IARC MONOGRAPHS

# SOME CHEMICALS PRESENT IN INDUSTRIAL AND CONSUMER PRODUCTS, FOOD AND DRINKING-WATER

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

# ANTHRAQUINONE

## 1. Exposure Data

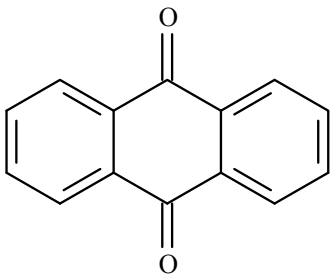
### 1.1 Chemical and physical data

From HSDB (2010), IPCS-CEC (2005), and NTP (2005)

#### *1.1.1 Nomenclature*

*Chem. Abstr. Services Reg. No.*: 84-65-1
*Chem. Abstr. Name*: Anthraquinone; 9,10-anthraquinone
*Synonyms:* Anthracene, 9,10-dihydro-9,10-dioxo-; anthradione; 9,10-anthracenedione; bis-alkylamino anthraquinone; 9,10-dioxoanthracene; 9,10-dihydro-9,10-dioxoanthracene.
*RTECS No.*: CB4725000
*EINECS No.*: 201-549-0

#### *1.1.2 Structural and molecular formulae and relative molecular mass*



$C_{14}H_8O_2$
Relative molecular mass: 208.21

#### *1.1.3 Chemical and physical properties of the pure substance*

*Description*: Light yellow crystals
*Boiling-point*: 380 °C
*Melting-point*: 286 °C
*Vapour pressure*: $1.16 \times 10^{-7}$ mm Hg at 25 °C
*Solubility in water:* 1.35 mg/L at 25 °C
*Density:* 1.44 g/cm$^3$ at 20 °C
*Flash-point*: 185 °C
*Relative vapour density (air = 1)*: 7.16
*Auto-ignition temperature:* 650 °C
*Octanol/water partition coefficient*: log $K_{ow}$, 3.39
*Henry's law constant*: $2.35 \times 10^{-8}$ atm.m$^3$/mol at 25 °C (estimated)

#### *1.1.4 Technical products and impurities*

No data were available to the Working Group.

#### *1.1.5 Analysis*

A series of methods to measure anthraquinone in different media has been reported (HSDB, 2010; Table 1.1).

### 1.2 Production and use

#### *1.2.1 Production*

According to HSDB (2010), at least six methods are available for the manufacture of anthraquinone: (a) oxidation of naphthalene to

**Table 1.1 Selected methods of analysis of anthraquinone**

| Medium | Method | Detection limit | Recovery |
|---|---|---|---|
| Seeds, crops and soil | Electron-capture detector | 0.05 ppm | 94–100% |
| Soils and sediment | GC/MS | 29.7 µg/kg | NR |
| Rainwater | GC/MS | 0.05–0.10 ng/L | NR |
| Filtered wastewater and natural water | GC/MS | 0.11 µg/L | NR |
| Airborne particulate matter | Capillary GC and GC/MS | NR | NR |
| Fish tissue | Capillary GC and GC/MS | 0.2 ppb | 72% |

GC, gas chromatography; MS, mass spectrometry; NR, not reported
Adapted from HSDB (2010)

naphthaquinone, which is then condensed with butadiene to yield tetrahydroanthraquinone, then dehydrogenated to produce anthraquinone; (b) industrial preparation from phthalic anhydride and benzene; (c) oxidation of anthracene with concentrated nitric acid; (d) dimerization of styrene to 1-methyl-3-phenylindane using phosphoric acid as a catalyst, followed by catalytic vapour-phase oxidation to anthraquinone; (e) oxidation of anthracene with chromic acid in 48% sulfuric acid or oxidation with air in the vapour phase; and (f) condensation of 1,4-naphthoquinone with butadiene.

In the United States of America, anthraquinone is listed as a chemical with a high production volume. As from 1986, between 250–500 tonnes per year were either produced or imported there. A major increase was then reported in 1998 and 2002 when volumes reached 5000–25 000 tonnes per year (HSDB, 2010).

In the People's Republic of China, production reached 37 500 tonnes in 2008 due to continuously increasing demand (CRI, 2011).

### *1.2.2 Use*

Anthraquinone is an important and widely used raw material for the manufacture of vat dyes, which are a class of water-insoluble dyes that can easily be reduced to a water-soluble and usually colourless leuco form that readily impregnates fibres and textiles. Their principal properties are brightness and good fastness. Anthraquinone is also used as a seed dressing or in seed treatments. Other major uses are as a pesticide, as a bird repellent (especially for geese), and as an additive in chemical alkaline pulp processes in the paper and pulp industry (HSDB, 2010).

## 1.3 Occurrence and exposure

### *1.3.1 Natural occurrence*

Natural pigments that are derivatives of anthraquinone are found in plants (e.g. aloe latex, senna and rhubarb), fungi, lichens and some insects (HSDB, 2010).

### *1.3.2 Occupational exposure*

Occupational exposure to anthraquinone can occur during its production, its use in the manufacture of other chemicals or its direct use. Workers in transport-related industries are also potentially exposed to anthraquinone during its release from diesel and gasoline engine vehicles (see Table 1.2).

The National Occupational Exposure Survey, conducted from 1981 to 1983, estimated that 6187 workers were potentially exposed to anthraquinone in the USA, mostly in the printing and publishing industry (5475 workers), but also in photographic processing machine operations, in the air transport industry, and in geology and geodesy (NIOSH, 1990).

## Table 1.2 Environmental occurrence of anthraquinone from combustion sources

| Source | Sample | Concentration or release rates | Reference |
|---|---|---|---|
| Diesel engine automobiles | Particulate emissions | NR | Yu & Hites (1981), Choudhury (1982) |
| Diesel engine automobiles | Particulate matter, 5 samples | 47.7 µg/g | Layshock *et al.* (2010) |
| | Diesel extract, 3 samples | 5.23 µg/g | |
| Diesel and gasoline vehicles, Japan | Particulate emissions from exhaust pipes | 1.3–52 µg/g | Oda *et al.* (1998) |
| Diesel vehicles | Particulate matter | 18–43 µg/g | Jakober *et al.* (2007) |
| | | 40.4 µg/g | Cho *et al.* (2004)[a] |
| | | 58 µg/g | Valavanidis *et al.* (2006)[a] |
| | | 34 µg/g | Zielinska *et al.* (2004)[a] |
| Diesel vehicles | Emission rates | 15.46 µg/km | Sidhu *et al.* (2005) |
| Car with a catalyst<br>Car without a catalyst car<br>Heavy-duty diesel trucks | Emission rates | 4.4 µg/km<br>24.3 µg/km<br>23.5 µg/km | Rogge *et al.* (1993) |
| Heavy-duty diesel trucks | Emission rates | 21–27 µg/L of fuel consumed | Jakober *et al.* (2007) |
| Vehicle-related | Tyre wear particles | ND | Tong *et al.* (1984)[b] |
| | Brake lining | 0.31 µg/g | |
| | Road dust particles | 0.41 µg/g | |
| Small craft gas turbine engine | Particulate emissions | 0.06–58.49 ng/m$^3$ | Robertson *et al.* (1980)[b] |
| Burning cereal straw | Organic extracts of emissions | 995 µg/kg fuel | Ramdahl & Becher (1982)[b] |
| Domestic waste uncontrolled burning[c] | Open-air burn sample | | Sidhu *et al.* (2005) |
| | Concentration | 1.72 ng/µL | |
| | Emission rate | 0.28 mg/kg | |
| Forest litter[d], Amazon | Smoke particulate matter | 2.8 µg/m$^3$ | Radzibinas *et al.* (1995)[b] |
| Residential oil burner | Particulate samples | NR | Leary *et al.* (1987)[b] |
| Municipal waste incinerators (4) | Extracts of air samples (2/4 samples) | 2.9–9.0 µg/mL | James *et al.* (1985)[b] |
| Municipal waste incinerators, | Fly ash | | Eiceman *et al.* (1979) |
| Japan | 2/2 samples | NR | |
| Ontario, Canada | 1/2 samples | NR | |
| The Netherlands | 1 sample | ND | |
| Municipal solid waste incinerator, Japan | Fly ash | NR | Akimoto *et al.* (1997) |

[a] Cited by Jakober *et al.* (2007)
[b] Cited by HSDB (2010)
[c] Experimental burn of household garbage
[d] Controlled burn
ND, not detected; NR, not reported

**Table 1.3 Environmental occurrence of anthraquinone from industrial sources**

| Source | Sample | Concentration | Reference |
|---|---|---|---|
| Near a chemical factory, former Czechoslovakia | Mosses, 2/6 samples<br>Needles, 3/6 samples<br>Earthworm, 2/5 samples<br>Air, 1/8 samples | 0.176–4.95 µg/g<br>0.460–1.92 µg/g<br>0.473–4.72 µg/g<br>44.5 ng/m$^3$ | Holoubek *et al.* (1991)[a] |
| Dye manufacturing plant | Raw wastewater<br>Final effluent | 49–110 µg/L (49–110 ppb)<br>ND | Games & Hites (1977)[a] |
| Timber production or organic and plastics production | Industrial wastewater, 2/79 samples | NR | Bursey & Pellizzari (1982)[a] |
| Wood preserving plant (abandoned) | Groundwater<br>Stream water that flowed through site | 132 mg/L<br>2 µg/L | Middaugh *et al.* (1991)[a] |
| Coal tar creosote waste site, Germany | Soil, 2 samples | 2 and 20 µg/g | Meyer *et al.* (1999)[a] |

[a] Cited by HSDB (2010)
ND, not detected; NR, not reported

Although no data on the number of workers exposed to anthraquinone were available from occupational surveys, a series of studies on health effects at a manufacturing plant in New Jersey, USA, reported that 842 workers were involved the production of anthraquinone dyes and intermediates (Delzell *et al.*, 1989; Sathiakumar & Delzell, 2000); however, neither the number of workers specifically exposed to anthraquinone nor their exposure levels were provided.

Anthraquinone was detected in air samples (297 ng/m$^3$) in a potroom where Söderberg electrodes were used for aluminium reduction (Thrane & Stray, 1986). Wei *et al.* (2010) measured personal exposure (as ambient particles) to anthraquinone and polycyclic aromatic hydrocarbons (PAHs) of two nonsmoking security guards at a kerbside gate on a busy road (8000–10 000 vehicles per day). The mean concentration of anthraquinone was 63.2 ng/m$^3$ (25th percentile, 26.1; 75th percentile, 86.8 ng/m$^3$; 58 samples). The major source of the organic carbons detected in the personal monitors was gasoline engines.

Anthraquinone is used as a catalyst in the pulp industry to improve delignification of wood and increase pulp yield. A study designed to develop analytical procedures for the detection of anthraquinone in pulp process liquors found that the concentrations (mg/L) of anthraquinone were 0.04–0.66 in filtrates from bleaching, 0.13–0.75 in wash liquors, 0.5–11.5 in alkaline pulp liquors and 3.0–170 in black liquors (Nelson & Cietek, 1983).

### *1.3.3 Environmental occurrence*

Anthraquinone is ubiquitous in the environment, and has been detected in the air, water (including surface, ground- and drinking-water), soil, plants, fish/seafood and animal tissue (see Table 1.3, Table 1.4, and Table 1.5). The major sources of environmental exposure are both natural and anthropogenic. Anthraquinone and other oxygenated PAHs are formed from direct combustion processes (see Table 1.2) or the degradation of PAHs by atmospheric oxidants (Layshock *et al.*, 2010). Specifically, anthraquinone is formed from anthracene through photolytic and biodegradation processes (HSDB, 2006). The levels of oxygenated PAHs in the soil and air have increased in recent years (Layshock *et al.*, 2010). Moreover, anthraquinone may be released directly into the environment through its use as a bird repellent or via various wastestreams

through its use as an additive in the soda and kraft chemical alkaline pulp processes in the paper and pulp industry, and in the production of various dyes (HSDB, 2006).

*(a) Release/effluent*

Table 1.2 summarizes studies of environmental exposure to anthraquinone from combustion sources, many of which detected anthraquinone in particulate matter from vehicles with diesel or gasoline engines at concentrations ranging up to 58 µg/g. Estimated emission rates of anthraquinone in diesel emission particles were reported to be 24.88 µg/mile [15.46 µg/km]. Another study reported emissions rates from exhaust pipes of various vehicles ranging from 4.4 µg/km for cars with a catalyst and 24.3 µg/km for cars without a catalyst to 23.5 µg/km for heavy-duty diesel trucks. Jakober *et al.* (2007) reported emission rates of 21–27 µg anthraquinone/L of fuel consumed from heavy-duty diesel vehicles. Anthraquinone is also released as particles from the combustion of plants, fuel or waste, and has been detected in municipal waste incinerators (fly ash or air samples) in Japan and Canada. The emission rate for a sample from an open-air domestic waste incinerator was 0.28 mg/kg.

Anthraquinone has also been detected in the environment near industrial or abandoned sites (Table 1.3). It was found in earthworms, mosses and ambient air near a chemical factory in former Czechoslovakia; in raw waste water at a dye manufacturing plant; in industrial wastewater from timber production or organic and plastics production; in groundwater and stream water from an abandoned wood preserving plant; and in soil samples from coal-tar creosote waste sites. Coal may be another source of exposure to anthraquinone, which was detected (0.7 µg/L) in an extract of model coal piles (Texas lignite) leached with distilled water under simulated rainfall conditions (Stahl *et al.*, 1984, cited in HSDB, 2006).

*(b) Ambient air*

HSDB (2006) reviewed information on and calculated parameters related to the environmental fate of anthraquinone in ambient air, water and soil. When released into the air, it is expected to remain in the vapour and particulate phases. Albinet *et al.* (2008) reported that the fraction of oxygenated PAHs in the particulate phase in the French alpine valleys mainly comprised the heaviest compounds. However, most studies have measured anthraquinone in particles. Leotz-Gartziandia *et al.* (2000) found higher levels of anthraquinone in the particulate phase than in the gaseous phase in samples of air from near a motorway in France. Particle-phase anthraquinone can be removed by wet or dry deposition (HSDB, 2006), and has been found in precipitations (see Table 1.5). Vapour-phase anthraquinone is degraded in the atmosphere by a reaction with photochemically produced hydroxyl radicals, and has an estimated atmospheric half-life of 11 days. The presence of sunlight may accelerate the degradation of anthraquinone by ozone in the atmosphere (HSDB, 2006).

Anthraquinone has been detected in ambient air (usually in particulate matter) near roadways, and in urban, suburban and rural areas (see Table 1.4). In general, levels are higher in the winter than in the summer, and in urban areas than in rural areas. However, a study in Algeria found higher levels in the summer, which the authors presumed were due to increased generation of ozone and hydrogen radicals by strong solar radiation (Yassaa *et al.*, 2001). Albinet *et al.* (2007) reported that anthraquinone was the most abundant oxygenated PAH detected in the Marseilles area of France, and accounted for 20% of total oxygenated PAHs. Gasoline engines were an important source of this exposure.

## Table 1.4 Environmental occurrence of anthraquinone in ambient air

| Source | Sample | Concentration | Reference |
|---|---|---|---|
| **Roads** | | | |
| Freeway tunnel, Japan | Air samples | 52 µg/g (extract mass) | Oda *et al.* (1998)[a] |
| Freeway tunnel, Japan | Air samples – 5 sites | 29–56 ng/m$^3$ | Oda *et al.* (2001) |
| | Dust guardrails – 5 sites | 9.2 (6.3–14) ng/m$^3$[b] | |
| **Urban/suburban** | | | |
| Barcelona, Spain | *Organic extracts from airborne particulates* | | Bayona *et al.* (1994)[a] |
| | Spring | 0.009 ng/m$^3$ | |
| | Summer | ND | |
| | Autumn | 0.026 ng/m$^3$ | |
| | Winter | 0.021 ng/m$^3$ | |
| Barcelona, Spain | *Aerosol samples* | | Galceran & Moyano (1993)[a] |
| | Summer | 0.082 ng/m$^3$ | |
| | Winter | 0.075 ng/m$^3$ | |
| Duisburg, Germany | Particulate matter | 0.22–1.89 ng/m$^3$ | Koenig *et al.* (1983)[a] |
| Munich, Germany | Particulate matter | 0.96 (0.16–1.85) ng/m$^3$[b] | Schnelle-Kreis (2001)[c] |
| Augsburg, Germany | Urban particulate matter | 0.39 (0.11–0.58) ng/m$^3$[b] | Sklorz *et al.* (2007) |
| Chamonix Valley, French Alps, 2002–03 | *Air particulates Suburban (7 samples)* | | Albinet *et al.* (2008) |
| | Winter | 1.42 ng/m$^3$ | |
| | Summer | 1.59 ng/m$^3$ | |
| | *Traffic (14 samples)* | | |
| | Winter | 3.60 ng/m$^3$ | |
| | Summer | 0.97 ng/m$^3$ | |
| Maurienne Valley, French Alps, 2002–03 | *Air particulates Suburban (7 samples[d])* | | Albinet *et al.* (2008) |
| | Winter | 2.76 ng/m$^3$ | |
| | Summer | 0.34 ng/m$^3$ | |
| Paris, France | Air particulates | 0.070 ng/m$^3$ | Nicol *et al.* (2001) |
| Paris, France | Near motorway | | Leotz-Gartziandia *et al.* (2000) |
| | Particles | ~22 ng/m$^3$[e] | |
| | Gas | ~2 ng/m$^3$[e] | |

**Table 1.4 (continued)**

| Source | Sample | Concentration | Reference |
|---|---|---|---|
| Marseilles area, France | *Air particulates* | | Albinet *et al.* (2007) |
| | Urban | 1.40 (0.378–2.57) ng/m$^3$[b] | |
| | Suburban | 0.77 (0.073–2.79) ng/m$^3$[b] | |
| England, United Kingdom | Air particulates | 0.210 ng/m$^3$ | Kelly *et al.* (1993)[f] |
| Santiago, Chile, 2000 | *Particulate matter* | | María del Rosario Sienra (2006) |
| | *Providencia* | | |
| | Winter | 1.58 ng/m$^3$ | |
| | Spring | 0.56 ng/m$^3$ | |
| | *Las Condes* | | |
| | Winter | 0.67 ng/m$^3$ | |
| | Spring | 0.38 ng/m$^3$ | |
| Toronto, Canada | Ambient air levels | 0.0009 –0.0013 ng/m$^3$ | Harkov (1986)[a] |
| California and Louisiana, USA | Air particulates, 2/7 sites | NR | Kolber *et al.* (1982)[a] |
| Portland, OR, USA | Gas phase | 2.5 ng/m$^3$ | Ligocki & Pankow (1989)[a] |
| February to April 1984 and February to April 1985 | Particulate phase | 0.59 ng/m$^3$ | |
| St Louis, MO, USA | Air particles | NR | Ramdahl & Becher (1982)[a] |
| Los Angeles, CA, USA, 1993 | Ambient air/smog | 0.3 ng/m$^3$ | Fraser *et al.* (2000)[a] |
| Southern California, USA, 1995 | Air particulate (12 sites) | 0.011–0.22 ng/m$^3$ | Manchester-Neesvig *et al.* (2003)[a] |
| Washington DC, USA | Urban dust, 3 samples[g] | 1.60 µg/g | Layshock *et al.* (2010) |
| Washington DC, USA | Urban dust[h] | 2.24 µg/g | Albinet *et al.* (2006) |
| | | 0.220 µg/g | Fernandez & Bayona (1992) |
| | | 2.70 µg/g | Durant *et al.* (1998)[i] |
| | | 2.03 µg/g | Cho *et al.* (2004)[i] |
| Algiers, Algeria | *Particles* | | Yassaa *et al.* (2001) |
| | *Downtown* | | |
| | Winter | 1.0 ng/m$^3$ | |
| | Summer | 6.2 ng/m$^3$ | |
| | *Landfill* | | |
| | Winter | 0.1 ng/m$^3$ | |
| | Summer | 1.5 ng/m$^3$ | |
| **Rural** | | | |
| Chacaltaya, Bolivia | Air, 2 samples, 1975 | 0.064–0.065 ng/ m$^3$ | Cautreels *et al.* (1977) |
| Antwerp, Belgium | Air, 4 samples, 1976 | 0.57–1.0 ng/ m$^3$ | Cautreels *et al.* (1977) |
| Japan | Air sample | 2.8 µg/g (total weight mass) | Oda *et al.* (1998)[a] |

**Table 1.4 (continued)**

| Source | Sample | Concentration | Reference |
|---|---|---|---|
| Chamonix Valley, French Alps, 2002–03 | *Air particulates*<br>*Altitude* | | Albinet *et al.* (2008) |
| | Winter | 0.15 ng/m$^3$ | |
| | Summer | 0.05 ng/m$^3$ | |
| | *Rural* | | |
| | Winter | 0.57 ng/m$^3$ | |
| | Summer | 0.26 ng/m$^3$ | |
| Maurienne Valley, French Alps, 2002–03 | *Air particulates*<br>*Tigny, 14 samples* | | Albinet *et al.* (2008) |
| | Winter | 1.77 ng/m$^3$ | |
| | Summer | 0.47 ng/m$^3$ | |
| | *Soliéres, 14 samples* | | |
| | Winter | 2.36 ng/m$^3$ | |
| | Summer | 0.13 ng/m$^3$ | |

[a] Cited by HSDB (2010)
[b] Mean and range
[c] Cited by María del Rosario Sienra (2006)
[d] Modane site, no winter samples were available for the other suburban site, Orelle; summer samples at Orelle (0.37 ng/m$^3$) were comparable with Modane site
[e] Estimated from graph
[f] Cited by Nicol *et al.* (2001)
[g] Sample SRM 1649b
[h] Sample SRM 1649a sample collected in 1970s, authors used different chromatography methods, as cited by Albinet *et al.* (2006)
[i] As cited by Albinet *et al.* (2006)
ND, not detected; NR, not reported

## Table 1.5 Environmental occurrence of anthraquinone in water and soil

| Location or source | Source/sample | Concentration | Reference |
|---|---|---|---|
| **Surface water** | | | |
| Rhine river | Surface water | NR | Meijers & van der Leer (1976)[a] |
| Baltic sea | Surface and deep water – 3 sites | NR | Ehrhardt *et al.* (1982)[a] |
| Iowa, USA | Stream water | 0.066 µg/L (max) | Kolpin *et al.* (2004)[a] |
| **Drinking-water** | | | |
| Kitakyushu, Japan | Drinking-water – tap | 5.2 ng/L | Akiyama *et al.* (1980) |
| Tsukuba, Japan | Drinking-water – tap | NR | Shiraishi *et al.* (1985)[a] |
| Athens, GA, USA | Drinking-water – tap | 20–100 ng/L | Thruston (1978)[a] |
| Ottawa, Canada | Drinking-water supply | 1.8–2.4 ng/L | Benoit *et al.* (1979a)[a] |
| Great Lakes, Canada | *Drinking-water – 12 municipal water supplies*<br>Winter<br>Summer | <br>ND–63.5 ng/L<br>0.2–72 ng/L | Williams *et al.* (1982) |
| Unspecified | Drinking-water treatment plants, 6 sites, June to October | 0.6–2.1 ng/L | Benoit *et al.* (1979b)[a] |
| **Precipitation** | | | |
| Oregon, USA | *Rain, 8/9 storms*<br>Spring<br>Autumn | <br>2.2–16 ng/L<br>18–74 ng/L | Pankow *et al.* (1984)[a] |
| Portland, OR, USA | Rain, 7/7 storms, February to April 1984 | 1.5–3.6 ng/m$^3$ | Ligocki *et al.* (1985)[a] |
| Norway | Precipitation | NR | Lunde (1976)[a] |
| **Soil and sediment** | | | |
| Roadside (traffic pollution), Czech Republic | Soil | NR | Zdráhal *et al.* (2000) |
| Tunnel roadway | Soil, 5 sites | 1.2[b] (0.2–2.1) µg/g soil | Oda *et al.* (2001) |
| Sewage area, Marseilles, France | Marine sediments, 9/10 sites | 2–400 ng/g | Milano & Vernet (1988)[a] |
| Dokai Bay, Japan | Marine sediment | NR | Terashi *et al.* (1993)[a] |
| USA, 20 river basins, 1992–95 | 22.2% of 536 sediment samples | Highest, 2 100 µg/kg; 50th percentile, < 50 µg/kg | Lopes & Furlong (2001)[a] |
| New York Bay and Newark Bay, USA | *Marine sediments*<br>Clean-up scheme 3 (2 samples)<br>Clean-up scheme 4 (3 samples) | <br>1.70 mg/kg<br>1.53 mg/kg | Layshock *et al.* (2010) |

[a] Cited by HSDB (2010)
[b] Mean
ND, not detected; NR, not reported.

*(c) Water and soil*

Anthraquinone that is released into water is expected to adsorb onto suspended solids and sediment. Experimental studies have shown that the majority of the anthraquinone added was degraded within 3 days in both surface water (82%) and groundwater (91%) (reviewed by HSDB, 2006). Natural bacterial populations in groundwater and activated sludge were also shown to degrade anthraquinone (range, 50–100%) in experiments that lasted between 5 days and 3 weeks. Anthraquinone may also be removed through photolysis by sunlight, and its direct photolysis half-life is about 9 minutes in aqueous solution. It is not sensitive to aqueous environmental hydrolysis, and volatilization is not expected to be an important factor in its removal (HSDB, 2006).

Studies that evaluated levels of anthraquinone in water are reported in Table 1.5. It has been detected in groundwater from industrial sites (see Table 1.3), surface water and drinking-water (at concentrations up to 100 ng/L) in Japan, the USA and Canada (Table 1.5), and also in precipitations in the USA and Norway. Although its estimated bioconcentration factor is low (12; HSDB, 2006), anthraquinone has been detected at a concentration of 42 ng/g wet tissue (42 ppb) in bullhead catfish fish from the Black River in Ohio, USA (Vassilaros *et al.*, 1982), and in the tissue (180.8 µg/kg) of mussels from the Guanabara Bay in Brazil (Layshock *et al.*, 2010).

In soil, anthraquinone is predicted to be slightly mobile or immobile based on its estimated soil absorption coefficients of 2755–17 416 that were determined using reference European soils (Gawlik *et al.*, 1998). Similar to observations in water, volatilization of anthraquinone from moist or dry soil is not expected (HSDB, 2006). Biodegradation also appears to be the most important factor that influences the removal of anthraquinone from soil; 67% of the anthraquinone added was biodegraded in a mixed soil population within 12 weeks. Other studies have reported half-lives in different soils of 3–10 days, and a study that used a mixed bacterial population found that 6.5% of the initial concentration of anthraquinone remained in the soil after 3 days (reviewed by HSDB, 2006).

Anthraquinone has been detected in the soil from roadways and in marine sediments from areas near sewage plants in France, and in river basins and bays in the USA (see Table 1.5). McKinney *et al.* (1999) proposed that the ratio of anthracene to anthraquinone in marine sediments could be used as an environmental marker of the source of contamination. They measured the concentrations of anthracene and anthraquinone in several samples of coastal marine sediments from four urban harbour sites in New England (USA) and two remote sites (Long Island Sound in New York, and the Slocums River, Massachusetts). The ratio of anthracene to anthraquinone was less than 1 (0.317–0.772) at the urban sites, suggesting that the source of the exposure was predominantly discharge, whereas the ratio at remote sites was greater than 1 (2.45–2.81), suggesting that the source was primarily atmospheric deposition. They also evaluated the oxidation of anthracene and reported that the compound was stable and did not rapidly undergo oxidation under normal conditions found in the marine environment, although, under extreme conditions, it could be photo-oxidized by exposure to ultraviolet radiation.

### *1.3.4 Other occurrence*

Anthraquinone has been detected in fish, mussel tissue and plants (HSDB, 2006). Exposure to anthraquinone from food stuffs can also occur through its leaching from packaging. An experimental study (Louch, 2008) that evaluated the migration of anthraquinone from an unbleached kraft linerboard sample (representing a pizza delivery box) found that the mean level in the

baked pizza crust was 196.1 ng, indicating a 3.6% migration of anthraquinone.

## 1.4 Regulations and guidelines

According to European Union (EU) Commission directive 2007/565/EC, anthraquinone has been phased out as a repellent and attractant since 22 August 2008 in EU Member States (ESIS, 2010).

In the USA, anthraquinone has been accepted by the Environmental Protection Agency as a bird repellent for use near airports since 1998 (US EPA, 1998).

# 2. Cancer in Humans

No studies of human cancer were identified that evaluated exposure to anthraquinone *per se*; however, a series of publications on dye and resin workers in the USA, who were exposed to anthraquinone, was available. These workers were potentially exposed to anthraquinone during its production or its use to manufacture anthraquinone intermediates. Effect estimates were reported for subjects who worked in anthraquinone production areas, but they were also exposed to other chemicals, and effects specific for exposure to anthraquinone were not analysed. A study of substituted anthraquinone dyestuff workers in Scotland (United Kingdom) was also available; however, it was unclear whether anthraquinone was used to produce the intermediates in this study (Gardiner *et al.*, 1982), which was therefore not reviewed by the Working Group. The main findings of the epidemiological studies of anthraquinone dye workers and cancer risk are summarized in Table 2.1.

## 2.1 Cohort and nested case–control studies

### *2.1.1 USA*

#### *(a) Background*

Delzell and colleagues evaluated mortality among manufacturing workers at a dye and resin plant in New Jersey. The study was initiated because of reported cases of central nervous system neoplasms. The findings were reported in a series of publications, including an analysis of mortality for the initial cohort as of 1985 (Delzell *et al.*, 1989), two nested case–control analyses — one of central nervous system neoplasms and the other of lung cancer (Barbone *et al.*, 1992, 1994) — that included both deaths and incident cases, and an analysis of mortality for an expanded cohort followed until 1996 (Sathiakumar & Delzell, 2000).

The plant comprised three major production areas: (1) South dyes, where anthraquinone dyes and intermediates were produced; (2) North dyes, where azo dyes and intermediates were produced; and (3) plastics and additives (P&A), where various resins and additives for resins were produced. This section focuses on data and findings for workers in the anthraquinone dye area. Production of anthraquinone ceased in 1980, production of anthraquinone dye intermediates and dye synthesis ceased in 1983 and the plant closed in 1996. Production of epichlorohydrin (Group 2A, IARC, 2000), another chemical produced in the anthraquinone dye area that has been associated with an increased risk of lung cancer, was only carried out for 5 years (1961–65) but potential exposure to epichlorohydrin occurred during the production of epoxy resins in the P&A production area. Table 2.2 lists the processes and the associated raw materials or intermediates in the anthraquinone dye area (South dyes area) that could potentially confound the association between exposure to anthraquinone and the risk of lung cancer.

## Table 2.1 Cohort studies of anthraquinone dye workers[a]

| Reference, study location and period | Total No. of subjects | Follow-up period | Exposure assessment | Organ site | Exposure categories | No. of cases/ deaths | Relative risk (RR) (95%CI) | Covariates | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Sathiakumar & Delzell (2000), New Jersey, USA, 1952–96 | 3266 dye and resin manufacturing workers (2 859 men, 407 women) | 1952–96 | Occupational history (job title, work area, and duration) from plant records | | | | **SMR** | Age | Local reference |
| | | | | All deaths | Overall | 728 | 0.90 (0.83–0.97) | Age, calendar time and other work area | Elevated risk for lung cancer was also observed among maintenance workers and elevated risks for other cancers (e.g. bladder, CNS and stomach) were observed among workers employed in the other production areas. [Overlaps with Delzell *et al.* (1989) and Barbone *et al.* (1992, 1994)] |
| | | | | Lung | South dyes: White men | | | | |
| | | | | | Total | 32 | 1.68 (1.15–2.37) | | |
| | | | | | Yr since hire/yr worked | | | | |
| | | | | | < 20/ < 5 | 3 | 1.06 (0.22–3.10) | | |
| | | | | | < 20/ > 5 | 5 | 1.79 (0.58–4.18) | | |
| | | | | | > 20/ < 5 | 13 | 2.42 (1.29–4.14) | | |
| | | | | | > 20/ > 5 | 11 | 1.37 (0.68–2.45) | | |
| | | | | | | | **RR** | | |
| | | | | | Never | 48 | 1.0 (ref.) | | |
| | | | | | Ever | 32 | 1.7 (1.1–2.6) | | |
| | | | | | Yr since hire/yr worked | | | | |
| | | | | | < 20/ < 5 | 3 | 0.9 (0.3–3.0) | | |
| | | | | | < 20/ > 5 | 5 | 1.7 (0.7–4.6) | | |
| | | | | | > 20/ < 5 | 13 | 2.4 (1.2–4.5) | | |
| | | | | | > 20/ > 5 | 11 | 1.5 (0.7–2.9) | | |

## Table 2.1 (continued)

| Reference, study location and period | Total No. of subjects | Follow-up period | Exposure assessment | Organ site | Exposure categories | No. of cases/ deaths | Relative risk (RR) (95%CI) | Covariates | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Barbone *et al.* (1992) New Jersey, USA, before 1988 | Nested case–control study*; 51 white men who developed lung tumours from the dye and resin manufacturing workers cohort[a] | | Work history obtained from plant personal records; information on potential confounders obtained by interviews (subjects or next of kin) and plant medical records | Lung | Work area or building | | **OR** | Cigarette smoking; outside employment was considered but was not a confounder | In a separate analysis considering possible exposure to asbestos (mainly a concern among pipe-cleaners), a non-significant association was observed with risk of lung cancer. Risk of lung cancer was also found to be associated with exposure to ECH when restricted to concentrations in the low cumulative exposure category. * 102 controls (2 per case) were matched on yr of birth, and employment status at the date of diagnosis (for living lung cancer cases), and who were not known to have died before the date of death or diagnosis of the case. [Overlaps with Delzell *et al.*, 1989; Barbone *et al.*, 1994; Sathiakumar & Delzell, 2000] |
| | | | | | AQ dyes and ECH production | 21 | 2.4 (1.1–5.2) | | |
| | | | | | > 10 or more yr since first employment | | 4.6 (0.9–23) | | |
| | | | | | AQ dye and ECH area | | | | |
| | | | | | AQ production | 6 | 12 (1.4–99) | | |
| | | | | | AQ intermediate dye production | 8 | 1.8 (0.6–5.1) | | |
| | | | | | AQ dye synthesis | 8 | 1.2 (0.5–2.9) | | |
| | | | | | AQ dye standardization | 8 | 3.3 (1.0–11) | | |

**Table 2.1 (continued)**

| Reference, study location and period | Total No. of subjects | Follow-up period | Exposure assessment | Organ site | Exposure categories | No. of cases/ deaths | Relative risk (RR) (95%CI) | Covariates | Comments |
|---|---|---|---|---|---|---|---|---|---|
| Barbone *et al.* (1994)<br>New Jersey, USA, before 1988 | Nested case–control study*; 11 white men who developed CNS tumours from the dye and resin manufacturing workers cohort[a] | | Work history obtained from plant personal records; information on potential confounders obtained by interviews (subjects or next of kin) and plant medical records | CNS | Work area, process, line, duty<br>AQ dyes<br>AQ intermediate dyes<br>Production<br>Laboratory<br>Other AQ dyes<br>Production<br>Laboratory<br>Maintenance | <br><br>3<br>3<br>1<br>1<br>1<br>1<br>0 | **OR**<br><br>∞ (1.7–∞)<br>∞ (1.7–∞)<br>NR<br>0.3 (0.1–3.2)<br>0.3 (0.1–3.9)<br>1.0 (0.1–13)<br>0.0 (0.0–4.6) | Unadjusted [cigarette smoking, outside employment, head radiation, head trauma, history of epilepsy and use of antiepileptic drugs were considered, but were not confounders] | All 3 cases in the AQ work area had an induction time of 20 yr or more. Routine exposure to ECH was also associated with CNS tumours (OR, 4.2; 95%CI: 0.7–26; 4 exposed cases); some of the exposed cases occurred among workers who worked in AQ intermediate dyes.<br>* 44 controls (4 per case) matched by yr of birth and who had not died before the date of diagnosis or death for living cases. Matching criterion was employment as of date of diagnosis. [Overlaps with Delzell *et al.*, 1989; Barbone *et al.*, 1992; Sathiakumar & Delzell, 2000] |

[a] Findings for the early update of the cohort and effect estimates for workers in production areas other than anthraquinone dye area not included

AQ, anthraquinone; CI, confidence interval; CNS, central nervous system; ECH, epichlorohydrin; NR, not reported; OR, odds ratio; SMR, standardized mortality ratio; yr, year or years

**Table 2.2 Selected raw materials or intermediates used in different processes associated with anthraquinone dyes**

| Processes or lines | Selected raw materials or intermediates |
|---|---|
| AQ production (South dyes) | Anthracene, vanadium pentoxide |
| AQ intermediate dyes (including AQ sulfonate, amino-AQ other substituted AQs) | AQ, sulfuric acid, mercury, AQ sulfonates, ammonia, arsenic acid, *m*-nitrobenzene sulfonic acid, methanol, |
| AQ dye synthesis | AQ intermediates, aniline, substituted anilines, benzene, nitrobenzene, chorobenzene, chlorotoluenes, pyridine, alcohols, tetrachloroethylene |
| AQ dye standardization (final formulation – mixing, milling, drying) | Dye dusts, 2,4,5-trichlorophenol |
| Epichlorohydrin production | Allyl chloride, chloride lime |

AQ, anthraquinone
From Delzell *et al.* (1989), Sathiakumar & Delzell (2000)

No data on exposure levels were available. [The Working Group noted that the major limitation of these studies was that they did not assess exposure to specific chemicals; risk estimates were calculated for employment in the various production areas or for different processes. These studies also had limited statistical power to detect effects for specific cancers because of the small numbers of exposed cases.] Table 2.1 reports the findings (overall and those for employment in anthraquinone production areas) from the latest update of the cohort and the two nested case–control studies.

### (b) *Cohort study: 1986 follow-up*

The initial retrospective cohort included all men (2642) who were employed at this plant for at least 6 months from 1 January 1952 (opening of the plant) until 1 January 1985 (Delzell *et al.*, 1989), and follow-up was from 1 July 1952 until 31 December 1985. Subjects were classified into work areas using work history information and standardized mortality ratios (SMRs) were calculated using national rates. Excesses of lung cancer and central nervous system tumours were found in certain subgroups of workers and the associations were evaluated in more detail in two nested case–control studies.

### (c) *Nested case–control study of cancer of the lung*

A nested case–control analysis of lung cancer was conducted among the dye and resin workers (Barbone *et al.*, 1992). The cases comprised 51 (47 decedent and 4 living) male white workers who developed lung cancer before 1 October 1988. Two controls per case (102) were selected from the cohort, matched on year of birth and employment status at the date of diagnosis (for living lung cancer cases), and were not known to have died before the date of death or diagnosis of the case. Workers were assigned to one of the three production areas (see above) and processes within the production areas (processes that involved anthraquinone are described in Table 2.2), based on personnel records. Employees in each production area/process were also classified by duties — production, laboratory or maintenance — for each of the production areas. In addition to the production categories, workers could also be assigned to central laboratories and central maintenance for activities that were not carried out in one of the production areas or services. Cumulative potential exposure to epichlorohydrin and asbestos was calculated for each subject by multiplying each category of potential contact with epichlorohydrin by the number of years worked in that category, and then adding the findings for all categories. Information on

potential confounders was obtained from interviews, using a structured questionnaire, with study subjects or their next of kin, and from plant medical records. Subjects were also classified according to high-risk employment before and after working at the plant. Odd ratios (ORs) were calculated with and without adjustment for cigarette smoking (using detailed information on individuals) and employment in outside industries, but only smoking was found to be a confounder in certain analyses. When smoking was not found to be a confounder in the analyses, unadjusted odds ratios were reported.

Statistically significant (or borderline significant) elevated risks for lung cancer were found among workers in the anthraquinone and epichlorohydrin production area (OR, 2.4; 95% confidence interval [CI]: 1.1–5.2; 21 exposed cases, 24 exposed controls) and, within this area, for anthraquinone production (OR, 12; 95%:CI, 1.4–99; six exposed cases, one exposed control), and anthraquinone dye standardization (OR, 3.3; 95%CI: 1.0–11; eight exposed cases, six exposed controls). The odds ratio among workers in the anthraquinone intermediate dye production process was 1.8 (95%CI: 0.6–5.1; eight exposed cases, 10 exposed controls). [The Working Group noted that none of the reported odds ratios was adjusted for smoking because the authors ruled it out as a confounder in their analyses.]

The smoking-adjusted odds ratios among workers with 10 or more years since first employment in the anthraquinone and epichlorohydrin production area was 4.6 (95%CI: 0.9–23). An excess of lung cancer was also found for employees in the epichlorohydrin production process who had worked in the anthraquinone production area (three exposed cases, no exposed controls). For all workers (in the entire plant and not just the anthraquinone production area), the odds ratio for potential exposure to epichlorohydrin was 1.7 (95%CI: 0.7–4.1; 12 exposed cases, 18 exposed controls). The risk was concentrated among individuals with low cumulative or short duration of potential exposure to epichlorohydrin. [The Working Group noted that the increased risk for workers in the anthraquinone dye area was probably independent of the increased risk associated with exposure to epichlorohydrin because the later analysis included only three of the 21 cases observed among anthraquinone production workers.] Elevated odds ratios were also found for some other production areas or processes, but were not statistically significant.

### *(d) Nested case–control study of tumours of the central nervous system*

The relationship between central nervous system tumours and exposure to epichlorohydrin was evaluated in greater detail in a nested case–control study (Barbone *et al.*, 1994). [The Working Group noted that some of the workers exposed to epichlorohydrin were also exposed to anthraquinone.] Cases included 11 (eight decedent and three living) white men who developed tumours of the central nervous system (seven astrocytomas and glioblastomas, two meningiomas and two other benign tumours) before 1988. For each case, four controls ($n$ = 44) were matched on year of birth and employment status at the date of diagnosis (for living cases), and were not known to have died before the date of death or diagnosis of the case. Exposure was assessed as described above for lung cancer. Odds ratios were calculated with and without adjustment for cigarette smoking, outside employment, head radiation, head trauma, history of epilepsy and use of antiepileptic drugs. The author stated that none of these were found to be confounders, and thus unadjusted odds ratios were provided (see Table 2.1).

Statistically significant risks for central nervous system tumours were found among workers in the anthraquinone dye area; the associated odds ratios and the number of exposed cases with duties involving anthraquinone intermediate dyes and their production within this area were identical (OR, ∞; 95%CI: 1.7–∞;

three exposed cases). The only other statistically significant odds ratio was for workers involved in the epoxy resin line in the P&A area; elevated but statistically non-significant risks were observed for maintenance and production activities in the azo dye production area. [Results for epichlorohydrin are presented here because some of the workers exposed to epichlorohydrin were also exposed to anthraquinone.] Detailed analyses of routine exposure to epichlorohydrin found a statistically significant odds ratio for routine potential exposure (OR, 4.2; 95%CI: 0.7–26; four exposed cases) and acute exposure (OR, ∞; 95%CI: 1.5–∞; three exposed cases), and positive associations (not statistically significant) with 'cumulative potential exposure' ($P_{trend}$ = 0.11), and 'duration of routine potential exposure' ($P_{trend}$ = 0.11). Potential exposure to epichlorohydrin primarily occurred in the epoxy plastic and additives division of the P&A production area. [The Working Group noted that three of the four epichlorohydrin-exposed cases worked in either the anthraquinone intermediate dye or azo dye areas.]

*(e) Cohort study: 1996 follow-up*

The cohort was later expanded and updated to include all (3266) workers (men and women) employed for at least 6 months from 1 January 1952 until 1 January 1996 who were followed until 1 January 1996 (Sathiakumar & Delzell, 2000). The average length of follow-up was 27 years. Local rates were used to calculate SMRs. In addition, Poisson regression analysis was used to estimate the lung cancer risk for subjects in a particular area using subjects who had never worked in the area as the comparison group and adjusting for potential confounding by age, calendar period and employment in other high-risk areas.

Mortality from all causes was significantly decreased (SMR, 0.90; 95%CI: 0.83–0.97; 728 observed deaths). Mortality in the entire cohort was elevated, but not statistically significantly, for several cancers including lymphosarcoma and cancer of the colon, lung, liver, genital tissue, bladder and the central nervous system. A statistically significantly increased risk of mortality from lung cancer was found among workers in the anthraquinone production (South dyes) area (SMR, 1.68; 95%CI: 1.15–2.37; relative risk for ever versus never exposure, 1.7; 95%CI: 1.1–2.6; 32 exposed cases for both analyses). Both external (SMR) and internal (Poisson regression) analyses by time since first employment and duration of exposure among hourly paid white men showed similar results, with slightly higher risks among longer-term workers than shorter-term workers for those with less than 20 years since first employment; this effect was not observed among workers with more than 20 years since first employment. Mortality was highest among workers with 20 or more years since first employment and duration of employment less than 5 years (see Table 2.1). [The lack of a clear exposure–response relationship could be because length of employment is a poor surrogate for exposure to a carcinogenic substance.]

## 3. Cancer in Experimental Animals

Carcinogenicity studies of oral administration of anthraquinone to mice and rats have been conducted by the National Toxicology Program (NTP, 2005), the results of which are summarized in Table 3.1.

### 3.1 Oral administration

#### *3.1.1 Mouse*

Groups of 50 male and 50 female B6C3F$_1$ mice were fed diets containing 0, 833, 2500 or 7500 ppm anthraquinone (equivalent to average daily doses of approximately 90, 265 or 825 and 80, 235 or 745 mg/kg body weight (bw) for males and females, respectively) for 105 weeks. The incidence of hepatocellular adenoma, carcinoma,

## Table 3.1 Carcinogenicity studies of oral administration of anthraquinone in the diet to rats and mice

| Species, strain (sex) Duration | Dosing regimen, Animals/group at start | Incidence of tumours | Significance | Comments |
|---|---|---|---|---|
| Mouse, B6C3F$_1$ (M) 2 yr | Oral (feed) 0, 833, 2 500 or 7 500 ppm 50 animals/group | Liver (hepatocellular adenoma): 21/50, 32/50, 38/50, 41/49 | $P = 0.011$ (833 ppm)<br>$P < 0.001$ (2500 ppm)<br>$P < 0.001$ (7500 ppm)<br>$P < 0.001$ (trend) | |
| | | Liver (hepatocellular carcinoma): 8/50, 13/50, 17/50, 21/49 | $P = 0.026$ (2500 ppm)<br>$P < 0.001$ (7500 ppm)<br>$P < 0.001$ (trend) | |
| | | Liver (hepatocellular adenoma or carcinoma): 25/50, 34/50, 41/50, 46/49 | $P = 0.043$ (883 ppm)<br>$P < 0.001$ (2500 ppm)<br>$P < 0.001$ (7500 ppm)<br>$P < 0.001$ (trend) | |
| | | Liver (hepatoblastoma): 1/50, 6/50, 11/50, 37/49 | $P = 0.053$ (833 ppm)<br>$P = 0.002$ (2500 ppm)<br>$P < 0.001$ (7500 ppm)<br>$P < 0.001$ (trend) | |
| | | Liver (hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma): 26/50, 35/50, 43/50, 48/49 | $P = 0.045$ (833 ppm)<br>$P < 0.001$ (2500 ppm)<br>$P < 0.001$ (7500 ppm)<br>$P < 0.001$ (trend) | Historical incidence for 2-yr feed studies with untreated control groups (mean ± standard deviation): 440/850 (51.8 ± 8.3%); range, 40–68% |

**Table 3.1 (continued)**

| Species, strain (sex) Duration | Dosing regimen, Animals/group at start | Incidence of tumours | Significance | Comments |
|---|---|---|---|---|
| Mouse, B6C3F$_1$ (F) 2 yr | Oral (feed) 0, 833, 2 500 or 7 500 ppm 50 animals/group | Liver (hepatocellular adenoma): 6/49, 28/50, 27/50, 40/49 | $P < 0.001$ (833 ppm)<br>$P < 0.001$ (2500 ppm)<br>$P < 0.001$ (7500 ppm)<br>$P < 0.001$ (trend) | |
| | | Liver (hepatocellular carcinoma): 2/49, 3/50, 8/50, 8/49 | $P = 0.051$ (2500 ppm)<br>$P = 0.048$ (7500 ppm)<br>$P = 0.031$ (trend) | |
| | | Liver (hepatocellular adenoma or carcinoma): 6/49, 30/50, 30/50, 41/49 | $P < 0.001$ (833 ppm)<br>$P < 0.001$ (2500 ppm)<br>$P < 0.001$ (7500 ppm)<br>$P < 0.001$ (trend) | |
| | | Liver (hepatocellular adenoma, hepatocellular carcinoma or hepatoblastoma [including multiple]) (overall rate): 6/49, 30/50, 30/50, 41/49 | $P < 0.001$ (833 ppm)<br>$P < 0.001$ (2500 ppm)<br>$P < 0.001$ (7500 ppm)<br>$P < 0.001$ (trend) | Historical incidence for 2-yr feed studies with untreated control groups (mean ± standard deviation): 273/852 (32.0 ± 9.6%); range, 18–56% |
| | | Thyroid gland (follicular-cell carcinoma): 0/45, 0/48, 0/48, 2/48 | $P = 0.042$ (trend) | Historical incidence for 2-yr feed studies with untreated control groups (mean ± standard deviation): 2/847 (0.2 ± 0.7%); range, 0–2% |
| | | Thyroid gland (follicular-cell adenoma or carcinoma): 1/45, 1/48, 2/48, 4/48 | NS (2500 ppm)<br>NS (7500 ppm)<br>$P = 0.078$ (trend) | Historical incidence for 2-yr feed studies with untreated control groups (mean ± standard deviation): 15/847 (1.8 ± 1.7%); range, 0–6% |

**Table 3.1 (continued)**

| Species, strain (sex) Duration | Dosing regimen, Animals/group at start | Incidence of tumours | Significance | Comments |
|---|---|---|---|---|
| Rat, F344 /N (M) 2 yr | Oral (feed) 0, 469, 938, 1 875 or 3 750 ppm 50–60 animals/group | Kidney (renal tubule adenoma): 1/50, 3/50, 9/50, 5/50, 3/50 | $P = 0.010$ (938 ppm)<br>$P = 0.474$ (trend) | Historical incidence for 2-yr feed studies with untreated control groups (mean ± standard deviation): 7/902 (0.8 ± 1.2%); range, 0–4% |
| | | Urinary bladder (transitional epithelial papilloma): 0/50, 1/50, 3/50, 7/50, 3/49 | $P = 0.011$ (1875 ppm)<br>$P = 0.053$ (trend) | Historical incidence for 2-yr feed studies with untreated control groups (mean ± standard deviation): 2/891 (0.2 ± 0.7%); range, 0–2% |
| Rat, F344/N (F) 2 yr | Oral (feed) 0, 469, 938, 1 875 or 3 750 ppm 50–60 animals/group | Kidney (renal tubule adenoma): 0/50, 4/50, 9/50, 7/50, 12/49 | $P = 0.002$ (938 ppm)<br>$P = 0.011$ (1875 ppm)<br>$P = 0.001$ (3750 ppm)<br>$P = 0.001$ (trend) | |
| | | Kidney (renal tubule adenoma or carcinoma): 0/50, 6/50, 9/50, 8/50, 14/49 | $P = 0.020$ (469 ppm)<br>$P = 0.002$ (938 ppm)<br>$P = 0.006$ (1875 ppm)<br>$P < 0.001$ (3750 ppm)<br>$P < 0.001$ (trend) | Historical incidence for 2-yr feed studies with untreated control groups (mean ± standard deviation): 1/901 (0.1 ± 0.5%); range, 0–2% |
| | | Urinary bladder (transitional epithelial papilloma or carcinoma): 0/49, 0/49, 0/49, 1/50, 2/49 | $P = 0.037$ (3750 ppm)<br>$P = 0.037$ (trend) | Historical incidence for 2-yr feed studies with untreated control groups (mean ± standard deviation): 2/891 (0.2 ± 0.7%); range, 0–2% |
| | | Liver (hepatocellular adenoma): 0/50, 2/50, 6/50, 4/50, 3/49 | $P < 0.05$ (938 ppm) | Historical incidence for 2-yr feed studies with untreated control groups (mean ± standard deviation): 4/901 (0.4 ± 1.1%); range, 0–4% |

F, female; M, male; NS, not significant; yr, year or years
From NTP (2005)

and adenoma or carcinoma (combined) was increased with a positive trend in both males and females, and was increased in all groups exposed to 2500 ppm or more. The incidence of hepatoblastoma was statistically significant increased in males exposed to 2500 or 7500 ppm, and one hepatoblastoma occurred in a 7500-ppm female. Thyroid follicular-cell adenomas were present in all groups of females; moreover, two 7500-ppm females developed follicular-cell carcinomas. The incidence of follicular-cell carcinoma and adenoma or carcinoma (combined) in 7500-ppm females exceeded the historical control ranges (NTP, 2005).

#### *3.1.2 Rat*

Groups of 50 male and 50 female F344/N rats were fed diets containing 469, 938 or 1875 ppm anthraquinone for 105 weeks. Further groups of 60 males and 60 females received 0 or 3750 ppm anthraquinone for the same period. These dietary concentrations resulted in average daily doses of approximately 20, 45, 90 and 180 and 25, 50, 100 and 200 mg/kg bw anthraquinone for males and females in the 469-, 938-, 1875- and 3750-ppm groups, respectively. At 2 years, animals in the highest-dose group weighed less than those in the control group. Positive trends in the incidence of renal tubule adenoma and of renal tubule adenoma or carcinoma (combined) in females were observed, and the incidence of adenoma or carcinoma (combined) in all groups of exposed females was significantly increased. Renal tubule carcinomas developed in two 469-ppm, one 1875-ppm and two 3750-ppm females. The incidence of renal tubule adenoma in the 938-ppm males was significantly greater than that in the controls, and that in all exposed groups of males exceeded the historical control range; no renal tubule carcinomas were observed in male rats. Papillomas of the transitional epithelium of the kidney were observed in two males exposed to 938 ppm and one male exposed to 3750 ppm; none occurred in females. At least one male in each exposed group had a transitional epithelial papilloma of the urinary bladder; the incidence in the 1875-ppm group was significantly greater than that in the controls, and that in groups exposed to 938 ppm or more exceeded the historical control range. A positive trend in the incidence of papilloma or carcinoma (combined) was found in females. The incidence of hepatocellular adenoma in the 938-ppm females was significantly greater than that in controls, and that in females exposed to 938 ppm or more exceeded the historical control range (NTP, 2005).

[The Working Group noted that tumours of the kidney and urinary bladder, and hepatoblastomas are rare spontaneous neoplasms in experimental animals.]

## 4. Other Relevant Data

### 4.1 Absorption, distribution, metabolism, and excretion

#### *4.1.1 Humans*

No data were available to the Working Group.

#### *4.1.2 Experimental systems*

In male F344 rats, [$^{14}$C]anthraquinone was well absorbed (> 99.8% of the administered dose) from the gastrointestinal tract following oral doses ranging from 0.35 to 350 mg/kg bw. Following absorption, anthraquinone was distributed to various tissues, with highest concentrations in the adipose tissue. It was not bioaccumulated in any particular tissue and, by 96 hours after administration, more than 95% of the dose had been metabolized and eliminated in the bile, faeces and urine. 2-Hydroxyanthraquinone was the major metabolite detected in the urine of rats exposed to anthraquinone intravenously or orally (NTP, 2005). In earlier studies,

1-hydroxy- and 2-hydroxyanthraquinone were identified in the urine of rats that received daily oral doses of anthraquinone (Sato *et al.*, 1956), and 1-hydroxyanthraquinone induced tumours of the liver, stomach and large intestine in rats (Mori *et al.*, 1990). The presence of the sulfate and glucuronide conjugates — 2-hydroxy-9,10-anthraquinone, 8,10-dihydroxyanthracene and 2,9,10-trihydroxyanthracene — in rat urine samples after 4 days of dietary administration of 9,10-anthraquinone has been reported (Sims, 1964).

Single-dose toxicokinetic studies have been conducted in F344/N rats and B6C3F$_1$ mice (NTP, 2005). Toxicokinetic parameters were derived but no modelling of plasma concentration-time profiles to a best fit curve was conducted. Intravenous administration showed biphasic curves in both male and female rats that are best described as a two-compartment open model, and the half-life for plasma anthraquinone was 10–12 hours. Oral administration by gavage also gave results that best fit a two-compartment model. Maximum concentration values were proportional to dose and were observed at 8–18 hours. The half-life could not be estimated reliably at higher doses. The areas under the curve were also proportional to dose. In mice, similar two-compartment behaviour was estimated with a half-life in plasma of 4 hours following intravenous administration. Following oral administration to mice, the half life was 4–6 hours and the areas under the curve were proportional with dose.

## 4.2 Genetic and related effects

### *4.2.1 Humans*

No data were available to the Working Group.

### *4.2.2 Experimental systems*

The genetic toxicology of anthraquinone has been reviewed (Butterworth *et al.*, 2001, 2004; NTP, 2005). The data on the genotoxicity of anthraquinone derived from different bacterial systems are conflicting and inconclusive with regard to its in-vitro mutagenic potential. In particular, positive and negative results have been reported for anthraquinone in *Salmonella* mutation assays. Early studies reported that neither anthraquinone nor its metabolites were genotoxic in *Salmonella* bacterial mutagenicity assays (Brown & Brown, 1976; Gibson *et al.*, 1978; Salamone *et al.*, 1979). In later studies, anthraquinone was found to be mutagenic in the *Salmonella* mutagenicity assay in the absence of metabolic activation (Liberman *et al.*, 1982; Zeiger *et al.*, 1988). Moreover, none of the negative bacterial studies reported purity (NTP, 2005). [The contradictory results for anthraquinone may be attributable to variable amounts of contaminants resulting from the different production methods or testing methods.] It has been suggested that the carcinogenicity of anthraquinone might be due solely to the presence of 9-nitroanthracene, which was present as a contaminant at a level of approximately 0.1% in the anthraquinone sample (Butterworth *et al.*, 2001, 2004), and was found in the NTP report to be a weak mutagen (NTP, 2005). It was also noted that the mutagens claimed to be other impurities in the test material were point-of-contact carcinogens and that forestomach tumours had not been reported in the 2-year bioassay. The amount of 9-nitroathracene in the anthraquinone given in the 2-year bioassay was reported to be 0.09% w/w, and the two other contaminants (anthrone and phenanthrene) were present at levels of 0.05% and 0.008% and were also negative or mainly negative in mutagenicity assays (NTP, 2005). These three compounds were the major contaminants identified and it was concluded that they were non-mutagenic or weakly mutagenic (NTP, 2005).

Two rat metabolites of anthraquinone — 1-hydroxy- and 2-hydroxyanthraquinone — were examined for mutagenicity in the *Salmonella* assay (Tikkanen at al., 1983; Butterworth *et al.*, 2004). Anthrone and 2-hydroxyanthraquinone were reported to be weak mutagens in *S. typhimurium* (NTP, 2005). Anthrone was also reported to give negative results in several other studies. 2-Hydroxyanthraquinone was negative in TA98 but gave positive results in TA100 in the presence of metabolic activation (Tikkanen *et al.*, 1983; Butterworth *et al.*, 2004). 1-Hydroxyanthraquinone was negative in the absence of and positive in the presence of metabolic activation in TA1537 (Butterworth *et al.*, 2004). In another study, 1-hydroxyanthraquinone was negative in TA98 and TA100, whereas 2-hydroxyanthraquinone was positive in TA98 with and without metabolic activation and negative in TA100 (NTP, 2005).

NTP (2005) indicated that 2-hydroxyanthraquinone is a more potent mutagen in *S. typhimurium* TA98 than 9-nitroanthracene. Based on the amount of 2-hydroxyanthraquinone eliminated in the rat urine and the maximal amount of 9-nitroanthracene to which rats might have been exposed as a consequence of its presence as a contaminant (0.1%) in the anthraquinone sample, it was concluded that the level of 2-hydroxyanthraquinone present in exposed rats was at least 5.8-fold that of 9-nitroanthracene. Because anthraquinone is metabolized to at least one mutagenic metabolite with greater mutagenic potency than 9-nitroanthracene, NTP (2005) concluded that the carcinogenic activity of anthraquinone may occur via a mutagenic mechanism regardless of the presence of the contaminant.

NTP (2005) reported the in-vivo induction of strand breaks in the liver and kidney cells of CD-1 mice treated intraperitoneally with 250 mg/kg bw anthraquinone (Cesarone *et al.*, 1982) and dose-related increases in micronuclei in Syrian hamster embryo cells treated with 3.13–25 µg anthraquinone (99% pure)/ml (Gibson *et al.*, 1997).

In the rodent hepatocyte DNA repair assay, 1-hydroxyanthraquinone gave positive results (Mori, 1989).

In the NTP (2005) study, male and female mice fed anthraquinone (99.8% pure) in the diet at concentrations of 135–2350 mg/kg bw per day (1875–30 000 ppm) for 14 weeks showed significant increases in the frequency of micronucleated normochromatic erythrocytes in the peripheral blood compared with controls. In an acute bone-marrow micronucleus test performed with male mice given 500–2000 mg/kg bw anthraquinone by intraperitoneal injection, micronucleated red blood cells were slightly decreased in a dose-related manner. Butterworth *et al.* (2001) reported no significant increase in micronuclei in bone-marrow polychromatic erythrocytes of mice administered anthraquinone by gavage at concentrations of 1250, 2500 and 5000 mg/kg bw.

In the Syrian hamster embryo cell transformation assay, anthraquinone gave negative results (Kerckaert *et al.*, 1996). Anthraquinone did not induce an increased incidence of mutations in the presence or absence of metabolic activation at the $Tk^{-/+}$ locus in L5178Y mouse lymphoma cells (Butterworth *et al.*, 2001). No significant increase in cells with chromosomal aberrations, polyploidy, or endoreduplication was observed in Chinese hamster ovary cells incubated with anthraquinone (up to 50.0 µg/mL) (Butterworth *et al.*, 2001).

Anthraquinone was not found to be mutagenic in h1A1v2 human B-lymphoblastoid cells that constitutively express cytochrome P450 (CYP)1A1 (Durant *et al.*, 1996).

## 4.3 Mechanistic considerations

In subchronic studies, histological lesions were observed in the kidney, liver, spleen, bone marrow and thyroid glands of male and female

rats and the urinary bladder of female rats. Variably sized eosinophilic hyaline droplets occurred within the renal tubules in treated males and females. α2u-Globulin was increased to the same degree in all treated male rats. The incidence of hyperplasia of the transitional epithelium of the renal pelvis was increased in all exposure groups in 2-year feed studies. In the 14-week study, the liver weights of all exposed male and female mice were significantly greater than those of the controls. Anthraquinone-treated mice showed centrilobular hypertrophy of hepatocytes with enlarged nuclei (NTP, 2005). Centrilobular hypertrophy of liver cells was also pronounced in 2-year studies of exposure to anthraquinone, but information regarding subcellular structural changes was lacking.

A 32-day feeding study of anthraquinone in F344/N rats (NTP, 2005) investigated CYP activity in the liver, 8-hydroxy-2′-deoxyguanosine (8-OHdG) and 2′-deoxyguanosine concentrations in the liver and kidney and cell proliferation in the liver, kidney and urinary bladder. At day 8, CYP1A1 and CYP2B1 were increased in male and female liver and were treatment-related and treatment- and dose-related, respectively. At the sasme time-point, 8-OHdG and 2′-deoxyguanosine were both slightly decreased in male and female kidney but variable results were found in the liver. Cell proliferation in males and females was increased in the bladder but not in the kidney. At the end of the 32-day study, males and females both had increased levels of hyaline droplets. However, the nephropathy reported in males was not consistent with chronic progressive nephropathy.

The induction of certain drug-metabolizing enzymes in the liver and small intestine of rats was investigated following intragastric administration of 100 mg/kg anthraquinone for 3 days (Longo *et al.*, 2000). In the liver, anthraquinone induced both CYP1A2 and CYP2B, but not CYP1A1. The mechanism by which hepatic enzymes are induced by anthraquinone and some related compounds is not known, but it did not induce CYP1A2 or CYP2B in the small intestine mucosa of rats (Longo *et al.*, 2000).

# 5. Summary of Data Reported

## 5.1 Exposure data

Anthraquinone is widely used as an intermediate for the manufacture of dyes for fibres and textiles. It is also used as a bird repellent and as an additive in the pulp and paper industry. Workers may be exposed by inhalation of dust or by dermal contact. Anthraquinone may be formed from direct combustion processes in motor vehicle engines or as a result of degradation of polycyclic aromatic hydrocarbons by atmospheric oxidation. It is ubiquitous in the environment, where it is released via wastewater streams during its production and use, and has been detected in air, water (including surface, ground- and drinking-water), soil, plants, fish and animal tissues.

## 5.2 Human carcinogenicity data

The Working Group identified a series of publications on dye and resin workers in a single facility in the USA who were potentially exposed to anthraquinone during its production or its use to produce anthraquinone intermediates. These publications reported on findings from the initial cohort, nested case–control analyses of lung cancer and central nervous system tumours, and updated findings on an expanded cohort. An excess risk of mortality from lung cancer was found among workers employed in the anthraquinone dye production area in both nested case–control and cohort analyses. Workers in this production area were potentially exposed to anthraquinone, anthraquinone dye intermediates, anthracene, vanadium pentoxide

and epichlorohydrin. Within the anthraquinone dye production area, risk for lung cancer was increased 12-fold for workers producing anthraquinone itself, but this was based on only a few exposed cases. The increased risk did not appear to be due to cigarette smoking, or exposure to asbestos or epichlorohydrin. An excess incidence of central nervous system tumours was also found among workers employed in the anthraquinone dye production area, but this was based on only three exposed cases who may also have been exposed to epichlorohydrin, which was also associated with an increased risk of these tumours. The major limitations of these studies were that: (1) risk estimates were calculated for men employed in anthraquinone and anthraquinone dye production, but exposure to anthraquinone per se was not evaluated; (2) the statistical power to detect effects for specific cancers was limited because of small numbers of exposed cases; and (3) the ability to evaluate potential confounding from other occupational exposures was also limited.

## 5.3 Animal carcinogenicity data

In a 2-year study, anthraquinone caused an increased incidence of benign or malignant neoplasms in mice and rats. In mice, treatment-related hepatoblastomas occurred in males, and hepatocellular adenomas and carcinomas in males and females. Treatment-related tumour formation in male rats included renal tubule adenoma of the kidney and transitional epithelial papillomas of the urinary bladder. Treatment-related tumours in female rats included renal tubule adenomas and carcinomas combined, transitional epithelial-cell papillomas and carcinomas of the urinary bladder combined, and hepatocellular adenomas.

Tumours of the kidney and urinary bladder, and hepatoblastomas are rare spontaneous neoplasms in experimental animals.

## 5.4 Other relevant data

While no data were available on the metabolism of anthraquinone in humans, many studies have investigated its metabolism in rodents. Anthraquinone is almost completely absorbed after oral administration and is distributed systemically. There is no evidence of its bioaccumulation. 1- and 2-Hydroxyanthraquinones are the metabolites formed in rodents that are relevant to the mechanistic considerations of the parent compound.

Anthraquinone itself gave conflicting results in bacterial mutagenesis and other genotoxicity studies. 2-Hydroxyanthraquinone, the major urinary metabolite of anthraquinone, is mutagenic. Furthermore, 1-hydroxyanthraquinone has been shown to be carcinogenic in rats. Other mechanisms by which anthraquinone causes cancer are not well established. Increased cell proliferation and cytotoxicity have been observed in the urinary tract and kidneys in treated male and female rats. Although accumulation of hyaline droplets consistent with 2u-globulin nephropathy has been observed in the kidney of treated male rats, a similar phenotype, albeit weaker in severity, has also been observed in females.

There is moderate evidence that genotoxicity may play a role in the mechanism of action for anthraquinone-induced cancer. The relevance of the tumour response in experimental animals to humans cannot be excluded.

# 6. Evaluation

## 6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of anthraquinone.

## 6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of anthraquinone.

## 6.3 Overall evaluation

Anthraquinone is *possibly carcinogenic to humans (Group 2B)*.

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