

CHEMICAL AGENTS AND RELATED OCCUPATIONS

VOLUME 100 F
A REVIEW OF HUMAN CARCINOGENS

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opinions of an IARC Working Group on the
Evaluation of Carcinogenic Risks to Humans,
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OF CARCINOGENIC RISKS
TO HUMANS

OCCUPATIONAL EXPOSURES DURING ALUMINIUM PRODUCTION

Aluminium production was considered by previous IARC Working Groups in 1983, 1987, and 2005 ([IARC, 1984](#), [1987](#), [2010](#)). Since 2005 new data have become available, which have been incorporated in this *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

The aluminium-production industry as referred to in this *Monograph* involves processes such as the electrolytic reduction of alumina to aluminium, and the casting of aluminium into ingots. The mining of bauxite, production of alumina from bauxite, alloying and fabrication of sheet metal, wire, foil and other such products are not considered.

1.1 Natural occurrence

Aluminium, the third most abundant element in the earth's crust, occurs in nature in combination with silicon and oxygen (i.e. as aluminium silicate). When subject to tropical weathering, aluminium silicate may react to form aluminium hydroxide. Rock containing high concentrations of aluminium hydroxide is called bauxite. This rock is the usual starting material for the production of aluminium. Metallurgical-grade alumina (Al_2O_3) extracted from bauxite by the Bayer process is generally referred to as the ore ([Sanders, 2002](#)).

1.2 Manufacturing processes

The electrolytic process by which aluminium is produced was described in *IARC Monograph* Volume 34 ([IARC, 1984](#)). The process is briefly summarized here. Since 1886, nearly all aluminium has been produced by electrolysis of alumina dissolved in a molten cryolite (Na_3AlF_6)-based bath (also known as the Hall-Héroult process). Molten aluminium is deposited on the carbon cathode, which also serves as the melt container, and oxygen is simultaneously deposited on and consumes the carbon-carbon anode(s) of the electrolytic cell ([Sanders, 2002](#)).

A modern alumina-smelting cell consists of a rectangular steel shell lined with refractory insulation surrounding an inner lining of baked carbon. Electric current enters the cell through the anode (either pre-baked or continuously self-baking Søderberg anode) and leaves through steel (collector) bars connected to the carbon cathode at the bottom. Pre-baked anodes are produced by moulding petroleum coke and coal-tar pitch binder into blocks which are baked at 1000–1200 °C. Søderberg anodes are formed continuously from a paste of petroleum coke and coal-tar pitch. The paste is typically added

Table 1.1 Concentrations of PAHs in the ambient air and in the urine of workers in the aluminium industry^a

| Reference Country | Year of study | Job/task | No. of subjects | No. of samples | No. of smokers | PAH | Air levels ($\mu\text{g}/\text{m}^3$) | | Urine levels ($\mu\text{mol}/\text{mol}$ creatinine) | |
|-----------------------------------------------------------------------------------|---------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|----------------------------------------|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-----------------------|
| | | | | | | | Mean | Range | Mean | Range or SD |
| Göen et al. (1995) Germany | since 1990 | Aluminium smelter workers | 25 | 25 | NR | 1-Hydroxypyrene | | | [4.2] | [0.05–65] |
| Schoket et al. (1999) Hungary | before 1991 | Two aluminium plants Plant I Plant II | 70 24 45 | NR | | 1-Hydroxypyrene | | | 4.1 22.2 | 3.6 (SD) 14.2 (SD) |
| Carstensen et al. (1999a), Alexandrie et al. (2000) Sweden | 1995 | Pot-room workers | 97 93 94 96 95 94 96 | 97 93 94 96 95 94 96 | 31% | <i>Particulate phase</i> Total 22 Benzo[a]pyrene Pyrene <i>Gaseous phase</i> Total 7 Pyrene 1-Hydroxypyrene pre-shift post-shift | mg/m^3 13.2 ^c 0.97 ^c 1.11 ^c $\mu\text{g}/\text{m}^3$ 16.3 ^c 1.56 ^c | mg/m^3 0.01–270 0.02–23.5 0.07–34.4 $\mu\text{g}/\text{m}^3$ 0.01–132 0.01–9.5 | | |
| Friesen et al. (2006) Canada | 1975–2001 | All jobs Jobs in pot-room (anode operator/assistant, controlman, studblast operator, equipment operator, pot operator, foreman) Other jobs in pot-rooms Other jobs, not in pot-rooms | | | CTPV, 2624; B[a]P, 1275 | | CPTV model, 1977–2000 50–2000 50–700 50–150 | B[a]P model, 1977–2000 0.2–11 0.2–11 0.2–0.7 | | |

^a All studies are for the Söderberg process.

^b Conversions used: 1-OHP: 1 $\mu\text{mol}/\text{mol}$ creatinine = 1.93 $\mu\text{g}/\text{g}$ creatinine = 0.013 $\mu\text{mol}/\text{l}$ = 2.84 $\mu\text{g}/\text{l}$ = 2.84 ng/mL

^c Median

B[a]P, benzo[a]pyrene; NR, not reported; SD, standard deviation

to the top of the rectangular steel shell and bakes to form carbon as it passes through the casing, replacing the anode that is being consumed. Molten aluminium is generally removed from the cells daily by siphoning into a crucible ([Sanders, 2002](#)).

1.3 Human exposure

Workers in aluminium production are primarily exposed to polycyclic aromatic hydrocarbons (PAHs). Occupational exposures in this industry and the related carbon electrode-manufacturing industry have been monitored most intensively with respect to PAHs. Biomonitoring studies have focused primarily on exposures in the aluminium industry itself ([IARC, 1984, 2010; Table 1.1](#)) and in anode-manufacturing for the aluminium industry ([IARC, 1984, 2010; Table 1.2](#)). Other potential exposures in these occupational settings include: sulfur dioxide and fluorides; aluminium fluoride; fibrous sodium aluminium tetrafluoride particles; fluorspar; alumina; carbon monoxide; carbon dioxide; various trace metals, such as vanadium, chromium and nickel; asbestos; extreme heat; and high static magnetic fields ([Benke et al., 1998; Dufresne et al., 1996](#)).

Exposures to PAHs, sulfur dioxide and fluorides have decreased over time ([Benke et al., 1998](#)). At two plants that operated the vertical stud Söderberg pot-rooms in Norway, exposures have decreased fourfold on average between the late 1950s and the late 1980s ([Romundstad et al., 1999](#)). The decrease in exposure can be attributed to the implementation of improved control technology, increased use of effective devices for personal protection, and the increasing predominance of pre-bake pot-rooms ([Benke et al., 1998](#)), although this may only apply to the anode pre-baking plants. Concentrations of 1-hydroxypyrene in urine of workers in anode-manufacturing for the aluminium industry did not decrease considerably between the mid-1980s

and mid-1990s ([Table 1.2](#)). In a review of 15 studies, it was concluded that the use of biological monitoring has not led to a reduction in exposure ([Hopf et al., 2009](#)). The exposure models by [Friesen et al. \(2006\)](#) cover 25 years of extensive monitoring in a Canadian Söderborg smelter, and show a rapid decline in inhalation exposures before the early/mid-1980s, but a considerable levelling off more recently.

Dermal exposure to PAHs and the ensuing uptake through the skin may contribute to the internal exposure of workers to PAHs. [Vanrooij et al. \(1992\)](#) showed that dermal exposure does not necessarily correlate with exposure by inhalation of workers in the pot-rooms and the anode pre-bake plants. Levels of benzo[*a*]pyrene on the wrists of workers in the bake-oven area were twice as high as those of workers from the paste plant. The exposure of bake-oven workers to benzo[*a*]pyrene by inhalation, however, appeared to be four times lower than that of workers in the paste plant. Exposure to pyrene by both inhalation and dermal contact was higher in the paste plant. No information was available for temporal trends in dermal exposure in these workplaces.

2. Cancer in Humans

The cancer hazards associated with exposures in aluminium production were evaluated in *IARC Monograph Volume 92* ([IARC, 2010](#)). There was *sufficient evidence* from epidemiological studies of a carcinogenic effect of occupational exposure in aluminium production, based on a relatively large number of studies that showed a consistent excess of cancer of the bladder and a somewhat less consistent excess of lung cancer. The following review is based on studies of aluminium-smelter workers included in *IARC Monograph Volume 92* ([IARC, 2010](#)) and those published later.

Table 1.2 Concentrations of PAHs in the ambient air and in the urine of workers in anode-manufacturing for the aluminium industry

| Reference Country Year of study | Job/task | No. of subjects | No. of samples | No. of smokers | PAH | Air levels ($\mu\text{g}/\text{m}^3$) | | Urinary levels ($\mu\text{mol}/\text{mol}$ creatinine) ^a | |
|--------------------------------------------------------------|-------------------------------|--------------------|-------------------|-------------------|--------------------------------------------------------------|-----------------------------------------|---------------------------|-------------------------------------------------------------------------|------------------------|
| | | | | | | Mean | Range or SD | Mean | Range |
| Göen et al. (1995) Germany | Carbon-electrode production | 23 | 23 | NR | 1-Hydroxypyrene | | | [5.8–12.7] | [1.1–65] |
| Bentsen-Farmen et al. (1999) Norway | Electrode paste-plant workers | 17 | 17 | NR | Sum of 17 PAHs 1-Hydroxypyrene pre-shift post-shift | 38.0 | 41.6 (SD) | 3.93 10.20 | 3.20 (SD) 6.58 (SD) |
| Friesen et al. (2006) Canada 1975–2001 | carbon plant jobs | | | | | CPTV model, 1977– 2000 | B[a]P model, 1977–2000 | | |
| | | | | | | 50–300 | 0.2–5 | | |

^a Conversions used: 1-OHP: 1 $\mu\text{mol}/\text{mol}$ creatinine = 1.93 $\mu\text{g}/\text{g}$ creatinine = 0.013 $\mu\text{mol}/\text{l}$ = 2.84 $\mu\text{g}/\text{l}$ = 2.84 ng/mL

B[a]P, benzo[a]pyrene; CPTV, coal-tar pitch volatiles; SD, standard deviation

2.1 Cancer of the urinary bladder

A large cohort study from Québec, Canada (Gibbs *et al.*, 2007) showed an excess of bladder-cancer mortality with a statistically significant linear trend with cumulative exposure to benzo[*a*]pyrene B[*a*]P (see Table 2.1, available at <http://monographs.iarc.fr/ENG/Monographs/vol100F/100F-17-Table2.1.pdf>). The excess risk was evident only in workers who had been first employed before 1950, and smaller risks were noted in those first employed later (Gibbs & Sevigny, 2007a, b). An increased risk for bladder cancer and a significant exposure-response trend was found in a cohort study from British Columbia, Canada (Spinelli *et al.*, 2006; Friesen *et al.*, 2007). Both Canadian studies derived smoking-adjusted risk estimates. A significant excess for bladder cancer with a positive exposure-response trend was also found in a study of a Norwegian aluminium smelter (Romundstad *et al.*, 2000). Supporting evidence of a bladder-cancer excess comes from cohort studies from France (Mur *et al.*, 1987; Moulin *et al.*, 2000) and the United States of America (USA) (Rockette & Arena, 1983). A recently reported cohort study from Australia showed no excess of bladder cancer, although the follow-up was relatively short (Friesen *et al.*, 2009; Sim *et al.*, 2009). No bladder-cancer excess was found in a Swedish study (Björ *et al.*, 2008).

2.2 Cancer of the lung

An excess of lung cancer in aluminium-production workers has been reported although the data were less consistent than for bladder cancer. The large Quebec cohort showed a smoking-adjusted excess of lung cancer with an exposure-response trend (Gibbs *et al.*, 2007; Gibbs & Sevigny, 2007b; Armstrong & Gibbs, 2009). An excess of lung cancer, but no clear trend, was noted in the Swedish cohort (Björ *et al.*, 2008). The cohort from British Columbia

Canada showed no overall excess of lung cancer, but a trend with increasing cumulative exposure to B[*a*]P (Spinelli *et al.*, 2006; Friesen *et al.*, 2007). The Australian cohort showed no excess but a positive trend with exposure to dust, but not to B[*a*]P (Friesen *et al.*, 2009; Sim *et al.*, 2009). No excess of lung cancer was evident in the studies from France (Mur *et al.*, 1987; Moulin *et al.*, 2000), Norway (Romundstad *et al.*, 2000) or the USA (Rockette & Arena, 1983).

2.3 Synthesis

Overall, the cohort studies strongly support an association between work in aluminium smelters and bladder-cancer risk. Confounding or chance is not likely to explain the findings. There is an increased risk for cancer of the bladder from occupational exposure in aluminium smelters.

An increased risk for lung cancer has been found in several but not all epidemiological studies in the aluminium-production industry. Some studies also show a dose-response trend in terms of B[*a*]P-years. Confounding from smoking or chance is not likely to explain the findings. Based on these observations, there is evidence that risk for cancer of the lung is causally associated with work in aluminium smelters.

The exposure circumstances, especially levels of PAH in aluminium smelters, vary between industrial departments and also depend on the process used. However, data are not sufficient to disentangle the cancer risks associated with these different exposure situations.

3. Cancer in Experimental Animals

Two samples of airborne particulate polynuclear organic matter were collected from two sites in an aluminium-production plant. Each sample was tested by topical application of 50 mg in toluene (1:1) twice weekly to the skin of twenty C3H mice. Samples containing 0.11% and

0.62% B[a]P induced 15/18 and 15/17 malignant skin tumours, respectively. The average time of appearance of the first tumours was 24 and 18 weeks, respectively. No tumours were observed in 37 toluene-treated controls ([Bingham et al., 1979](#); [IARC, 1984](#)) [Duration of the study and sex of the animals unspecified; the control animals were from a different study of the same laboratory, with the same protocol.]

In addition, several individual polynuclear aromatic compounds for which there is *sufficient evidence* of carcinogenicity in experimental animals have been measured at high levels in air samples taken from certain areas in aluminium-production plants ([IARC, 1984, 2010](#)).

4. Other Relevant Data

4.1 Mechanistic evidence relevant to the carcinogenic hazard from occupational exposures during aluminium production

4.1.1 Experimental systems

Air-emission samples from an aluminium-smelting facility were mutagenic in *Salmonella typhimurium* strains TA98 and TA100. All samples were mutagenic in both strains in the presence of an exogenous metabolic activation system and some samples were mutagenic in strain TA98 in the absence of metabolic activation ([Alfheim & Wikstrom, 1984](#)). Air-particle samples collected on filters in the anode-paste plant and pot-room in a Søderberg aluminium-production facility were also mutagenic in strains TA100 and TA98, mainly after metabolic activation; some positive results were also obtained in TA98 without S9-mix ([Krøkje et al., 1985](#)).

PAHs have been detected and their concentrations measured in the atmosphere of different locations in an aluminium-production plant ([IARC, 1984](#)). These PAHs may contribute, in

part, to the genotoxic and tumorigenic activities of particulates collected from such plants.

Naphthalene, which is genotoxic and carcinogenic in experimental studies, has also been detected in the indoor atmosphere of an aluminium-production plant ([IARC, 2002](#); [Brusick et al., 2008](#)).

4.1.2 Humans

No increase in the frequency of sister chromatid exchange or chromosomal aberrations in peripheral blood lymphocytes was observed in workers in the aluminium industry. No effects on sperm morphology, sperm counts, or double Y-bodies were noted in aluminium-production workers compared with matched controls. There were mixed reports on the mutagenic activity in the urine of workers in the aluminium industry ([IARC, 1987](#)).

Human studies on the genotoxic effects of exposures during aluminium production have been reviewed in *IARC Monograph Volume 92* ([IARC, 2010](#)). In several studies, aromatic DNA adducts were analysed in peripheral blood lymphocytes of aluminium-production workers, with mixed results. In 172 Hungarian aluminium-plant workers, higher aromatic DNA-adduct levels were measured compared with those in controls ([Schoket et al., 1999](#)). Earlier studies from Hungary had observed aromatic DNA adducts in the lymphocytes of aluminium-plant workers at different locations, at different times of the year, and in different job categories ([Schoket et al., 1993a, b, 1995](#)). A significant linear correlation was observed between the total amount of aromatic DNA adducts in lymphocytes and the concentration of 1-hydroxypyrene in urine of Hungarian pot-room workers with the *GSTM1*-null genotype ([Schoket et al., 2001](#)). Other populations of aluminium-plant workers have also been studied, with generally positive results with respect to detection of aromatic DNA adducts ([Kriek et al., 1993](#); [Ovrebø et al.,](#)

1995; [van Schooten et al., 1995](#)). Ninety-eight Swedish pot-room workers were examined for the presence of aromatic DNA adducts and gene polymorphisms. No significant differences were observed in the levels of total or individual DNA adducts between pot-room workers and controls ([Tuominen et al., 2002](#)). Only one sample from the lymphocytes of 30 aluminium-plant workers was found to contain B[a]P-7,8-diol-9,10-oxide-DNA adducts ([Vahakangas et al., 1985](#)). In a group of 36 aluminium anode-plant workers, the percentage of subjects with DNA-adduct levels exceeding the 95 percentile control-subject value was small and not significant ([Pavanello et al., 1999](#)). Antibodies against B[a]P-7,8-diol-9,10-oxide-DNA were detected in the serum of 13.3% of 105 aluminium-plant workers ([Galati et al., 2001](#)).

The lymphocytes of 42 Italian aluminium-plant workers were examined for micronucleus formation and DNA-damage induction (single-cell gel electrophoresis assay). While none of the workers showed significant changes in the frequency of micronuclei, significant increases in DNA damage were noted, but only when the lymphocytes were cultured in the presence of cytosine arabinoside, a nucleoside analogue that blocks DNA synthesis ([Crebelli et al., 2002](#)).

Ninety-eight Swedish pot-room workers and 55 controls were examined for the presence of polymorphisms in genes encoding biotransformation enzymes, of gene mutations, DNA strand-breaks, and micronuclei in mononuclear blood cells, and of 8-oxodeoxyguanosine in urine. No correlations were found between any of the genotoxicity biomarkers and any of the exposure measures, e.g. length of employment in the pot-room, 1-hydroxypyrene in urine, or PAH-DNA adducts in peripheral lymphocytes, even when different genotypes for biotransformation enzymes were considered ([Carstensen et al., 1999b](#)).

4.2 Synthesis

Air-emission samples from aluminium smelters were mutagenic in bacteria. There were mixed reports on the mutagenicity of urine from exposed workers. DNA-adduct studies of blood samples from aluminium-smelter workers also gave mixed results.

Based on both experimental and human studies, there is weak-to-moderate evidence for a genotoxic mechanism underlying the effects of occupational exposures during aluminium production.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of occupational exposures during aluminium production. Occupational exposures during aluminium production cause cancer of bladder, and of the lung.

There is *sufficient evidence* in experimental animals for the carcinogenicity of airborne particulate polynuclear organic matter from aluminium-production plants.

Air-emission samples from aluminium smelters were mutagenic in bacteria. There were mixed reports on the mutagenicity of urine from exposed workers. DNA-adduct studies of blood samples from aluminium-smelter workers also gave mixed results.

Based on both experimental and human studies, there is weak-to-moderate evidence for a genotoxic mechanism underlying the effects of occupational exposures during aluminium production.

Occupational exposures during aluminium production are *carcinogenic to humans (Group 1)*.

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