and since then a large number of epidemiological studies have been made. They show a clear correlation between cancer mortality and work in chromate production. The mortality due to lung cancer has dropped in recent years. In a British follow-up study (Table 2), the lung cancer mortality was twice the adjusted national death rates among chromate production workers in two factories who were hired prior to 1958-1960, when the production process was modified and limestone was removed (21). In a third chromate factory, which was closed down in 1966, lung cancer mortality was less elevated. Lung cancer mortality was not elevated among workers hired after the process change. This improvement was attributed to the absence of calcium chromate, which was no longer formed during the production process, and to hygienic improvements in working conditions. No monitoring data are given, and there is no information on smoking habits or asbestos exposure. A similar process modification was made in Germany in 1957-1963 (56), and was also followed by a drop in lung cancer mortality (Table 2). The remaining elevation in risk was attributed to smoking and/or exposure to asbestos. No data on exposure prior to 1977 are given because of differences in analysis methods, but between 1977 and 1987 the measured annual averages were in the range 12 to 73 µg Cr/m^3 (56). When workers in an American chromate factory built in 1971 were followed up in 1989 (Table 2) there was no elevation in lung cancer mortality in the group of 353 workers who began work in the chromate industry in 1971. There was, however, an elevation (3 of 5 lung cancer cases) among the 45 workers who had transferred from another chromate production factory where exposure to total chromium (measured by personal monitors) was 5 to 20 times higher (50 to 5670 µg Cr/m^3, compared to a maximum of 289 µg Cr/m^3 with >99% of values below 50 µg Cr/m^3). The authors point out that the short follow-up period covered by the study combined with its small size weakens the results (80).

Chrome pigment production. Several epidemiological studies have reported an elevated incidence of lung cancer among workers in the pigment production industry, especially with production of zinc chromate (59). Exposure to lead chromate has also been associated with elevated risk of lung cancer (59). In a Japanese cohort study covering 666 workers in the chrome pigment industry, lung cancer mortality in 1989 was calculated for those who had been employed for at least a year between 1950

Table 2. Epidemiological studies of lung cancer mortality in workers occupationally exposed to chromium. The numbers of cases expected are derived from mortality in the general population in the same areas. SMR = Standard Mortality Ratio

Studied population	Cases observed	Cases expected	SMR (95% CI) *(90% CI)	Ref.
Two factories with chromate production Workers hired before 1958-60; 1422 subjects	175	88.97	1.97	21
Workers hired after 1960; 670 subjects	14	13.7	1.02 (0.56-1.71)	21
One factory with chromate production Workers hired before 1965; 199 subjects	12	9.91	1.21	21
Two factories with chromate production Workers hired before 1957-63; 739 subjects	66	32.27	2.27 (1.78-2.85)	56
Workers hired after 1957-63; 678 subjects	9	7.34	1.26 (0.58-2.38)	56
Chromate factory built in 1971 New employees; 353 subjects	2	2.1	0.97 *(0.17-3.06)	80
Workers transferring from another chromate factory; 45 subjects	3		1.22/3 years'exp. *(1.03-1.45)	80
Five factories with chromate pigment production New hires 1950-75; 666 subjects	3	2.95	1.02 (0.21-2.98)	49
One factory with nickel/chrome plating New hires 1946-75; 812 men950 women	men: 40 women: 15	25.41 8.57	1.57 (1.13-2.14) 1.75 (0.98-2.89)	92

and 1975 (Table 2). The study found no elevation in risk of lung cancer associated with exposure to chromates of zinc, lead or strontium. No exposure data are given (49).

Chrome plating. Elevated mortality due to lung cancer among chrome platers exposed to hexavalent chromium has been found in earlier studies (58), and has also been found in a more recent follow-up study from Great Britain (Table 2), which calculated mortality in 1995 for chrome platers who had worked for at least six months between 1946 and 1975 (92). More than five years of occupational exposure to hexavalent chromium (but also to some nickel) was correlated to an elevated risk of death due to lung cancer (Table 2). It was estimated that prior to 1973 the air levels of hexavalent chromium were probably above 25 μg/m^3. Smoking habits are not covered.

No elevation in risk was seen for plating workers exposed to nickel only (92). In a later analysis based on these results, a risk estimate was calculated for lung cancer among chrome platers: the relative risk ranged from 1.22 to 1.62, depending on which defined confounding factors were present (93).

Ferrochrome. Earlier studies have not been able to establish whether ferrochrome work involves an elevated risk of lung cancer (58). There is no recent study focused on this question.

Welding. Hexavalent chromium compounds are formed during welding in stainless steel. There are several studies of the relationship between development of lung cancer and exposure to welding fumes from welding in stainless steel. A meta-analysis of five studies revealed an elevated risk of lung cancer (OR 1.9; 95% CI 1.3-2.9) when smoking and asbestos exposure were considered (89). In a case-control study, in which the cases consisted of lung cancer patients and the controls were drawn at random from the studied population, it was found that three of the cancer cases, but none of the controls, had welded alloys containing chromium and nickel for more than 6000 hours (48). It has been asserted that both welders who work with stainless steel and those who work with mild steel have an elevated risk of contracting lung cancer (5, 20, 38, 60, 72, 76). In 1997 Moulin published a meta-analysis of 49 published epidemiological studies of welders (31 cohort studies and 18 case-control studies) (77). In the conclusion he observed that the relative risk of lung cancer is 30 to 40% higher among welders than among the general population. The analysis shows elevated risk for welders of both mild steel and stainless steel. The analysis of the correlation between lung cancer and welding in mild steel is based on four studies. In the two studies with the highest risk estimates, the workers' known exposure to asbestos is not included in the calculations. In a follow-up study of stainless steel welders working for at least five years between 1950 and 1965, elevated lung cancer mortality was seen in a “high-exposure” group exposed to hexavalent chromium, probably above 20 µg/m^3 (75).

Nasal cancer

It has long been known that occupational exposure to hexavalent chromium carries a risk of developing sinonasal cancer (42). A Nordic case-control study was made to study nasal and sinonasal cancer and its correlation with various types of exposure. These cancers were more common among welders exposed to chromium and nickel (OR 3.3: 95% CI 1.1-9.4) (39). An elevated incidence of cancer in the nose or sinuses (4 observed cases, 0.26 expected; SMR 1538) was seen in welders with more than 20 years of employment and “high” exposure to hexavalent chromium (estimated from job category). In the chromate industry, the elevation in risk disappeared after the process changes in the 1960s. The accepted explanation was that calcium chromate was no longer formed (21). Four cases of cancer in the nasal region are described in a case report, all of them men employed at the same chromate factory for 19 to 32 years (85). Three of the men had previously been treated for lung cancer that developed after 6 to 15 years of work. No information is given on the number of workers at the factory, the type of exposure or the smoking habits of the

patients. There are also studies in which no elevation in the risk of nasal cancer is noted despite the higher risk of lung cancer (56).

Other cancers
Elevated risk of stomach and intestinal cancer has been noted in several studies of workers occupationally exposed to chromium. It is reasonable to assume that it may be attributed to particles of hexavalent chromium that are swallowed, exposing the mucous membranes of the stomach and digestive tract (59). Elevated risks not only for lung cancer, but for stomach and kidney cancer as well, have been observed among welders (52). Despite the elevated risk of lung cancer, no elevation in mortality due to gastrointestinal cancer has been seen among chromate workers employed prior to 1965 (21).

Animal data
The IARC, in its 1990 monograph, stated that there is "sufficient evidence" that the hexavalent compounds calcium chromate, zinc chromate, strontium chromate and lead chromate are carcinogenic to laboratory animals; "limited evidence" that the hexavalent chromium compounds chromium trioxide (chromic acid) and sodium dichromate are carcinogenic to laboratory animals; "inadequate evidence" that metallic chromium, barium chromate and trivalent chromium compounds are carcinogenic to experimental animals; and "inadequate evidence" that welding fumes are carcinogenic to laboratory animals. There are no subsequent studies either supporting or contradicting these assessments.

Dose-response/dose-effect relationships

There are clear problems with deriving a reliable dose-response relationship for hexavalent chromium, since exposure data is sparse even in recent studies. In addition, there is often simultaneous exposure to nickel, asbestos and/or tobacco smoke, making it difficult to distinguish the specific effect of chromium. As shown by the summary in Table 3, bronchial irritation has been reported at chromic acid levels of 1-2 µg/m^3 in air, and transient reductions in lung function parameters and chrome sores in the nose have been reported at levels of 2-20 µg/m^3. Perforated nasal septa are reported at exposures of 11 µg/m^3 hexavalent chromium, and their frequency rises with increasing exposure. At a total chromium level of 4-6 µg/m^3 there are effects on the kidneys, with increased excretion of NAG and ß$_2$-microglobulin. Renal effects have been observed among welders with urine chromium levels of 30 µg/g creatinine, and 15 µg/g creatinine has therefore been proposed as the threshold value for renal toxicity. Identical exposures seem to give rise to different chromium levels in biological samples from different individuals and also to differences in the severity of the toxic effects. Elevated frequencies of chromatid breaks have been observed in blood samples from stainless steel welders exposed to 35 µg/m^3 hexavalent chromium (0.6-252 µg/m^3), elevated frequencies of DNA-protein cross-linking at 70-80 µg/m^3, and elevated frequencies of DNA strand breaks at 100 µg/m^3. The lung cancer incidence among workers exposed to chromium is

Table 3. Reports on health effects other than lung cancer associated with occupational exposure to chromium

Exposure (µg/m^3)		Exposure situation	No. of subjects	Observed effects	Ref
Total Cr	CrO_3				
	1-1.9	Plating	19	16% w/observed nasal irritation 21% w/atrophy in nasal mucuos membranes	65
	2-20	Plating	24	Transient reductions in lung function parameters; 50% w/nasal irritation 33% w/atrophy 21% w/perforated nasal septum	65
4 (0.4-183)		Plating	34	24% w/elevated NAG excretion 15% w/elevated ß$_2$-microglobulin excr.	69
	4-8	Plating	13	15% w/elevated ß$_2$-microglobulin	67
	11-20	Plating	5	60% w/elevated ß$_2$-microglobulin 40% w/perforated nasal septum	67
11 (0.5-40)		Plating	29	48% w/chrome sores in nose 10% w/perforated nasal septum	64
15 (4-74)		Plating	17	59% w/nasal irritation 82% w/skin irritation 65% w/chrome sores (skin)	70
>20		Welding stainless steel	37	35% w/respiratory symptoms	88
>20		Welding railroad tracks	8	50% w/respiratory symptoms	88
28 (0.7-168)		Plating	31	68% w/sores in nose 35% with perforated nasal septum	64
<50 (usually)		Chromate production	43	21% w/elevated excretion of retinol-binding protein	30
64 (7-161)		Welding stainless steel	52	17% w/elevated ß$_2$-microglobulin	107
75 (7.5-422)	35 (0.6-252)	Welding stainless steel	42	Elevated frequency of chromatid breaks	44
70-80 (estimated)		Welding stainless steel	39	Elevated frequency of DNA-protein cross-linking	82
100 (estimated)		Welding stainless steel	39	Elevated frequencies of DNA strand breaks and sister chromatid exchanges	112

lower today than it was thirty years ago, probably because process methods and working conditions have been improved and exposure has been reduced. The Dutch Expert Committee for Occupational Standards has recently concluded that 40 years of exposure to 8 µg respirable hexavalent chromium dust/m^3, with linear extrapolation, yields an additional lung cancer mortality risk of 1.4 cases per 100 exposed workers (22).

Conclusions

The critical effect of occupational exposure to hexavalent chromium is its irritation of mucous membranes in the upper and lower respiratory passages. Mutagenic effects have also been observed in blood samples from chromium-exposed welders. Hexavalent chromium is corrosive to skin and mucous membranes, and skin contact can also induce contact allergy. Asthma has also been described. Hexavalent chromium is carcinogenic. Occupational exposure has been found to induce cancer in lungs and nose. Hexavalent chromium has caused reproductive disturbances in experimental animals.

Trivalent chromium can cause skin irritation and allergic contact eczema. There are no data from which to determine a critical effect of exposure to trivalent chromium, metallic chromium or other chromium compounds.

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Consensus Report for Pentyl Acetate (Amyl Acetate)

June 14, 2000

Pentyl acetate has several isomeric forms, and they often occur in mixtures. Industrial grade pentyl acetate consists mostly of 1-pentyl acetate (4). In this report "pentyl acetate" is placed in quotation marks to indicate that the isomer(s) referred to was not specified: in most cases, however, it is probably 1-pentyl acetate.

Chemical and physical data. Uses

1-pentyl acetate

CAS No.:	628-63-7
Synonyms:	n-amyl acetate, 1-amyl acetate
Formula:	$CH_3COO(CH_2)_4CH_3$
Boiling point:	149°C
Melting point:	-70.8°C
Density:	0.879 g/ml (20°C)
Vapor pressure:	0.53 kPa (20°C)
Saturation concentration:	5230 ppm (20°C)

3-methylbutyl acetate

CAS No.:	123-92-2
Synonyms:	isopentyl acetate, i-pentyl acetate, isoamyl acetate, i-amyl acetate
Formula:	$CH_3COO(CH_2)_2CH(CH_3)_2$
Boiling point:	142°C
Melting point:	-78.5°C
Density:	0.876 g/ml (15°C)
Vapor pressure:	0.53 kPa (20°C)
Saturation concentration:	5230 ppm (20°C)

2-methylbutyl acetate

CAS No:	624-41-9
Synonyms:	(isoamyl acetate)*
Formula:	$CH_3COOCH_2CH(CH_3)CH_2CH_3$
Boiling point:	141-142°C
Melting point:	-
Density:	0.880 g/ml (12.5°C)
Vapor pressure:	-

1-methylbutyl acetate

CAS No:	626-38-0
Synonyms:	2-pentyl acetate, 2-amyl acetate, sec-amyl acetate,** 2-acetoxypentane
Formula:	$CH_3COOCH(CH_3)(CH_2)_2CH_3$
Boiling point:	134°C
Melting point:	-78.5°C
Density:	0.864 g/ml (20°C)
Vapor pressure:	0.93 kPa (20°C)
Saturation concentration:	9180 ppm (20°C)

3-pentyl acetate

CAS No.:	620-11-1
Synonyms:	3-amyl acetate, 3-acetoxypentane
Formula:	$CH_3COOCH(CH_2CH_3)_2$
Boiling point:	133°C
Melting point:	-
Density:	0.871 g/ml (20°C)
Vapor pressure:	-

1,1-dimethylpropyl acetate

CAS No.:	625-16-1
Synonyms:	tert-amyl acetate, 2-methyl-2-butyl acetate
Formula:	$CH_3COOC(CH_3)_2CH_2CH_3$
Boiling point:	124.5°C
Melting point:	-
Density:	0.874 g/ml (19°C)
Vapor pressure:	-

For all the above isomers: Molecular weight: 130.18

Conversion factors: 1 ppm = 5.402 mg/m^3 (20°C), 1 mg/m^3 = 0.185 ppm (20°C)

* irregular name that may occur in older literature.

** "sec-amyl acetate" usually refers to this isomer, but not always.

Pentyl acetate at room temperature is a clear, colorless liquid with a characteristic fruity odor (4, 13, 21). The odor thresholds reported in various studies range from about 0.01 to 7 ppm for 1-pentyl acetate, and from 0.001 to 200 ppm for 3-methyl-butyl acetate (2). Pentyl acetate is only slightly soluble in water, but the isomers differ somewhat in this respect (6, 31). Pentyl acetate – especially 1-pentyl acetate and 1-methylbutyl acetate – is used as a solvent for paints, imitation leather, printing products, cellulose, furniture polish etc. (13). 1-Pentyl acetate has been used medically as an anti-inflammatory agent (4, 6). In nature, 1-pentyl acetate has been

identified in fruits, and 3-methylbutyl acetate occurs as a pheromone in certain beetles (13).

Uptake, biotransformation, excretion

Pentyl acetate is readily absorbed in the lungs. One work (21) reports partition coefficients of 92 for 1-pentyl acetate and 59 for 3-methylbutyl acetate in human blood/air *in vitro.* Substantial uptake of pentyl acetate in liquid form can also occur via the skin. Skin uptake has been calculated on the basis of physical data for 1-pentyl acetate: the calculated rate of uptake via skin exposed to a saturated aqueous solution of 1-pentyl acetate was 0.46 mg/cm^2/hour (14). This is equivalent to about 35% of uptake from inhalation exposure to 100 ppm (525 mg/m^3).

Pentyl acetate is hydrolyzed in the body to acetate (acetic acid), a substance common in normal metabolism, and pentanol (amyl alcohol), and then further biotransformed (4). *In vitro* data suggest that in the liver and respiratory passages of experimental animals 1-pentyl acetate is rapidly hydrolyzed by carboxyl esterases (10). Pentanol, which is a substrate for the enzyme alcohol dehydrogenase, is a competitive inhibitor of ethanol metabolism (4).

Toxicology

Human data

In one study, ten volunteers with unimpaired sense of smell were exposed (nasal inhalation) for 10 seconds to 0, 1.3, 4, 13 or 42 ppm "pentyl acetate." Two other substances were also tested in this study. The subjects could detect the odor of "pentyl acetate" at all concentrations. They also rated nasal irritation on a scale of 0 (none at all) to 100 (equivalent to the strongest irritation previously experienced). Their ratings averaged about 4 for the control exposure, 10 for 1.3 ppm, 20 for 4 ppm, and 25 for the exposure to 42 ppm "pentyl acetate." The tidal volume of nasal inhalation ("pentyl acetate") was reduced by about 50 ml at 1.3 ppm and 70 ml at 42 ppm (37). The authors regarded the reductions as significant at 4 ppm and above, although no statistical analysis is presented. It is difficult to assess the results of this study, since a) the effects of the exposures to "pentyl acetate" were not well described and it is not clear what caused the reduction in tidal volume, and b) there are virtually no comparable studies of other air contaminants using this method. This study has therefore not been taken into consideration in the assessment of the irritating qualities of "pentyl acetate."

In other studies, anosmic subjects (with no sense of smell) were used to determine the threshold value for nasal irritation (1, 9, 36). In one work, the threshold concentration for 1-pentyl acetate was reported to be 1648 ppm. In this experiment, 4 subjects tested the substance by "sniffing" vapors of different concentrations sprayed into the nostrils (1, 9). A threshold value of 266 ppm for "pentyl acetate" is reported in an abstract (4 subjects, nasal inhalation) (36).

An older study in which ten persons were exposed in a chamber to "pentyl acetate" for 3 to 5 minutes reports that some of them experienced slight throat discomfort

(subjective assessments) at an air concentration of 100 ppm, and at 200 ppm most of them reported throat irritation. Some subjects reported substantial throat irritation as well as mild irritation of eyes and nose at this concentration, and at 300 ppm most of them suffered eye and nose irritation. The majority judged 100 ppm to be the highest concentration acceptable for an 8-hour workday (29). Slight irritation of respiratory passages, eyes, nose and throat is also reported in another older study in which subjects in an exposure chamber were exposed to 185 ppm 3-methylbutyl acetate for 5 minutes; at 1850 ppm the irritation was more pronounced, especially in the respiratory passages (16). In an experiment made in the early 1900s, two subjects were exposed to 925 ppm 3-methylbutyl acetate for 30 minutes. They initially reported throat irritation, including some coughing, and later on they reported additional symptoms including eye irritation, nasal secretion, dry throats, tightness in the chest and slight drowsiness (23).

Studies of workers occupationally exposed to pentyl acetate are scarce. There are a few reports mentioning dizziness, faintness, drowsiness, coughing, nausea and effects on the optic nerve, but no air concentrations are given (4, 18, 23). Irritation of the conjunctiva, but no effect on the cornea, is reported in an Italian study of workers exposed to "pentyl acetate" in the range 3750 to 15,000 ppm along with ethyl acetate (4).

Animal data

Pentyl acetate has low acute toxicity, both when given orally and when applied to skin. The LD_{50} for oral administration to rats and rabbits has been reported to be between 6.5 and 16.6 g/kg (20, 22, 28, 35). For skin application of the mixed isomers (24 hours, rabbits) the LD_{50} was reported to be >20 ml/kg (>about 17.4 g/kg) (35).

Descriptions of the effects of inhaled pentyl acetate on experimental animals mention primarily irritation of eyes and respiratory passages and symptoms indicating effects on the central nervous system (Table 2). The threshold concentration for stimulation of the trigeminal nerve (irritation) in anesthetized rats exposed to "pentyl acetate" was reported to be 252 ppm (34). The RD_{50} for 1-pentyl acetate (the concentration causing a 50% reduction in respiratory rate, a measure of sensory irritation in the respiratory passages) was reported to be about 1500 ppm in some short-term experiments with mice (3, 8, 27; cited in 33), whereas the reported RD_{50} for 3-methylbutyl acetate (mice) is 1056 ppm (27; cited in 33). Irritation of eyes and respiratory passages has also been observed in experimental animals after a minute or so of exposure to about 2000 ppm 1-methylbutyl acetate or 3-methylbutyl acetate (Table 2).

In order to elucidate the effects on the central nervous system, the locomotion and behavior of mice were observed during 20 minutes of exposure to 500, 1000, 2000, or 4000 ppm "pentyl acetate" (7). Significant reductions in activity and difficulty in rousing the animals were noted at 4000 ppm. It was also reported that animals exposed to 2000 or 4000 ppm were easy to remove after the exposure period because they were lethargic. At exposure to 1000 ppm or higher there were mouth movements, and tremor and muscle spasms were noted when the animals were handled. Concentration-dependent effects on locomotion were noted during the exposures to

the higher dose levels (which levels are not reported). Older studies report disturbed balance in experimental animals after a few hours of exposure to various isomers of pentyl acetate at air concentrations of about 3000-5000 ppm or higher (Table 2).

Effects other than those on the respiratory passages and central nervous system have been reported in a few studies of 3-methylbutyl acetate and "pentyl acetate" (Table 2). Some older studies report albuminuria, pathological changes in kidneys, liver, spleen, heart and adrenals, and secondary anemia in experimental animals repeatedly exposed to air concentrations of 1850 to 4800 ppm (16, 31). These studies were not made in accordance with modern praxis, and the validity of the results is thus difficult to judge. An EU document (13) reports that "metabolic imbalance in the liver" was observed in rabbits exposed to 1850 ppm "pentyl acetate" 2 hours/day for 120 days. No further details of this study are given and the source of the information is obscure. An Italian study cited in the Swedish criteria document (4) reports that effects on the liver were noted in histological examination and serum enzyme analyses of rabbits that had been exposed to 4300-5600 ppm "pentyl acetate" 1 hour/day for 50 weeks. In a study with guinea pigs, 750 or 1500 mg/kg of undiluted 1-pentyl acetate injected into the abdominal cavity resulted in elevated activity (dose-dependent) of the enzyme ornithine carbamyl transferase (OCT) in serum, and histopathological examination revealed moderate fat deposition in the liver in the low-dose group (three of four animals in the high-dose group died). The authors concluded that 1-pentyl acetate has relatively low hepatotoxicity (12).

Damage to the corneal epithelium – no longer visible after a day or so – was reported when liquid "pentyl acetate" was applied to the eyes of rabbits for 2 minutes (18). Slightly reddened mucous membranes and watery eyes were reported in another study (16) in which 3-methylbutyl acetate was dropped into the eyes of rabbits. In a standardized test for eye irritation using rabbits, "pentyl acetate" was ranked 2 on a ten-point scale (35) and in the same study minor indications of local irritation (ranked 3 on the scale) were noted when undiluted "pentyl acetate" was applied to the skin of rabbits (35). Undiluted pentyl acetate (60% 1-pentyl acetate, 35% 2-methylbutyl acetate and 5% 3-methylbutyl acetate) applied to the skin of guinea pigs and left for 24 hours under occlusion caused minimal irritation. The results of the Guinea Pig Maximization Test indicated that this mixture might also possibly be somewhat skin-sensitizing (5).

Mutagenicity, carcinogenicity, effects on reproduction

In *in vitro* tests with various strains of *Salmonella typhimurium,* both with and without metabolic activation, 3-methylbutyl acetate had no mutagenic effect, and it induced no DNA damage when tested *in vitro* on *B. subtilis* and *E. coli* (19, 26, 38, 39). No mutagenicity/genotoxicity was observed when 3-methylbutyl acetate was tested on *Saccharomyces cerevisiae* (25, 40), and results were also negative when it was tested for mutagenic activity or chromosomal aberrations on mammalian cells *in vitro* (19, 26). It is also reported that no mutagenic activity (gametes) was observed when 3-methylbutyl acetate (>99% pure) was given to *Drosophila* orally (4800 ppm in diet), or via injection (14,000 ppm; 14 mg/g solvent) (17). In a study in which

grasshopper embryos were exposed to vapor of "pentyl acetate" (air concentration not reported), cytogenetic assays revealed no effects on mitosis (24).

There are no carcinogenicity data for any of the isomers.

Data on reproduction toxicity are also extremely sparse. From an *in vitro* test with hydra cells, it was concluded that the embryonic cells were no more sensitive than maternal cells to the toxic effects of "pentyl acetate" and 3-methylbutyl acetate (30). In addition to this study, there are two unpublished papers (Union Carbide, 1994 a, b) which are cited in the German threshold limit document (11). In these studies rats and rabbits were exposed to 500, 1000, or 1500 ppm pentyl acetate (65% 1-pentyl acetate and 35% 2-methylbutyl acetate) 6 hours/day on days 6-15 (rats) or 6-18 (rabbits) of gestation. On the basis of these studies 1-pentyl acetate and 2-methyl-butyl acetate were judged to be not damaging to fetuses of rabbits exposed to 1500 ppm and rats exposed to 500 ppm (11). Somewhat lower fetal weights and elevated incidences of some variations (including incomplete inflation of alveoli, effects on ossification) were noted in fetuses of the rats exposed to 1000 and 1500 ppm (11).

Dose-effect/dose-response relationships

There are no data on occupational exposure that can be used as a basis for describing a dose-response or dose-effect relationship for pentyl acetate. Several studies, however, report irritation of mucous membranes in the respiratory passages and eyes of subjects exposed to pentyl acetate in exposure chambers (Table 1). In an older study, slight throat discomfort was reported by some of the subjects exposed to 100 ppm "pentyl acetate" for 3 to 5 minutes in an exposure chamber. Lower air concentrations were not reported. Moderate throat irritation and slight irritation of eyes and nose were reported at 200 ppm, and it is stated that a majority of the subjects experienced throat irritation at this air concentration. At 300 ppm, most of the subjects reported irritation of eyes and nose as well (29). In another older study (16), some subjects reported mild irritation of eyes, nose, throat and respiratory passages after 5 minutes in a chamber containing 185 ppm 3-methylbutyl acetate, and at an air concentration of 1850 ppm (5 minutes) the subjects reported moderate irritation of eyes, nose, throat and respiratory passages, with symptoms including cough, chest tightness, shallow breathing and watery eyes (16). Available data do not allow a potency ranking of the different isomers.

Dose-effect relationships observed in laboratory animals exposed by inhalation to the different isomers of pentyl acetate are summarized in Table 2.

Conclusions

The critical effect of exposure to pentyl acetate is judged to be irritation of the respiratory passages, which has been reported by people briefly exposed to air concentrations of 100 ppm or higher. There are no reliable studies of lower exposures. The available data do not allow individual assessments of the isomers.

Table 1. Effects on human subjects experimentally exposed to vapor of pentyl acetate

Exposure	Isomer	Effects	Ref.
2000 ppm, brief	1-methylbutyl acetate	"extremely unpleasant"	32
1850 ppm, 5 min.	3-methylbutyl acetate	moderate irritation of airways, eyes, nose, throat (cough, chest tightness, shallow breathing, watery eyes)	16
1648 ppm, 2 seconds	1-pentyl acetate	threshold for nasal irritation.	1, 9
925 ppm, 5 or 30 min.	3-methylbutyl acetate	irritation of throat and eyes, nasal secretion, dry throat, chest tightness, slight drowsiness	23
266 ppm	"pentyl acetate"	threshold for nasal irritation with nasal breathing	36
200 ppm, 3 to 5 min.	"pentyl acetate"	throat irritation in majority of 10 subjects, mild eye and nose irritation in a few of them	29
185 ppm, 5 min.	3-methylbutyl acetate	slight irritation of respiratory passages, eyes, nose and throat	16
100 ppm, 3 to 5 min.	"pentyl acetate"	slight throat discomfort in a few of 10 subjects	29

Table 2. Effects on experimental animals exposed to pentyl acetate by inhalation

Exposure	Isomer	Species	Effects	Ref.
7500 ppm 2 hours/day 60 days	"pentyl acetate"	rabbit	some degeneration of optic nerve	4, 18
5000 ppm 13 hours 30 min.	1-methylbutyl acetate	guinea pig	eye and nose irritation after 1 min.; tear flow after 5 min.; loss of muscular coordination after 90 min; narcosis after 5 to 9 hours, slight hemorrhaging in lungs	32
4300-5600 ppm 1 hour/day 50 weeks	"pentyl acetate"	rabbit	liver damage	4
4800 ppm 1 hour/day 40 days	"pentyl acetate"	rabbit	inflammatory changes in respiratory passages, kidney damage, changes in spleen, liver and heart, anemia	31

Table 2. Cont.

Exposure	Isomer	Species	Effects	Ref.
4700 ppm 2 hours/day 4 days	"pentyl acetate"	guinea pig	inflammatory changes in respiratory passages, kidney damage, hepatitis, changes in adrenals and spleen	31
4400 ppm 6 hours 45 min.	3-methylbutyl acetate	cat	watery eyes, salivation, disturbed balance after 2-3 hours, deep narcosis after 5-6 hours	16
4000 ppm 20 min.	"pentyl acetate"	mouse	reduced activity, pronounced lethargy, effects on locomotion, tremor, spasms, eye irritation	7
2850 ppm 6 hours	3-methylbutyl acetate	cat	watery eyes, salivation, disturbed balance after 5 hours 35 min.	16
2000 ppm 13 hours 30 min	1-methylbutyl acetate	guinea pig	nasal irritation after 1 min., eye irritation after 1 to 30 min.	32
2000 ppm 20 min	"pentyl acetate"	mouse	effects on locomotion, tremor, spasms	7
1850 ppm 2 hours/day 120 days	"pentyl acetate"	rabbit	"metabolic imbalance in the liver"	13
1850 ppm 8 hours/day 6 days	3-methylbutyl acetate	cat	watery eyes, salivation, inflammatory changes in respiratory passages, indications of kidney damage, cirrhosis	16
1850 ppm	3-methylbutyl acetate	cat	immediate coughing and irritation of mucous membranes in eyes, nose and mouth	15
1562 ppm, 5 min.	1-pentyl acetate	mouse	RD_{50}	33
1531 ppm, 10 min.	1-pentyl acetate	mouse	RD_{50}	33
1438 ppm, 30 min.	1-pentyl acetate	mouse	RD_{50}	8
1056 ppm, 5 min.	3-methylbutyl acetate	mouse	RD_{50}	33
1000 ppm, 20 min.	"pentyl acetate"	mouse	tremor/shaking, spasms	7
252 ppm, 10 seconds	"pentyl acetate"	rat	threshold concentration for stimulation of trigeminal nerve	34

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Consensus Report for Wood Dust

June 25, 2000

This report is based on the criteria document previously published in *Arbete och Hälsa* (9), two subsequently published critical reviews of the international literature (8, 43), and research published in 1986 –1998. The text contains a number of abbreviations, which are defined in Appendix 1.

Introduction

Wood dust is usually divided into two types: softwood and hardwood (29). In general, the first type comprises conifers, and includes the spruce (*Picea*), pine (*Pinus*) and larch (*Larix*) of northern latitudes as well as cedar (*Cedrus, Chamaecyparis, Thuja*), cypress (*Cupressus*), hemlock (*Tsuga*) and redwood (*Sequoia*). The hardwoods include deciduous trees such as ash (*Fraxinus*), aspen (*Populus*), birch (*Betula*), beech (*Fagus*), oak (*Quercus*) and cherry (*Prunus*), as well as tropical trees such as the mahogany family (*Meliaceae*) and teak (*Tectona*). The types most widely used in the Swedish wood processing industry and in wood-working classes in schools are spruce, pine, ash, aspen, birch, beech, oak, cherry, abachi (*Triplochiton scleroxylon*), jelutong (*Dyera costulata*), mahogany and teak. A list of the Latin and popular names of most of the softwoods and hardwoods mentioned in this report is given in Appendix 2.

Chemical characteristics

Wood consists primarily of cellulose, hemicellulose and lignin. Some kinds of wood contain other substances (extractants), which are usually sorted into three main groups: aliphatic substances (mainly oils and waxes), terpenes, and phenolic substances. Wood may also contain small amounts of minerals, proteins, acids, alkaloids, and carbohydrates such as glucosides and saponins.

Physical characteristics

Wood particles vary in size and shape. The size of the wood particles generated during processing depends on such factors as the type of wood, its water content and the processing method. Hardwood dust is usually finer than softwood dust, and its respirable fraction (see below) is thus usually greater (43).

Sampling wood dust

An individual’s exposure to wood dust is measured by outfitting the person with a pump connected by a plastic tube to a special cassette containing a filter 37 mm in

diameter. The amount of dust collected on the filter is weighed, providing a measure of the amount of dust the person is exposed to. This measure is called the total dust concentration, or total dust. Sweden has now adopted a new international standard for dust measurement, SS-EN 481 (53), which defines the following categories:

inhalable dust = the total amount of airborne particles that can be inhaled through the mouth and nose. These particles are up to 50-100 µm in size.

thoracic fraction = that portion of the inhalable particles that passes the larynx. These particles are <10 µm in size.

respirable fraction = that portion of the inhalable particles that penetrates to the parts of the respiratory passages that lack cilia. The particle size is <4 µm.

Different types of filter cassettes are used for measuring total dust and measuring inhalable dust in accordance with the new standard. Consequently, in parallel measurements of the same person made with the different methods, the total dust value obtained may be lower than the measured concentration of inhalable dust.

Assessments of the correlation between exposure and effects on health are currently based on total dust values. In the future, it is likely that health effects will be related to dust concentrations established with other sampling methods.

Air concentrations of wood dust around work with wood

Exposures to wood dust at sawmills and joinery shops in various countries are shown in Table 1.

For 48 workers at four different Swedish sawmills processing dry pine (12), exposure to pinewood dust, measured as total dust, ranged from 0.1 to 1.1 mg/m^3 (GM=0.3 mg/m^3). For 38 carpenters at four different joinery shops in Sweden, exposure to pinewood dust, measured as total dust, ranged from 0.1 to 4.6 mg/m^3 (11). Exposure to wood dust during different operations in wood processing industries in Sweden has recently been surveyed (34). The highest exposures were measured around sawing (0.2-4.1 mg/m^3), inspection (0.4-5.6 mg/m^3) and finishing (0.3-7.3 mg/m^3). Of 125 whole-day averages, 16% exceeded the exposure limit of 2 mg/m^3. The workers were monitored with the total dust and inhalable dust methods simultaneously, and the readings for inhalable dust were about three times as high as those for total dust.

In a study of 200 workplaces in the Danish wood and furniture industry, it was found that sanding by hand generated the highest total dust concentrations, with a geometric mean (GM) of 3.71 mg/m^3. A combination of turning, surface grinding and cross-cutting also yielded relatively high concentrations (GM=1.42-1.68 mg/m^3). In this study, a total of 752 total dust measurements were made with personal monitors (60). Exposure to inhalable dust was measured with personal monitors at seven wood processing businesses in England (21): exposures ranged from 0.3 to 55.2 mg/m^3. A Dutch study (49) reports exposures to inhalable wood dust during different operations in two joinery shops and a furniture factory. Whole-day measurements were made – 199 with personal monitors and 164 with stationary monitors. Sanding produced the highest exposure (>5 mg/m^3). Other tasks producing relatively large amounts of dust were sawing, routing and sweeping up.

Table 1. Air concentrations (mg/m^3) of wood dust measured by personal monitors in sawmills and joinery shops in various countries. (T = total dust; I = inhalable dust; GM = geometric mean)

Country	Range	Dust type	Ref.
Sweden (1996, 1997)	0.10-4.6 (T)	Softwood	11, 12
Sweden (1997)	0.10-7.30 (T)	Softwood, hardwood	34
Denmark (1993)	0.51-3.71 (T) (GM)	Softwood, hardwood	60
England (1991)	0.30-55.2 (I)	Softwood,hardwood	21
Netherlands (1995)	0.82-9.79 (I) (GM)	Not reported	49
Canada (1994)	<0.08-52.0 (T)	Softwood	55

Personal monitors were used to measure exposure to wood dust around sawing of floated (wet) logs at two Canadian sawmills; they showed an average exposure of 0.51 mg/m^3 (<0.08-52 mg/m^3). Of the 237 total dust samples taken in this study, 85 (36%) were below the detection limit of 0.08 mg/m^3 (55).

No studies were found relating the size distribution of wood dust particles to either the type of workplace or the task being performed.

Uptake, distribution, excretion

The literature contains no studies, either human or animal, on uptake, distribution or excretion of wood dust.

Toxic effects

Animal data

In patch tests with guinea pigs, extracts from the softwoods Western red cedar (*Thuja plicata*), Douglas fir (*Pseudotsuga menziesii*) and hemlock had different sensitizing potential. However, the sensitizing potential was found to be dependent on the solvent used for extraction (43). Inhalation studies with guinea pigs have been difficult to interpret, since it has been impossible to determine whether the observed effects were caused by the wood dust or by the mildew and lichens occurring naturally in the wood (43).

Male rats (Sprague-Dawley) were given single intratracheal instillations of 1 ml physiological saline solution containing either 15 mg respirable pinewood dust, 15 mg pinewood dust from which the cellulose had been removed with an organic solvent, or 15 mg pure cellulose (54). The control group was given the saline solution alone. Histopathological examinations of lung tissue after one week and one month revealed fibrosis-like changes in the rats exposed to the pinewood dust and the cellulose, but no pathological changes were seen in the lungs of the rats given the

cellulose-free extract. The authors attributed the results to the cellulose in the wood dust.

Human data

Upper respiratory passages

Effects on the nose noted after exposure to wood dust are hypersecretion, congestion and reduced mucociliary clearance (9).

Male employees (n=168) at furniture factories in Australia, who worked with the hardwoods Tasmanian oak, teak and nyatoh (*Palaquium sp., Payena sp.*), as well as a species of pine (*Pinus radiata*), were interviewed about respiratory symptoms. Their average exposure to wood dust, measured as inhalable dust, was 3.7 mg/m^3 (0.4-24 mg/m^3, 171 measurements). The carpenters reported more symptoms of eye, ear and nose irritation than a control group (n=46) made up of plumbers, refrigeration mechanics, electricians and general mechanical workshop staff. The authors did not find a statistically significant correlation between the reported symptoms and the measured amounts of wood dust the individual subjects were exposed to. Since it is likely that the members of the control group were also exposed to irritating substances, the correlation between subjective symptoms and wood dust may have been underestimated (47). Male carpenters in New Zealand (n=44) who worked with rimu (*Dacrydium cupressinum*) reported more symptoms such as work-related coughs and sniffles, nasal congestion and rhinitis, than a control group of office workers (n=38) matched for age and smoking habits. The difference was statistically significant ($p < 0.01$). Measured concentrations of wood dust ranged from 1.0 to 25.4 mg/m^3 (median 3.6 mg/m^3), and 32% of the samples were above the exposure limit of 5 mg/m^3. No relationship between severity of symptoms and wood dust concentrations or length of employment is reported in this study (46).

In another study, eye irritation and chronic sniffles were significantly correlated ($p < 0.05$) to exposure to hardwood dust. No wood dust concentrations were reported (17).

Symptoms such as rhinitis, nasal congestion, and irritation and itching in the nose at the end of the workweek were more common among 39 woodworking teachers exposed to total dust concentrations in the range 0.12 to 1.18 mg/m^3 (respirable fraction 0.02-0.21 mg/m^3), mostly from pine, than in a control group (n=32) consisting of other personnel at the school. The symptoms diminished during periods away from work, and mucociliary clearance deteriorated during the week. The study revealed no correlation and no dose-effect relationship between dust concentration and nasal symptoms (64). In another Swedish study, 40 woodworking teachers were screened for inflammatory markers in nasal lavage fluid, but no clear indications of inflammation were found (65).

A case of allergic rhinitis and conjunctivitis was diagnosed in a goldsmith who had been exposed to dust from spindle tree wood (*Euónymus europaeus*) (24).

Lower respiratory passages

Western red cedar (*Thuja plicata*). Vedal et al. (58) reported an 8% prevalence of occupational asthma among 652 examined sawmill workers who handled Western

red cedar (WRC). The criteria for the occupational asthma diagnosis were recurring cough, wheezing, phlegm, breathing difficulty or tightness in the chest; that these symptoms were not experienced before employment at the sawmill; and that they improved during weekends or longer absences from work. Occupational asthma was more common among those employed for 10 years or longer. Exposure levels for 334 workers were estimated from readings from 46 monitoring stations, 32 personal monitors, occupational title and workplace. The prevalence of work-related eye symptoms increased with exposure to total dust concentrations ≥2.0 mg/m^3 (p=0.02). After adjustment for smoking habits, height, age and ethnic background, the workers exposed to dust concentrations ≥2.0 mg/m^3 had significantly lower FVC and FEV_1 values ($p < 0.05$) than controls (440 male office workers).

Vedal et al. monitored bronchial hyperresponsiveness in 227 of these workers in a longitudinal study stretching over three years (59). Bronchial hyperresponsiveness was diagnosed by provocation with methacholine. Fifteen percent of the subjects had a diagnosed non-specific bronchial hyperresponsiveness during the entire study period, and 17% of the subjects either developed it or recovered from it during the course of the study. The prevalence of IgE antibodies specific for plicatic acid was higher among subjects with bronchial hyperresponsiveness during the entire three-year period than among those who either did not have it or developed/recovered from it during that time. This indicates that immunological sensitivity to plicatic acid is associated with development of non-specific bronchial hyperresponsiveness upon exposure to WRC.

Four sawmill workers who developed WRC asthma did not have non-specific bronchial hyperresponsiveness before the occupational asthma was diagnosed – it developed along with the asthma. According to the authors, this indicates that the hyperresponsiveness is not a predisposing factor for the asthma. The criteria for the asthma diagnoses were ≥15% reduction in FEV_1 within 12 hours after the end of the workday and a positive reaction to provocation with plicatic acid (5).

In an 11-year follow-up study of 243 non-asthmatic sawmill workers who handled WRC, these workers were found to have a chronic decline of FEV_1 and FVC that was significant when compared to controls (140 office workers). Measurements of total dust (n=916) were made with personal monitors on five occasions during the 11-year period (1982 –1993). Cumulative exposure was estimated on the basis of employment history, and average exposures were calculated by dividing the cumulative exposure by the duration of employment. The sawmill workers were divided into three exposure groups – low, medium and high – with average exposures of 0.13, 0.30 and 0.60 mg/m^3 respectively. During the study period, FVC and FEV_1 in both the high-exposure and medium-exposure groups declined significantly more than in controls. There was also a significant dose-response relationship between exposure and annual reduction of FVC. The authors present this as evidence that an average exposure of about 0.3 mg/m^3 to wood dust from Western red cedar for at least 11 years causes a reduction in lung function (45).

Eastern white cedar (*Thuja occidentalis*) also contains plicatic acid. Occupational asthma was diagnosed in 7% (3) of 42 employees and former employees at a sawmill

handling this type of wood. The criterion for the diagnosis was a positive reaction to provocation with plicatic acid. The three employees with asthma had worked at the sawmill for an average of 13 months. Total dust values ranged from 0.9 to 12.2 mg/m^3, and 50% of the measurements showed concentrations exceeding 2 mg/m^3 (40).

Redwood (*Sequoia sempervirens*) dust can also cause occupational asthma (8, 43). At present it is impossible to determine an exposure limit for dust of either WRC or redwood that will eliminate this risk (43). The elevated risk of asthma from exposure to WRC dust is believed to be due to sensitization to plicatic acid (43).

There are also several case reports (see Table 2) of occupational asthma after exposure to other types of wood dust, mostly from hardwoods and exotic woods but also in some cases softwoods. Although sensitization to softwoods that do not contain plicatic acid has not been reported (43), this type of dust is regarded as an irritant. The underlying reason for its irritative effect, however, is unknown (43).

Other conifers. In a cross-sectional study (19), 103 sawmill workers exposed to dust from spruce, pine and Douglas fir were examined for symptoms involving the respiratory passages, and lung function was tested. The control group comprised 52 machinists who were not exposed to wood dust. The average exposures to wood dust, expressed as inhalable dust, were 0.2-1.1 mg/m^3 for the low-exposure job categories and 1.3-6.3 mg/m^3 for the high-exposure ones. Exposure to mildew was measured with personal monitors, and ranged from 5000 to 33,000 cfu/m^3 (cfu = colony-forming units), which can be regarded as fairly low. The measured dust exposure for the control group was 2.5 mg/m^3. Their exposure to mildew was not measured. There was no significant difference between the groups in either FEV_1 or FVC. Subjects in the high-exposure group reported work-related coughs, shortness of breath and wheezing significantly more often than controls, and the authors regard these symptoms as indications of bronchial hypersensitivity.

Workers (n=94) handling pine and spruce at a Canadian sawmill were tested with spirometry (FEV_1 and FVC) and given a questionnaire covering job history, smoking habits etc. Each of them was given prick tests for wheat, rye, Alternaria, cat dander, household dust and birch. The control group consisted of 165 oilfield workers from the same geographical area, matched for age, height and smoking habits. FEV_1 and $FVC_{\%}$ were significantly lower among the sawmill workers than in the control group, which the authors regard as indicating an obstructive reduction in lung function. The greatest difference between exposed subjects and controls was noted for smokers. Symptoms in the form of breathing difficulty or wheezing were reported significantly more often by the sawmill workers, with odds ratios (OR) of 2.83 (95% CI=1.47-5.46) and 2.58 (95% CI=1.18-5.62) respectively. Workers who had been employed at the sawmill for longer than three years had significantly higher odds ratios for asthma-like symptoms (OR=3.67; 95% CI=1.00-13.5) and bronchitis (OR=2.14; 95% CI=1.02-4.52). Air concentrations of wood dust with a particle size ≤10 µm were measured with stationary monitors at five different places (average 1.35 mg/m^3; range 0.1-2.2 mg/m^3). The authors attribute the symptoms reported by the sawmill workers to wood dust, but also discuss the possibility that they may have been caused by exposure to other substances in the air in a sawmill, such as terpenes (25).

Table 2. Case reports of occupational asthma attributed to woods other than Western red cedar. All cases were given an inhalation provocation test and FEV_1 was registered. Subjects with a FEV_1 reduction of 20% or more were classified as having occupational asthma. (n.p. = not performed; RAST = radioallergosorbent test; ppt = precipitating antibodies; REIA = reversed enzyme immunoassay)

Latin name	Common name	No. of persons	Inhalation	Skin test	Serology	Ref.
Fraxinus excelsior	European ash	1	rapid reaction	n.p.	n.p.	51
Fraxinus excelsior	European ash	1	rapid + late reaction	positive	positive RAST	13
Fraxinus americana	White ash	1	rapid reaction	n.p.	negative RAST	37
Phoebe porosa	Brazilian walnut	1	rapid reaction	n.p.	positive ppt	30
Balfourodendron riedelianum	Pau Marfim	1	rapid reaction	positive	positive RAST, negative ppt	1
Dalbergia nigra	Brazilian rosewood	1	late reaction	positive	n.p.	16
Quercus robur	British oak	3	rapid reaction (3) late reaction (2)	n.p.	n.p.	39
Myrocarpus fastigiatus	Cabreuva	1	late + systemic reactions	n.p.	n.p.	28
Diospyros crassiflora	Ebony	1	late reaction	negative	n.p.	36
Triplochiton scleroxylon	African maple/obeche	4	rapid reaction (4)	positive (4)	negative ppt (4) positive REIA	26
Thuja occidentalis	Eastern white cedar	1	late reaction	n.p.	positive RAST	4
Picea mariana, *Abies balsamea*, *Pinus banksiana*	Black spruce pine Balsam fir Jack pine	11	no reaction	positive (7)	n.p.	38

A group of 145 non-smoking African workers (77 men and 68 women) exposed to dust from pine and from a type of fiberboard were tested with spirometry and questioned about symptoms involving the eyes and upper respiratory passages (50). Total dust was measured with stationary monitors in various parts of the workplaces (average=3.82 mg/m^3; SD=1.34 mg/m^3). The controls were a group of non-smokers (77 men and 75 women). The male carpenters had significantly lower FVC, FEF and PEF values than the male controls. The proportion of men with an obstructive reduction in lung function ($FEV_{\%}$ <70%) was significantly higher in the exposed group. The exposed workers also reported symptoms such as coughing and nasal problems significantly more often than controls, and these symptoms were more common among those who had been employed longer. The women did not have lower lung function values – a result the authors explain by stating that they worked in less dusty parts of the factory than the men, but they give no dust measurements supporting this.

Workers (n=48) in four different sawmills where concentrations of pinewood dust (measured as total dust) were between 0.1 and 1.1 mg/m^3 showed a statistically significant reduction in TLco during an 8-hour workday. Eye irritation also increased significantly during the workday. Exposures to terpenes (registered by personal monitors) ranged from 11 to 158 mg/m^3, and a combined effect of wood dust and terpenes can therefore not be ruled out (12). For employees (n=38) at four different joinery shops, FEV_1 at the beginning of the workday was lower than for unexposed controls, and the FEV_1/FVC quotient was also significantly lower than controls. This is an indication of obstructive reduction in lung function, and it was attributed to exposure to softwood dust (pine/spruce) and/or terpenes (11).

In a Swedish questionnaire survey of 130 woodworking teachers, they reported more skin, eye, nose, throat and lung problems than a control group of other employees (n=112) at the same schools, matched for age, sex and smoking habits (OR=12.4; 95% CI=2.96-110.5). The problems were more pronounced when the ventilation in the workshop was poor, when there were dust-spreading machines, and when cleaning stirred up dust. The authors concluded that wood dust was the probable reason for the reported health problems. Pine was the most frequently used type of wood, but linden (*Tilia*), birch and alder, as well as plywood and particle board, were also used fairly often. Exotic woods were seldom used. There were also other substances, such as vapors from solvents, water-soluble glues and varnish, which according to the authors may have contributed to the effect (66). No dust measurements were made. In a follow-up study it was found that IgE-mediated allergy was not the underlying reason for the symptoms reported by the teachers (65).

Tropical and other hardwoods. Male carpenters in New Zealand (n=44), who worked with rimu (*Dacrydium cupressinum*), were screened for occupational asthma. They were given a questionnaire to fill in, and PEF was measured daily for 10 consecutive days (both workdays and weekend). The criteria for occupational asthma were a history of work-related respiratory symptoms of suspected asthma type (identified by the answers on the questionnaire) and a variation in PEF >15% for at

least two days within the ten-day period. Five workers met these criteria for occupational asthma. Measured wood dust concentrations ranged from 1.0 to 25.4 mg/m^3 (median 3.6 mg/m^3), and 32% of the readings were above the exposure limit of 5 mg/m^3. Measured formaldehyde levels in the workplaces ranged from 0.01 to 0.27 mg/m^3 (46).

After adjustment for smoking habits, reduced lung function was more prevalent (29.4%) among 109 sawmill workers exposed to dust from sheesham (*Dalbergia sissoo*) and mango (*Mangifera indica*) than in a group of 88 controls with the same socioeconomic and ethnic background (2.2%). The reductions in lung function were mostly of the restrictive type. The FEV_1/FVC quotient is not given, and no dust concentrations are reported (48).

Goldsmith and Shy (17) studied workers exposed to hardwood dust during carpentry. There was a correlation between PEF reduction during a workday and work with hardwoods ($p < 0.03$).

Persons exposed to hardwood dust during production of wood powder for incense sticks were examined in a study in Taiwan. MMF, PEFR and $FEF_{25\%}$ were significantly lower in exposed workers than in controls, for both smokers and non-smokers. Measured wood dust concentrations (total dust) ranged from 4.4 to 22.4 mg/m^3, and the respirable fraction made up 2.4 to 50.2% (35).

Other studies. In a literature review by Halpin et al. (20), the authors concluded that allergic alveolitis is a rare disease among sawmill workers except in Sweden, where the prevalence of symptoms compatible with this diagnosis is 5 to 10 % in groups with high exposure to wood dust. A case report from the UK describes a 34-year-old sawmill worker who developed allergic alveolitis after 3.5 years of employment. The man worked mostly with spruce, but also Douglas fir and occasionally other types of conifers. Immunological tests showed IgG antibodies for mildew and wood dust extract. The authors attribute his allergic alveolitis to the mildew, but suggest that the wood dust may have had a synergistic effect (20). In another study by the same authors (19), 103 sawmill workers were tested for immunological reaction to a number of mildew species that may occur in and around a sawmill. The control group consisted of 52 machinists. All five of the persons who had symptoms resembling allergic alveolitis had high IgG-binding to *Trichoderma koningii*.

Carosso et al. (3) measured FVC, FEV_1, $FEV_{\%}$, TLco and Kco (the ratio between TLco and alveolar volume) in a group of carpenters and a control group matched for age, height, weight and smoking habits. The carpenters were divided into a healthy exposed group (A1, n=55), an exposed group with chronic cough and dyspnea (B1, n=15), a group with dyspnea during work and bronchial hyperresponsiveness (B2, n=20), and a group not exposed to wood dust (C, n=53). The asthmatic group (B2) had positive prick tests for wood extract significantly more often than the others; FVC and $FEV_{\%}$ were significantly higher in B1 than in the other groups; FEV_1 was significantly lower in B1 than in B2, and in B2 than in A1 or controls. TLco and Kco showed significant differences between all groups (B1 <B2 <A1 <C). There were significant negative correlations between FEV_1, MEF_{50}, TLco and Kco and the duration of exposure to wood dust. There were no significant differences in

alveolar volume between the groups. The authors concluded that exposure to wood dust or other substances around work with wood can induce chronic obstructive lung disease. They attributed the reduction in diffusion capacity to an alveolitis-like allergic reaction. Neither the types of wood nor the amounts of wood dust the subjects were exposed to are reported.

Cryptogenic fibrosing alveolitis is a rare lung disease: in the UK it affects about 20 adults per 100,000. In an epidemiological study of persons with this disease, the patients or their survivors were sent a questionnaire by post. The study covered 218 patients and 569 controls matched for age, sex and town of residence. Follow-up telephone interviews were made with 165 cases and 408 controls. All 165 cases and a control for each patient were tested for serum IgE, rheumatoid factor and anti-nuclear antibodies, and given prick tests for common allergens. After adjustment for smoking habits, exposure to wood dust was identified as a risk factor (OR=1.71; 95% CI=1.01-2.92). No support was found for an interaction between exposure to wood dust and rheumatoid factor, anti-nuclear antibodies, positive prick test for allergens or IgE concentration (27).

Skin

Handling wood or wood dust and skin contact with airborne wood dust can cause both irritative and allergic contact eczema. Occupational eczema occurs among lumberjacks, carpenters and others who work in forestry, furniture production and cabinetry. Hand eczema has been reported among persons who do wood inlay with exotic woods (22).

Many tropical tree species contain quinones, which are powerful contact allergens. Allergic contact eczema can also be caused by terpenes and colophony from conifers. Swedish hardwoods such as alder, ash, beech, birch and poplar contain several substances that occasionally cause cases of contact allergy. Dust from lichens on tree trunks contains several allergenic acids that can cause contact allergy easily misdiagnosed as allergy to wood dust (10, 44).

In a Swedish survey (42) of 84 male woodworking teachers that worked with spruce, juniper, pine and birch, two of them had positive patch tests for pine, spruce and colophony, and one also had a positive reaction to juniper. The authors concluded that persons sensitized to colophony may develop contact eczema from wood dust. The one-year prevalence for all types of hand eczema among the studied teachers was 19%, whereas the reported prevalence among men in the general population was 9%.

In a patch-test screening of woodworking teachers, it was found that 19% of them (16/84) had a positive reaction to extract of jelutong (*Dyera costulata*). Half of these reported skin symptoms that could be related to their exposure to that type of wood. The extract was tested on guinea pigs, and the results indicated that jelutong contains potent contact allergens (41).

Medical examinations of 479 workers in the furniture industry in Singapore, who were exposed mostly to hardwoods, revealed occupation-related skin problems (itching and irritation) in 3.8% of them (15).

Mutagenicity

In vitro and in vivo

Beechwood dust dissolved in a polar solvent caused point mutations in bacteria and single-strand DNA breaks in rat hepatocytes. Extract from spruce did not have these effects (29).

Lung cells from human embryos were exposed to a pesticide-free methanol extract (pH=3.0) of beech, oak or pine, either with or without metabolic activation (S9). Dose-dependent chromosome breaks were caused by oak, and dose-dependent chromatid breaks were caused by both beech and oak, without metabolic activation. It was concluded that wood dust from beech and oak contains genotoxic substances, but these substances have not been identified (63).

Beech extract in a polar solvent induced micronuclei in rat tissue *in vivo* (29). Two intraperitoneal injections of an aqueous extract of birch dust, given on consecutive days, induced micronuclei in the erythrocytes of mice. Heat-treating the extract significantly reduced the formation of micronuclei (31).

Human data

The frequency of micronuclei in peripheral leucocytes was studied in 83 workers exposed to birch dust. The group of workers with the highest average exposure (1.6 mg/m^3) had a significantly ($p < 0.01$) higher frequency of micronuclei than the control group (88 waiters/waitresses). The frequency of micronuclei did not increase with the duration of employment, and was higher in non-smokers than in smokers (31).

Carcinogenicity

Animal data

The IARC has concluded that there are insufficient data to allow determination of whether there is a relationship between wood dust and cancer in animals (29).

In the British criteria document (43), which treats only exposure to softwood dust, it was concluded that there were no reliable studies on whether this type of dust can cause cancer in animals.

Human data

According to the IARC (29), wood dust can cause sinonasal adenocarcinoma. This conclusion is based primarily on studies of exposure to hardwood dust. No correlation has been found between exposure to wood dust and squamous cell carcinoma in the nose or tumors in the throat, trachea, lungs, lymphatic or circulatory system, stomach, large intestine or colon (29).

A correlation between exposure to wood dust and sinonasal adenocarcinoma has been described for European workers exposed to wood dust, but case-control studies from America have shown little or no increase in risk for adenocarcinoma. The reason for the discrepancy is not known. The authors propose as possible explanations that other types of wood are used, that the processing methods are different,

that the dust exposure is different and/or that there are other substances in the air in the European workplaces (2).

Since the IARC published its monograph on wood dust, further studies on cancer and wood dust have been published:

In a Canadian case-control study of 23 cases of myeloma, 54 cases of Hodgkin's lymphoma, and 215 cases of non-Hodgkin's lymphoma reported during a seven-year period (1979-1985), no correlation was found between exposure to wood dust and these forms of cancer. The exposure estimates were based on questionnaires and personal interviews of both cancer cases and controls (14).

In a Finnish case-control study, exposure to wood dust was surveyed among 136 men with cancers in the lungs or upper respiratory passages. There were three matched controls for each cancer case. For dust concentrations around 1 mg/m^3 from pine, spruce and birch, the study found no correlation to cancer in the lungs or upper respiratory passages or to nasal adenocarcinomas. Exposure estimates were based on workplace monitoring, workplace visits and personal interviews/questionnaires (32).

Similar results were reported in a recently published case-control study of 48 cases of nasal cancer (types not given) and matched controls. Exposure estimates were based on job titles and on interviews with cases and controls. The authors suggested that the reasons no correlation was found were the relatively low exposure to wood dust (<1 mg/m^3) and the fact that the dust was almost entirely from softwoods (56).

In a Belgian case study of 386 cases of sinus cancer reported in 1978-1994, there were 139 adenocarcinomas and 90 squamous cell carcinomas: 88 (63%) of the adenoma cases had jobs involving work with wood, and 9 (10%) of the 90 patients who had squamous cell carcinomas had been exposed to wood dust (57). The study does not report whether this was hardwood or/and softwood dust.

In a pooled re-analysis of 12 case-control studies of nasal cancer made in 7 different countries, it was found that there was a high risk of adenocarcinoma (OR=13.5; 95% CI=9.0-20.0) especially among male woodworkers exposed to dust from hardwoods. No dust concentrations are given. The workers were divided into three exposure groups, with estimated exposures of <1 mg/m^3, 1-5 mg/m^3, and >5 mg/m^3. For each cancer case there was at least one unexposed control. The highest exposure group included machine operaters in the wood processing industry, furniture makers and carpenters. The risk was most pronounced among those exposed to the highest concentrations of wood dust (OR=45.5; 95% CI=28.3-72.9), and it increased with duration of exposure. There was also a tendency to elevated risk among women (OR=2.5; 95% CI=0.5-12.3), but there were relatively few cases in the study. The results revealed no elevation in risk of squamous cell carcinoma in the nose (6).

A re-analysis of five published cohort studies on cancer mortality among workers exposed to wood dust revealed an elevated risk of cancer in the nose (types not reported) and throat. The nasal cancer was correlated to exposure to hardwood dust. Throat cancer was observed among furniture makers and workers exposed to dust from plywood. A trend toward elevated risk of multiple myeloma after exposure to wood dust was also found. The study did not find elevated risks for cancers in the lungs, larynx, stomach or large intestine. The authors point out that the lack of

exposure data and the lack of information on exposures to other substances such as formaldehyde, solvents and pesticides/herbicides may have led to an underestimate of the risks (7).

Leclerc et al. (33) made a case-control study among French workers whose nasal cancer was diagnosed during the years 1986 –1988. Of 207 cases, 82 were adenocarcinomas. Of these, 80 had been exposed to hardwood dust or a mixture of hardwood and softwood dust.

In a study (18) in which two different methods were used to weigh together the results of several epidemiological studies, it was found that workers exposed to wood dust (carpenters, workers in furniture factories, and all wood-related occupations) had an elevated risk of nasal adenocarcinoma. The risk was highest for the furniture makers (RR 30 and 71, compared to 18 and 35 for carpenters). There was no increase in the risk of squamous-cell carcinomas in the nose, however.

In a prospective register study made in the United States (52), an elevated risk of lung cancer was found among persons who reported exposure to wood dust (RR=1.17; 95% CI=1.04-1.31). In the study, consideration was given to smoking habits. One difficulty in interpreting the results is that there was some correlation between wood-dust exposure and exposure to asbestos. There was no observed elevation in the risk of nasal cancer (one case; RR 1.05).

There is a case-control study exploring the relationship between lung cancer and sensitivity to mutagens. Sensitivity was measured as chromatid breaks/lymphocytes in cell cultures briefly treated with bleomycin. The cases (n=108) were Americans of African or Mexican descent with newly diagnosed and untreated lung cancer. Controls (n=264) were persons from the surrounding communities, matched for ethnic background, age and sex. Information on exposure to wood dust was obtained from interviews and based on job descriptions. Exposure to wood dust was associated with an elevated risk of sensitivity to mutagens. No information is given on the type of wood dust or the level or duration of exposure (62).

A recently published German study (61) explores combination effects between malignant tumors in the nose and exposure to hardwood dust (beech and oak) and substances present in wood dust, such as pigments, paints and the insecticides lindane and pentachlorophenol (PCP). Genotoxic effects in the form of single-strand DNA breaks were studied in rat hepatocytes *in vitro*. The extracts from oak and beech caused single-strand DNA breaks, but so did PCP and lindane, 5 of 16 pigments, 2 of 11 paints, and 3 of 8 wood preservatives used in the German wood processing industry. Examination of samples of human nasal tissue revealed a higher fequency of dysplasias among subjects exposed to dust from beech and oak. Subjects exposed to wood preservatives had nasal dysplasias only if they had been simultaneously exposed to beech or oak dust. The effect was not statistically significant, however ($p > 0.07$). There were few cases. Most of the 147 cancer cases classified as occupational disease since 1985 were workers in smaller companies, and had been exposed to several other substances. The authors conclude from the presented data that combined exposure to wood dust and other substances present in the work environment causes nasal cancer.

Teratogenicity

Animal and human data
No data were found.

Dose-response/dose-effect relationships

Studies which give a correlation between dust concentrations and symptoms are presented in Table 3. Elevated occurrences of symptoms involving the upper and lower respiratory tract, as well as effects on lung function, have been observed with exposure to pinewood dust in the concentration range 0.1-6.3 mg/m^3. Asthma and/or reduction of lung function have been observed with exposure to WRC dust at average concentrations of 0.3-6.0 mg/m^3. Exposure to dust from eastern white cedar in the range 0.9-12 mg/m^3 caused occupational asthma in 3 of 42 workers. For dust from aspen, a reduction of lung function was documented at an average respirable content of 0.25 mg/m^3. Exposure to dust from other hardwoods in concentrations of 0.4-24 mg/m^3 has caused irritation in upper respiratory passages and declines in MMF, PEFR and $FEF_{25\%}$.

Conclusions

The critical effect of occupational exposure to wood dust is irritation of eyes and upper respiratory passages. Exposure to wood dust can cause sinonasal adenocarcinoma. This conclusion is based primarily on studies of exposure to hardwood dust.

Exposure to dust from Western red cedar (WRC) in the concentration range 0.3-0.6 mg/m^3 has caused asthma, chronic decline in lung function and irritation of eyes and upper respiratory passages. Exposure to wood dust from spruce and pine in the concentration range 0.1-6.3 mg/m^3 causes irritation of eyes and upper respiratory passages. One study indicates that long-term exposure to softwood dust at levels of about 1 mg/m^3 can affect lung function.

Exposure to hardwood dust causes acute irritation in eyes and upper respiratory passages and may also reduce lung function. There are not enough data to allow determination of the level at which these effects appear.

Skin exposure to wood dust can cause both allergic and non-allergic contact eczema.

Table 3. Dose-effect and dose-response relationships for effects on respiratory passages from occupational exposure to wood dust, measured as mg/m^3 total dust. (n.r. = not reported)

Average (range)	Wood type	Effects	Ref.
0.3 (0.1-1.1)	Pine	Decline of TLco, Eye irritation	12
n.r. (1.3-6.3)	Spruce, pine	Irritation in nose and eyes, bronchial hyperresponse	19
1.35 (0.1-2.2)	Spruce, pine	Reduction of FEV_1, $FEV_{\%}$ irritation in upper airways	25
3.82 (n.r.)	Pine, fiberboard	Reduction of FVC, PEF, FEF	50
0.13[1] (n.r.)	WRC	No reduction of FVC	45
0.30[1] (n.r.)	WRC	Reduction of FVC	45
0.61[1] (n.r.)	WRC	Reduction of FVC	45
0.46 (≤0.1-6.0)	WRC	Eye irritation, reduction of FEV_1, FVC, Asthma in 8% of 652 workers	58
2[3] (0.9-12)	Eastern white cedar	Asthma in 7% of 42 workers	40
0.27[2] (n.r.)	Aspen	Reduction of FEV_1, FVC	23
3.6[2] (1.0-25.4)	Rimu	Coughs, sniffles, rhinitis, nasal congestion	46
12.0 (4.4-22.4)	Hardwoods	Reduction of MMF, PEFR, $FEF_{25\%}$	35
3.7[3] (0.4-24)	Hardwoods	Irritated eyes, ears, nose	47
0.57 (0.12-1.18)	(n.r.)	Nasal irritation	64

[1] = geometric mean for 11 years of exposure

[2] = respirable fraction

[3] = median value

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Appendix 1. Abbreviations used in the text

Lung function

FVC	Forced Vital Capacity
FEV_1	Forced expiratory volume in one second
$FEV_{\%}$	FEV expressed in % of FVC
FEF	Forced expiratory flow
PEF	Peak expiratory flow
MMF	Flow between 25% and 75% of exhaled FVC
$FEF_{25\%}$	Forced expiratory flow at 25% of FVC

Other

CI	confidence interval
GM	geometric mean
OR	odds ratio
PCP	pentachlorophenol
WRC	Western red cedar

Appendix 2. Scientific and common names for most of the softwoods and hardwoods mentioned in this document

Genus/Species	Common name
Softwoods	
Abies	fir
Abies balsamea	Balsam fir
Chamæcyparis	cedar
Chamæcyparis thyoides	common white cedar
Cupressus	cypress
Juniperus	juniper
Larix	larch
Picea	spruce
Picea abies	spruce
Picea mariana	spruce
Pinus banksiana	Jack pine
Pinus radiata	pine
Pinus sylvestris	Scotch pine/Norway pine
Pseudotsuga menziesii	Douglas fir/Oregon pine
Sequoia sempervirens	redwood
Thuja occidentalis	eastern white cedar
Thuja plicata	western red cedar
Tsuga	hemlock
Hardwoods	
Alnus	alder
Balfourodendron riedelianum	Pau Marfim
Betula	birch
Chlorophora exelsa	African teak (iroko)
Dacrydium cupressinum	rimu/imou pine
Dalbergia nigra	Brazilian rosewood
Dalbergia sissoo	Sheesham/rosewood
Diospyros crassiflora	ebony
Dyera costulata	jelutong
Eucalyptus delegatensis, Eucalyptus regnans, Eucalyptus obliqua	Tasmanian oak
Euónymus europaéus	spindle tree
Fagus	beech
Fraxinus	ash
Jacaranda (south america)	palisander /rosewood
Juglans	walnut
Khaya	African mahogany
Mangifera indica	mango
Myocarpus fastigiatus	cabreuva
Palaquium spp	nyatoh
Phoebe porosa	Brazilian walnut
Populus	aspen
Prunus	cherry
Quercus	oak
Meliaceae[1]	mahogany
Tectona grandis	teak
Tilia	linden/lime /basswood
Triplochiton scleroxylon	Abachi /Africa maple /obeche

[1]Name of family

Consensus Report for Sodium Hydroxide

August 24, 2000

Chemical and physical data. Occurrence

CAS No.:	1310-73-2
Synonyms:	caustic soda, sodium hydrate, lye
Formula:	NaOH
Molecular weight:	40.01
Boiling point:	1390°C
Melting point:	318.4°C
Vapor pressure (20°C):	-
Solubility in water:	420 g/l at 0°C, 3470 g/l at 100°C

Sodium hydroxide is a white, hygroscopic substance that usually occurs in the form of pellets, flakes, sticks or clumps, or as a 45 to 75% solution in water. Sodium hydroxide is a strong base: a 0.1 M solution has a pH of 13. Sodium hydroxide dissolves in water, generating heat which may cause steam.

Sodium hydroxide is an extremely common industrial chemical. It is used in the manufacture of rayon and other textiles, soap, paper, aluminum, petroleum products, chemicals and paints, in batteries, in developing photographic film and for cleaning metals (1).

Uptake, biotransformation, excretion

Sodium hydroxide reacts with carbon dioxide to form sodium bicarbonate and sodium carbonate. Sodium hydroxide is completely ionized in water. Sodium ions are essential to human life, and are the most abundant cation in extracellular fluid. Isotope-labeled sodium can be detected in human blood immediately after intramuscular injection or application to intact skin, and within 3 minutes after oral intake. The biological half time for sodium in humans was measured after injection of isotope-labeled sodium: three excretion phases were observed, with half times of 8.5 days (49% of the dose), 13.5 days (51%) and 460 days (0.4%) (13).

Toxic effects

Human data

Sodium hydroxide's corrosive effects on skin are well documented (26). Malten and Spruit (21) report damage to intact skin from 1 hour of exposure to as little as a 0.03 M (0.12%) solution under occlusion. The EU has developed a system for classifying chemicals according to their skin irritation potential: according to this system a 0.5%

sodium hydroxide solution applied under occlusion for 1 hour is classified as irritating. After 1 hour the substance was classified as strongly irritating by half the volunteers in the test (14). In an *in vitro* test using skin cultivated from human keratinocytes (malpighian cells) to study corrosive substances (29), 2.4 minutes of exposure to a 10% solution of sodium hydroxide reduced viability to 50%. In a 1% solution 72% of the cells survived for 3 minutes.

Hughes concluded that the degree of damage from eye contact with an alkali solution is dependent on the concentration, exposure time and penetration rate (18). There are some case reports describing eye damage caused by alkali. Most of the occupational injuries are the results of splashes. Alkali burns occur primarily in the construction, chemical and manufacturing industries (19).

Sodium hydroxide reacts rapidly with carbon dioxide, forming carbonate, which makes air analyses uncertain. According to *Patty's Industrial Hygiene and Toxicology* (30), an air concentration of 250 mg/m^3 is potentially lethal, but no reference is given for this information. There are a few studies which describe damage to the respiratory passages from exposure to aerosols of products containing sodium hydroxide (16, 25, 32).

There is a study of 291 workers who had been exposed to sodium hydroxide dust for from 1 to 30 years. Time-weighted average exposures were calculated from monitoring data and subjective symptoms, and ranged from 0.5 to 2.0 mg/m^3, depending on the workplace. Subjective symptoms of irritation (not further described) were reported in the areas with the highest average air levels, and the measured exposure levels (19 monitoring occasions) ranged from 0 up to 6.7 mg/m^3. No significant increase in mortality related to exposure time or exposure levels was found in comparisons with national averages. A review of medical records revealed that medical treatment had been sought for irritation of skin, eyes and respiratory passages after episodes of acute exposure. No exposure levels were reported (27).

A group of 14 volunteers, all men with mild asthma, inhaled via the mouth alkaline aerosols in concentrations ranging from 4 to 127 mg/m^3 for 20 minutes. The aerosol was formed by the inflation of automobile air bags: it had a pH in the range 9.8 to 10.3 (no information is given on how this was measured) and consisted mostly of sodium carbonate, sodium bicarbonate and a small amount of sodium hydroxide. No further information on the exposure levels for sodium hydroxide are given. Lung function tests, FEV_1, and specific airway resistance revealed no statistically significant changes. Some subjective symptoms – breathlessness, a burning sensation in the throat and chest, cough reflex, chest tightness, etc. – were reported at the exposure levels above 80 mg/m^3 (12).

It is possible that the eyes are more sensitive than the lungs to aerosols of sodium hydroxide. When sodium hydroxide particles enter the respiratory passages they are rapidly transformed to less alkaline carbonate due to the presence of moisture and carbon dioxide. Particles entering the eye, however, can cause locally high concentrations on the eye's surface (9).

There are numerous case reports of accidents and suicide attempts with sodium hydroxide (17), usually involving oral intake.

Animal data

The LD_{50} for intraperitoneal injection to mice is 40 mg/kg. The LD_{50} for oral administration to rabbits is 500 mg/kg (31).

The skin-damaging effects of sodium hydroxide have been studied in the laboratory with rats and rabbits. A 4-hour exposure to a 2% solution of sodium hydroxide caused chemical burns on rabbit skin (33), whereas a 1% solution caused no damage. Bucher et al. (6) tested different concentrations of sodium hydroxide on mouse skin. Two hours of exposure to solutions of 0.5 and 2.5% caused severe irritation, and irritation from a 7.5% solution was judged to be extremely severe. A cat was used to study the effects of sodium hydroxide on the esophagus (2). The cat was anesthetized and the esophagus was opened. An 8% solution was applied for 30 seconds and then carefully rinsed off. After 2 hours there was severe reddening and fluid formation at the site of the application, and underlying muscles were also damaged.

Rabbits were used in a study of eye damage from sodium hydroxide (15). No damage resulted from application of a 0.5% solution in the following volumes: 0.003, 0.01, 0.03 and 0.1 ml. However, 0.003 ml of a 10% solution caused irritation. The rabbits had recovered after 7 days. Larger volumes – 0.01, 0.03, and 0.1 ml – of the 10% solution produced severe eye damage. In another study (3), 0.1 ml of a 1% or 10% sodium hydroxide solution was tested in rabbit eyes. The 1% solution caused irritation, but the damage healed. The 10% solution caused severe irritation which had still not healed after 21 days of observation. No irritation resulted from 0.1 ml of a 1% solution applied to the eye of a monkey (7), but in rabbits the treatment resulted in more severe damage. The cornea became opalescent, and took 14 days to heal.

Zwicker et al. (34) studied the effects of an aerosol mixture of sodium hydroxide, sodium hydrogen carbonate, sodium bicarbonate and sodium carbonate on juvenile and adult rats. The animals were exposed for 2 hours to 65 (nose only) or 250-3200 (whole-body) mg/m^3 of an aerosol consisting mostly of sodium carbonate. For one of the exposures all carbon dioxide was removed from the air. Even so, sodium hydroxide entering the exposure chamber was rapidly transformed to carbonate by the carbon dioxide in the air exhaled by the animals. The dose which had an effect on 50% of the exposed animals (ED_{50}) was determined. The effect, which was identified by histological examination, was acute laryngitis. No other damage could be found. The ED_{50} for adult animals was 510 mg/m^3 and for juveniles 489 mg/m^3. Juveniles developed more severe laryngitis than adult animals exposed to the same air concentration.

Carcinogenicity

Human data

In a few case reports, carcinoma of the esophagus has been connected to previous injury by lye (4, 5, 20, 28). This is probably due to the tissue damage and ulceration resulting from exposure to a strong alkali rather than to any carcinogenic activity of sodium hydroxide (22).

Teratogenicity

Animal data
Two µl of 0.001 M sodium hydroxide was added to the amniotic fluid of mice after 13 days of gestation (11). Mortality and the occurrence of cleft palate were registered. The treatment had no teratogenic effect, but caused high fetal mortality.

Mutagenicity

The chromosome-damaging effects of alkali were tested on hamster ovarian cells *in vitro*. In sodium hydroxide solutions without metabolic activation (S9 mix) there was no chromosome damage in the pH range 7.4 to 10.6 (24). A few chromosome aberrations were observed with the addition of S9 mix at pH 10.6 (16 mM sodium hydroxide). The frequency of aberrations increased with the amount of S9 mix added. The proposed explanation for this result was that chromosome-breaking products were formed by the breakdown of the S9 at high pH (24). Sodium hydroxide did not increase the transformation of Syrian hamster cells by the adenovirus SA7 (8). Genotoxic activity was assessed in Ames tests and in a DNA repair test using several strains of *S. typhimurium* and *E. coli*. It was concluded that sodium hydroxide was non-mutagenic (10). Several other strains of *E. coli* were used in another study (23) in which no mutagenic activity was observed.

Dose-effect/dose-response relationships

There are no data from which to determine a dose-effect or dose-response relationship for occupational exposure to sodium hydroxide. Sodium hydroxide solutions are extremely corrosive. One hour of exposure to a 0.12% solution (under occlusion) was irritating to the skin of human subjects. In eye irritation studies with rabbits, 0.1 ml of a 0.5% solution dropped into the eye caused no irritation, whereas 0.003 ml of a 10% solution produced reversible damage and 0.01 ml of the same 10% solution caused severe damage.

Conclusions

There are no data from which to determine a critical effect of occupational exposure to sodium hydroxide. However, because of its extremely high pH, the critical effect is judged to be irritation of eyes, respiratory passages and skin.

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Summary

Montelius J (ed). *Scientific Basis for Swedish Occupational Standards.* XXI. Arbete och Hälsa 2000:22, pp 1-85. National Institute for Working Life, Solna.

Critical review and evaluation of those scientific data which are relevant as a background for discussion of Swedish occupational exposure limits. This volume consists of the consensus reports given by the Criteria Group at the Swedish National Institute for Working Life from July, 1999 through August, 2000.

Key Words: Amyl acetate, Antimony, Chromium, Chromium trioxide, Occupational Exposure Limit (OEL), Pentyl acetate, Potassium dichromate, Potassium hydroxide, Risk assessment, Scientific Basis, Sodium hydroxide, Toxicology, Wood dust, Zinc chromate.

Sammanfattning

Montelius J (ed). *Vetenskapligt underlag för hygieniska gränsvärden.* XXI. Arbete och Hälsa 2000:22, s 1-85. Arbetslivsinstitutet, Solna.

Sammanställningar baserade på kritisk genomgång och värdering av de vetenskapliga fakta, vilka är relevanta som underlag för fastställande av hygieniskt gränsvärde. Volymen omfattar de underlag som avgivits från Kriteriegruppen för hygieniska gränsvärden under perioden juli 1999 - augusti 2000.

Nyckelord: Amylacetat, Antimon, Hygieniskt gränsvärde, Kaliumdikromat, Kaliumhydroxid, Krom, Kromtrioxid, Natriumhydroxid, Pentylacetat, Risk värdering, Toxikologi, Trädamm, Vetenskapligt underlag, Zinkkromat.

En svensk version av dessa vetenskapliga underlag finns publicerad i Arbete och Hälsa 2000:21.

APPENDIX

Consensus reports in this and previous volumes

Substance	Consensus date	Volume in Arbete och Hälsa	(No.)
Acetaldehyde	February 17, 1987	1987:39	(VIII)
Acetamide	December 11, 1991	1992:47	(XIII)
Acetic acid	June15, 1988	1988:32	(IX)
Acetone	October 20, 1987	1988:32	(IX)
Acetonitrile	September 12, 1989	1991:8	(XI)
Acrylamide	April 17, 1991	1992:6	(XII)
Acrylates	December 9, 1984	1985:32	(VI)
Acrylonitrile	April 28, 1987	1987:39	(VIII)
Aliphatic amines	August 25, 1982	1983:36	(IV)
Aliphatic hydrocarbons, C_{10}-C_{15}	June 1, 1983	1983:36	(IV)
Aliphatic monoketons	September 5, 1990	1992:6	(XII)
Allyl alcohol	September 9, 1986	1987:39	(VIII)
Allylamine	August 25, 1982	1983:36	(IV)
Allyl chloride	June 6, 1989	1989:32	(X)
Aluminum	April 21, 1982	1982:24	(III)
revised	September 14, 1994	1995:19	(XVI)
p-Aminoazobenzene	February 29, 1980	1981:21	(I)
Ammonia	April 28, 1987	1987:39	(VIII)
Amylacetate	March 23, 1983	1983:36	(IV)
revised	June 14, 2000	2000:22	(XXI)
Aniline	October 26, 1988	1989:32	(X)
Anthraquinone	November 26,1987	1988:32	(IX)
Antimony + compounds	December 8, 1999	2000:22	(XXI)
Arsenic, inorganic	December 9, 1980	1982:9	(II)
revised	February 15, 1984	1984:44	(V)
Arsine	October 20, 1987	1988:32	(IX)
Asbestos	October 21, 1981	1982:24	(III)
Barium	June 16, 1987	1987:39	(VIII)
revised	January 26, 1994	1994:30	(XV)
Benzene	March 4, 1981	1982:9	(II)
revised	February 24, 1988	1988:32	(IX)
Benzoyl peroxide	February 13, 1985	1985:32	(VI)
Beryllium	April 25, 1984	1984:44	(V)
Borax	October 6, 1982	1983:36	(IV)
Boric acid	October 6, 1982	1983:36	(IV)
Boron Nitride	January 27 1993	1993:37	(XIV)
Butadiene	October 23, 1985	1986:35	(VII)
1-Butanol	June 17, 1981	1982:24	(III)
Butanols	June 6, 1984	1984:44	(V)
Butyl acetate	June 6, 1984	1984:44	(V)
Butyl acetates	February 11, 1998	1998:25	(XIX)
Butylamine	August 25, 1982	1983:36	(IV)
Butyl glycol	October 6, 1982	1983:36	(IV)
Cadmium	January 18, 1980	1981:21	(I)
revised	February 15, 1984	1984:44	(V)

revised	May 13,	1992	1992:47	(XIII)
Calcium hydroxide	February 24,	1999	1999:26	(XX)
Calcium nitride	January 27,	1993	1993:37	(XIV)
Calcium oxide	February 24,	1999	1999:26	(XX)
Caprolactam	October 31,	1989	1991:8	(XI)
Carbon monoxide	December 9,	1981	1982:24	(III)
Cathecol	September 4,	1991	1992:47	(XIII)
Chlorine	December 9,	1980	1982:9	(II)
Chlorine dioxide	December 9,	1980	1982:9	(II)
o-Chlorobenzylidene malononitrile	June 1,	1994	1994:30	(XV)
Chlorocresol	December 12,	1990	1992:6	(XII)
Chlorodifluoromethane	June 2,	1982	1982: 24	(III)
Chlorophenols	September 4,	1985	1986:35	(VII)
Chloroprene	April 16,	1986	1986:35	(VII)
Chromium	December 14,	1979	1981:21	(I)
revised	May 26,	1993	1993:37	(XIV)
revised	May 24,	2000	2000:22	(XXI)
Chromium trioxide	May 24,	2000	2000:22	(XXI)
Coal dust	September 9,	1986	1987:39	(VIII)
Cobalt	October 27,	1982	1983:36	(IV)
Copper	October 21,	1981	1982:24	(III)
Cotton dust	February14,	1986	1986:35	(VII)
Creosote	October 26,	1988	1989:32	(X)
Cresols	February 11,	1998	1998:25	(XIX)
Cumene	June 2,	1982	1982:24	(III)
Cyanamid	September 30,	1998	1999:26	(XX)
Cyanoacrylates	March 5,	1997	1997:25	(XVIII)
Cycloalkanes, C_5-C_{15}	April 25,	1984	1984:44	(V)
Cyclohexanone	March 10,	1982	1982:24	(III)
revised	February 24	1999	1999:26	(XX)
Cyclohexanone peroxide	February 13,	1985	1985:32	(VI)
Cyclohexylamine	February 7,	1990	1991:8	(XI)
Desflurane	May 27,	1998	1998:25	(XIX)
Diacetone alcohol	December 14,	1988	1989:32	(X)
Dichlorobenzenes	February 11,	1998	1998:25	(XIX)
1,2-Dibromo-3-chloropropane	May 30,	1979	1981:21	(I)
Dichlorodifluoromethane	June 2,	1982	1982:24	(III)
1,2-Dichloroethane	February 29,	1980	1981:21	(I)
Dichloromethane	February 29,	1980	1981:21	(I)
Dicumyl peroxide	February 13,	1985	1985:32	(VI)
Dicyclopentadiene	March 23,	1994	1994:30	(XV)
Diethanolamine	September 4,	1991	1992:47	(XIII)
Diethylamine	August 25,	1982	1983:36	(IV)
2-Diethylaminoethanol	January 25,	1995	1995:19	(XVI)
Diethylene glycol	September 16,	1992	1993:37	(XIV)
Diethyleneglycol ethylether + acetate	December 11,	1996	1997:25	(XVIII)
Diethyleneglycol methylether + acetate	March 13,	1996	1996:25	(XVII)
Diethyleneglycol monobutylether	January 25,	1995	1995:19	(XVI)
Diethylenetriamine	August 25,	1982	1983:36	(IV)
revised	January 25,	1995	1995:19	(XVI)
Diisocyanates	April 8,	1981	1982:9	(II)
revised	April 27,	1988	1988:32	(IX)
Diisopropylamine	February 7,	1990	1991:8	(XI)
N,N-Dimethylacetamide	March 23,	1994	1994:30	(XV)
Dimethyl adipate	December 9,	1998	1999:26	(XX)
Dimethylamine	December 10,	1997	1998:25	(XIX)
N,N-Dimethylaniline	December 12,	1989	1991:8	(XI)

Dimethyldisulfide	September 9, 1986	1987:39	(VIII)
Dimethylether	September 14, 1994	1995:19	(XVI)
Dimethylethylamine	June 12, 1991	1992:6	(XII)
Dimethylformamide	March 23, 1983	1983:36	(IV)
Dimethyl glutarate	December 9, 1998	1999:26	(XX)
Dimethylhydrazine	January 27, 1993	1993:37	(XIV)
Dimethyl succinate	December 9, 1998	1999:26	(XX)
Dimethylsulfide	September 9, 1986	1987:39	(VIII)
Dimethylsulfoxide, DMSO	December 11, 1991	1992:47	(XIII)
Dioxane	August 25, 1982	1983:36	(IV)
revised	March 4, 1992	1992:47	(XIII)
Diphenylamine	January 25, 1995	1995:19	(XVI)
4,4'-Diphenylmethanediisocyanate	April 8, 1981	1982:9	(II)
Dipropylene glycol	May 26, 1993	1993:37	(XIV)
Dipropyleneglycol monomethylether	December 12, 1990	1992:6	(XII)
Disulfiram	October 31, 1989	1991:8	(XI)
Enzymes, industrial	June 5, 1996	1996:25	(XVII)
Ethanol	May 30, 1990	1991:8	(XI)
Ethanolamine	September 4, 1991	1992:47	(XIII)
Ethylacetate	March 28, 1990	1991:8	(XI)
Ethylamine	August 25, 1982	1983:36	(IV)
Ethylamylketone	September 5, 1990	1992:6	(XII)
Ethylbenzene	December 16, 1986	1987:39	(VIII)
Ethylchloride	December 11, 1991	1992:47	(XIII)
Ethylene	December 11, 1996	1997:25	(XVIII)
Ethylene chloride	February 29, 1980	1981:21	(I)
Ethylene diamine	August 25, 1982	1983:36	(IV)
Ethylene glycol	October 21, 1981	1982:24	(III)
Ethylene glycol methylether + acetate	June 2, 1999	1999:26	(XX)
Ethyleneglycol monoisopropylether	November 16, 1994	1995:19	(XVI)
Ethyleneglycol monopropylether + acetate	September 15, 1993	1994:30	(XV)
Ethylene oxide	December 9, 1981	1982:24	(III)
Ethylether	January 27, 1993	1993:37	(XIV)
Ethylglycol	October 6, 1982	1983:36	(IV)
Ferbam	September 12, 1989	1991:8	(XI)
Ferric dimethyldithiocarbamate	September 12, 1989	1991:8	(XI)
Flour dust	December 10, 1997	1998:25	(XIX)
Formaldehyde	June 30, 1979	1981:21	(I)
revised	August 25, 1982	1983:36	(IV)
Formamide	December 12, 1989	1991:8	(XI)
Formic acid	June 15, 1988	1988:32	(IX)
Furfural	April 25, 1984	1984:44	(V)
Furfuryl alcohol	February 13, 1985	1985:32	(VI)
Gallium + Gallium compounds	January 25, 1995	1995:19	(XVI)
Glutaraldehyde	September 30 1998	1999:26	(XX)
Glycol ethers	October 6, 1982	1983:36	(IV)
Glyoxal	September 13, 1996	1996:25	(XVII)
Grain dust	December 14, 1988	1989:32	(X)
Graphite	December 10, 1997	1998:25	(XIX)
Halothane	April 25, 1985	1985:32	(VI)
2-Heptanone	September 5, 1990	1992:6	(XII)
3-Heptanone	September 5, 1990	1992:6	(XII)
Hexachloroethane	September 15, 1993	1994:30	(XV)
Hexamethylenediisocyanate	April 8, 1981	1982:9	(II)

Hexamethylenetetramine	August 25, 1982	1983:36	(IV)
n-Hexane	January 27, 1982	1982:24	(III)
2-Hexanone	September 5, 1990	1992:6	(XII)
Hexyleneglycol	November 17, 1993	1994:30	(XV)
Hydrazine	May 13, 1992	1992:47	(XIII)
Hydrogen bromide	February 11, 1998	1998:25	(XIX)
Hydrogen fluoride	April 25, 1984	1984:44	(V)
Hydrogen peroxide	April 4, 1989	1989:32	(X)
Hydrogen sulfide	May 4, 1983	1983:36	(IV)
Hydroquinone	October 21, 1989	1991:8	(XI)
Indium	March 23, 1994	1994:30	(XV)
Industrial enzymes	June 5, 1996	1996:25	(XVII)
Isophorone	February 20, 1991	1992:6	(XII)
Isopropanol	December 9, 1981	1982:24	(III)
Isopropylamine	February 7, 1990	1991:8	(XI)
Isopropylbenzene	June 2, 1982	1982:24	(III)
Lactates	March 29, 1995	1995:19	(XVI)
Lactate esters	June 2, 1999	1999:26	(XX)
Lead, inorganic	February 29, 1980	1981:21	(I)
revised	September 5, 1990	1992:6	(XII)
Lithium boron nitride	January 27, 1993	1993:37	(XIV)
Lithium nitride	January 27, 1993	1993:37	(XIV)
Maleic anhydride	September 12, 1989	1991:8	(XI)
Manganese	February 15, 1983	1983:36	(IV)
revised	April 17, 1991	1992:6	(XII)
revised	June 4, 1997	1997:25	(XVIII)
Man made mineral fibers	March 4, 1981	1982:9	(II)
revised	December 1, 1987	1988:32	(IX)
Mercury, inorganic	April 25, 1984	1984:44	(V)
Mesityl oxide	May 4, 1983	1983:36	(IV)
Metal stearates, some	September 15, 1993	1994:30	(XV)
Methacrylates	September 12, 1984	1985:32	(VI)
Methanol	April 25, 1985	1985:32	(VI)
Methyl acetate	March 28 1990	1991:8	(XI)
Methylamine	August 25, 1982	1983:36	(IV)
Methylamyl alcohol	March 17, 1993	1993:37	(XIV)
Methyl bromide	April 27, 1988	1988:32	(IX)
Methyl chloride	March 4, 1992	1992:47	(XIII)
Methyl chloroform	March 4, 1981	1982:9	(II)
Methylene chloride	February 29, 1980	1981:21	(I)
4,4'-Methylene dianiline	June 16, 1987	1987:39	(VIII)
Methyl ethyl ketone	February 13, 1985	1985:32	(VI)
Methyl ethyl ketone peroxide	February 13, 1985	1985:32	(VI)
Methyl formate	December 12, 1989	1991:8	(XI)
Methyl glycol	October 6, 1982	1983:36	(IV)
Methyl iodide	June 30, 1979	1981:21	(I)
Methylisoamylamine	September 5, 1990	1992:6	(XII)
Methyl mercaptane	September 9, 1986	1987:39	(VIII)
Methyl methacrylate	March 17, 1993	1993:37	(XIV)
Methyl pyrrolidone	June 16, 1987	1987:39	(VIII)
Methyl-t-butyl ether	November 26, 1987	1988:32	(IX)
revised	September 30, 1998	1999:26	(XX)
Mixed solvents, neurotoxicity	April 25, 1985	1985:32	(VI)
Molybdenum	October 27, 1982	1983:36	(IV)
Monochloroacetic acid	February 20, 1991	1992:6	(XII)

Monochlorobenzene	September 16, 1993	1993:37	(XIV)
Monomethylhydrazine	March 4, 1992	1992:47	(XIII)
Mononitrotoluene	February 20, 1991	1992:6	(XII)
Monoterpenes	February 17, 1987	1987:39	(VIII)
Morpholine	December 8, 1982	1983:36	(IV)
revised	June 5, 1996	1996:25	(XVII)
Naphthalene	May 27, 1998	1998:25	(XIX)
Natural crystallinic fibers (except asbestos)	June 12, 1991	1992:6	(XII)
Nickel	April 21, 1982	1982:24	(III)
Nitroethane	April 4, 1989	1989:32	(X)
Nitrogen oxides	December 11, 1985	1986:35	(VII)
Nitroglycerin	February 13, 1985	1985:32	(VI)
Nitroglycol	February 13, 1985	1985:32	(VI)
Nitromethane	January 6, 1989	1989:32	(X)
Nitropropane	October 28, 1986	1987:39	(VIII)
2-Nitropropane	March 29, 1995	1995:19	(XVI)
Nitroso compounds	December 12, 1990	1992:6	(XII)
Nitrosomorpholine	December 8, 1982	1983:36	(IV)
Nitrotoluene	February 20, 1991	1992:6	(XII)
Nitrous oxide	December 9, 1981	1982:24	(III)
Oil mist	April 8, 1981	1982:9	(II)
Organic acid anhydrides, some	September 12, 1989	1991:8	(XI)
Oxalic acid	February 24, 1988	1988:32	(IX)
Ozone	April 28, 1987	1987:39	(VIII)
Paper dust	February 7, 1990	1991:8	(XI)
Pentaerythritol	November 16, 1994	1995:19	(XVI)
1,1,1,2,2-Pentafluoroethane	February 24, 1999	1999:26	(XX)
Pentyl acetate	June 14, 2000	2000:22	(XXI)
Peroxides, organic	February 13, 1985	1985:32	(VI)
Phenol	February 13, 1985	1985:32	(VI)
Phosphorous chlorides	September 30, 1998	1999:26	(XX)
Phosphorous oxides	February 11, 1998	1998:25	(XIX)
Phthalates	December 8, 1982	1983:36	(IV)
Phthalic anhydride	September 12, 1989	1991:8	(XI)
Piperazine	September 12, 1984	1985:32	(VI)
Plastic dusts	December 16, 1986	1987:39	(VIII)
Platinum	June 4, 1997	1997:25	(XVIII)
Polyaromatic hydrocarbons	February 15, 1984	1984:44	(V)
Polyisocyanates	April 27, 1988	1988:32	(IX)
Potassium aluminium fluoride	June 4, 1997	1997:25	(XVIII)
Potassium dichromate	May 24, 2000	2000:22	(XXI)
Potassium hydroxide	Marsh 15, 2000	2000:22	(XXI)
2-Propanol	December 9, 1981	1982:24	(III)
Propene	September 13, 1996	1996:25	(XVII)
Propionic acid	November 26, 1987	1988:32	(IX)
Propylacetate	September 14, 1994	1995:19	(XVI)
Propylene glycol	June 6, 1984	1984:44	(V)
Propylene glycol-1,2-dinitrate	May 4, 1983	1983:36	(IV)
Propylene glycol monomethylether	October 28, 1986	1987:39	(VIII)
Propylene oxide	June 11, 1986	1986:35	(VII)
Pyridine	May 13, 1992	1992:47	(XIII)
Quartz	March 13, 1996	1996:25	(XVII)
Resorcinol	September 4, 1991	1992:47	(XIII)

Selenium	December 11, 1985	1986:35	(VII)
revised	February 22, 1993	1993:37	(XIV)
Sevoflurane	May 27, 1998	1998:25	(XIX)
Silica	March 13, 1996	1996:25	(XVII)
Silver	October 28, 1986	1987:39	(VIII)
Sodium hydroxide	August 24, 2000	2000:22	(XXI)
Stearates, metallic, some	September 15, 1993	1994:30	(XV)
Stearates, non-metallic, some	November 17, 1993	1994:30	(XV)
Strontium	January 26, 1994	1994:30	(XV)
Styrene	February 29, 1980	1981:21	(I)
revised	October 31, 1989	1991:8	(XI)
Sulfur dioxide	April 25, 1985	1985:32	(VI)
Sulfur fluorides	March 28, 1990	1991:8	(XI)
Synthetic inorganic fibers	March 4, 1981	1982:9	(II)
revised	December 1, 1987	1988:32	(IX)
Synthetic organic and inorganic fibers	May 30, 1990	1991:8	(XI)
Talc dust	June 12, 1991	1992:6	(XII)
Terpenes, mono-	February 17, 1987	1987:39	(VIII)
Tetrabromoethane	May 30, 1990	1991:8	(XI)
Tetrachloroethane	June 4, 1997	1997:25	(XVIII)
Tetrachloroethylene	February 29, 1980	1981:21	(I)
1,1,1,2-Tetrafluoroethane	March 29, 1995	1995:19	(XVI)
Tetrahydrofuran	October 31, 1989	1991:8	(XI)
Tetranitromethane	April 4, 1989	!989:32	(X)
Thioglycolic acid	June 1, 1994	1994:30	(XV)
Thiourea	December 1, 1987	1988:32	(IX)
revised	June 2, 1999	1999:26	(XX)
Thiram	October 31, 1989	1991:8	(XI)
Thiurams, some	October 31, 1989	1991:8	(XI)
Titanium dioxide	February 21, 1989	1989:32	(X)
Toluene	February 29, 1980	1981:21	(I)
Toluene-2,4-diisocyanate	April 8, 1981	1982:9	(II)
Toluene-2,6-diisocyanate	April 8, 1981	1982:9	(II)
1,1,1-Trifluoroethane	February 24, 1999	1999:26	(XX)
Trichlorobenzene	September 16, 1993	1993:37	(XIV)
1,1,1-Trichloroethane	March 4, 1981	1982:9	(II)
Trichloroethylene	December 14, 1979	1981:21	(I)
Trichlorofluoromethane	June 2, 1982	1982:24	(III)
1,1,2-Trichloro-1,2,2-trifluoroethane	June 2, 1982	1982:24	(III)
Triethanolamine	August 25, 1982	1983:36	(IV)
Triethylamine	December 5, 1984	1985:32	(VI)
Trimellitic anhydride	September 12, 1989	1991:8	(XI)
Trimethylolpropane	November 16, 1994	1995:19	(XVI)
Trinitrotoluene	April 17, 1991	1992:6	(XII)
Vanadium	March 15, 1983	1983:36	(IV)
Vinyl acetate	June 6, 1989	1989:32	(X)
Vinyl toluene	December 12, 1990	1992:6	(XII)
White spirit	December 16, 1986	1987:39	(VIII)
Wood dust	June 17, 1981	1982:9	(II)
revised	June 25, 2000	2000:22	(XXI)
Xylene	February 29, 1980	1981:21	(I)
Zinc	April 21, 1982	1982:24	(III)

Zinc chromate	May 24, 2000	2000:22	(XXI)
Zinc dimethyl dithiocarbamate	September 12, 1989	1991:8	(XI)
Ziram	September 12, 1989	1991:8	(XI)

Sent for publication December 2000