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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

1-AMINO-2,4-DIBROMOANTHRAQUINONE

1. Exposure Data

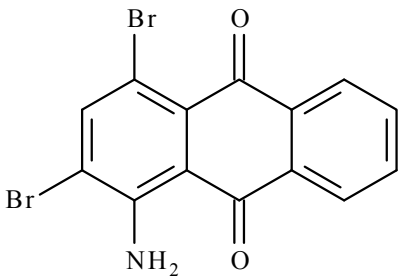
1.1 Chemical and physical data

From NTP (1996, 2002) and HSDB (2010)

1.1.1 Nomenclature

Chem. Abstr. Services Reg. No.: 81-49-2
Chem. Abstr. Name: 1-Amino-2,4-dibromo-9, 10-anthracenedione
Synonyms: ADBAQ; 2-amino-4-chloro-5-nitrophenol; 1-amino-2,4-dibromoanthra-9,10-quinone; 1-amino-2,4-dibromo-9,10-anthraquinone; 9,10-anthracedione, 1-amino-2,4-dibromo-; anthraquinone, 1-amino-2,4-dibromo-; dibromoaminoanthraquinone; 2,4-dibromo-1-anthraquinonylamine
RTECS No.: CB5500000
EINECS No.: 201-354-0

1.1.2 Structural and molecular formulae and relative molecular mass



$C_{14}H_7Br_2NO_2$
Relative molecular mass: 381.04

1.1.3 Chemical and physical properties of the pure substance

Description: Odourless reddish brown to orange powder
Melting-point: 226 °C
Vapour pressure: 1.4×10^{-9} mm Hg at 25°C (estimated)
Solubility: 0.015 mg/L in water at 25 °C, < 1 mg/mL in acetone at 23 °C, 1–10 mg/mL in dimethyl sulfoxide at 23 °C and << 1mg/mL in toluene at 23 °C
Flash-point: > 200 °C
Octanol/water partition coefficient: log K_{ow}, 5.31 (estimated)
Henry's law constant: 1.78×10^{-13} 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

1-Amino-2,4-dibromoanthraquinone has been analysed in various samples by gas chromatography/flame ionization detection and gas chromatography/mass spectrometry (Games & Hites, 1977).

1.2 Production and use

1.2.1 Production

1-Amino-2,4-dibromoanthraquinone is prepared from 1-aminoanthraquinone by bromination in dilute mineral acids (HSDB, 2010).

According to the non-confidential information on production volumes submitted to the United States Environmental Protection Agency by companies for chemicals under the 1986–2002 inventory update rule, production in the United States of America ranged between 10 and 500 thousand pounds in 1986 (HSDB, 2010).

1.2.2 Use

1-Amino-2,4-dibromoanthraquinone is an anthraquinone vat dye that is used as a dye or dye intermediate in the textile industry. Vat dyes are a class of water-insoluble dyes that can easily be reduced to a water-soluble and usually colourless leuco form that can readily impregnate fibres and textiles — typically cotton, wool and cellulose acetate. Their principal properties are brightness and good fastness (NTP, 1996, 2002). No data were available to the Working Group regarding specific uses of 1-amino-2,4-dibromoanthraquinone.

1.3 Occurrence

1.3.1 Natural occurrence

1-Amino-2,4-dibromoanthraquinone is not known to occur in nature.

1.3.2 Occupational exposure

Occupational exposure by inhalation of dust or by dermal contact to 1-amino-2,4-dibromoanthraquinone can occur during its production and its use as a chemical intermediate in the manufacture of dyes. No specific data were available to the Working Group on occupational exposure to 1-amino-2,4-dibromoanthraquinone.

1.3.3 Environmental occurrence

During its production and use, 1-amino-2,4-dibromoanthraquinone may be released to the environment (e.g., ambient air, water and soil) *via* wastewater streams. 1-Amino-2,4-dibromoanthraquinone was found at concentrations of 92–170 ppb in several samples of raw wastewater from a dye manufacturing plant, but was not detected in the final effluent (Games & Hites, 1977).

HSDB (2010) reviewed information on and or calculated parameters related to the environmental fate of 1-amino-2,4-dibromoanthraquinone in ambient air, water and soil. It is expected to exist only in the particle phase, but may be susceptible to photolysis by sunlight and particulates in the atmosphere may be removed by wet or dry deposition.

In aquatic environments, 1-amino-2,4-dibromoanthraquinone is expected to adsorb onto suspended solids and sediments and to be immobile. Although it is not clear how 1-amino-2,4-dibromoanthraquinone is removed from the soil or water, its volatilization from water, moist soil surfaces and dry soils and hydrolysis in aquatic environments are unlikely. No data were available to the Working Group on the biodegradation of 1-amino-2,4-dibromoanthraquinone, but its potential for bioconcentration in aquatic environments is high, and its estimated bioconcentration factor in fish is 380 (reviewed by HSDB, 2010).

1.4 Regulations and guidelines

No data were available to the Working Group.

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

Carcinogenicity studies of oral administration of 1-amino-2,4-dibromoanthraquinone to mice and rats in the diet have been conducted (NTP, 1996), the results of which are summarized in Table 3.1 and Table 3.2.

3.1 Oral administration

3.1.1 Mouse

See Table 3.1

Groups of 60 male and 60 female B6C3F$_1$ mice were fed 0, 10 000 or 20 000 ppm 1-amino-2,4-dibromoanthraquinone in the diet for 104 weeks. The average daily consumption was approximately 1690 or 3470 and 1950 or 4350 mg/kg bw 1-amino-2,4-dibromoanthraquinone for males and females, respectively. Ten animals from each group were evaluated histopathologically at 15 months. The incidence of hepatocellular adenoma, and adenoma or carcinoma (combined) was increased in the high-dose groups of males and females at the 15-month interim evaluation. At 2 years, statistically significant increases in the incidence of hepatocellular adenoma and carcinoma in males and females and in that of hepatoblastoma in high-dose males were observed. Squamous-cell papilloma of the forestomach occurred in 10 000-ppm females and 20 000-ppm males and females at the 15-month interim evaluation, and the incidence of squamous-cell papilloma and carcinoma was statistically significantly increased in all treated groups at 2 years. Alveolar/bronchiolar adenomas developed in all treated groups at 15 months, and the incidence of alveolar/bronchiolar adenoma was statistically significantly increased in all exposed groups at 2 years (NTP, 1996).

3.1.2 Rat

(a) Continuous exposure

See Table 3.1

Groups of 70 male and 70 female F344/N rats were fed 0, 5000 or 10 000 ppm 1-amino-2,4-dibromoanthraquinone in the diet for 103 weeks. Further groups of 50 males and 50 females were fed 2000 ppm 1-amino-2,4-dibromoanthraquinone for 104 weeks. These dietary concentrations were approximately equal to daily doses of 90, 240 or 490 and 110, 285 or 600 mg/kg body weight (bw) 1-amino-2,4-dibromoanthraquinone for males and females in the 2000-, 5000- and 10 000-groups, respectively. Ten animals from each group were evaluated histopathologically at 9 months. Additional groups of 10 animals from the 0- and 10 000-ppm groups were also evaluated histopathologically at 15 months. At the 15-month interim evaluation, hepatocellular adenoma or carcinoma (combined) occurred in 10/10 males and 9/10 females in the 10 000-ppm group. By the end of the 2-year study, the incidence of hepatocellular adenoma or hepatocellular carcinoma, or hepatocellular cholangiocarcinoma was increased in males and females in the 5000- and 10 000-ppm groups. In the 2000 ppm groups, that of hepatocellular adenoma or carcinoma (combined) was also increased in males and females. Adenomatous polyps (adenoma) of the large intestine (rectum) were found in 6/10 males and 2/10 females in the 10 000 ppm groups at the 15-month interim evaluation, and the incidence of adenomatous polyp (adenoma) or carcinoma of the large intestine (colon and rectum) was significantly increased in all treated groups after 2 years. In the kidney, the incidence of renal tubule adenoma or carcinoma (combined) was significantly increased in all treated groups after 2 years. The incidence of transitional-cell papilloma and carcinoma of the urinary bladder was increased at 2 years in males in the 10 000-ppm group, and in females in the 5000-ppm and 10 000-ppm groups (NTP, 1996).

Table 3.1 Carcinogenicity studies of oral administration of 1-amino-2,4-dibromoanthraquinone in the diet to rats and mice: effects after the 15-month interim evaluation and 2 years

Species, strain (sex) Duration	Dosing regimen, Animals/group at start	Incidence of tumours at the end of 2-year exposure (103–104 weeks)	Significance (logistic regression test)	Tumours at interim evaluations (significance by the Fisher exact test)	Comments
Mouse, $B6C3F_1$ (M) 2 yr	0, 10 000, or 20 000 ppm [approximately 0, 1690 or 3470 mg/kg bw/d] 60 animals/group	Liver (hepatocellular adenoma): 10/50, 38/51, 39/50	$P < 0.001$ (10 000 ppm) $P < 0.001$ (20 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0, 10 000, 20 000 ppm): Liver (hepatocellular adenoma): 0/10, 2/9, 4/10[b]	
		Liver (hepatocellular carcinoma): 9/50, 18/51, 21/50	$P = 0.017$ (10 000 ppm) $P = 0.003$ (20 000 ppm) $P = 0.002$ (trend)		
		Liver (hepatoblastoma): 0/50, 3/51, 5/50	$P < 0.05$ (20 000 ppm) (Fisher exact test)		
		Liver (hepatocellular adenoma or carcinoma): 18/50, 43/51, 42/50	$P < 0.001$ (10 000 ppm) $P < 0.001$ (20 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0, 10 000, 20 000 ppm): Liver (hepatocellular adenoma or carcinoma): 0/10, 3/9, 4/10[b]	Historical incidence for 2-yr feed studies with untreated control groups (mean ± SD): 531/1466 (36.2 ± 14.1%); range, 10–68%
		Forestomach (squamous-cell papilloma): 0/50, 13/51, 16/50	$P < 0.001$ (10 000 ppm) $P < 0.001$ (20 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0, 10 000, 20 000 ppm): Forestomach (squamous-cell papilloma): 0/10, 0/10, 5/10[b]	
		Forestomach (squamous-cell carcinoma): 0/50 12/51, 13/50	$P < 0.001$ (10 000 ppm) $P < 0.001$ (20 000 ppm) $P < 0.001$ (trend)		
		Forestomach (squamous-cell papilloma or carcinoma): 0/50, 19/51, 27/50	$P < 0.001$ (10 000 ppm) $P < 0.001$ (20 000 ppm) $P < 0.001$ (trend)		Historical incidence for 2-yr feed studies with untreated control groups (mean ± SD): 22/1474 (1.5 ± 2.0%); range, 0–6%
		Lung (alveolar/bronchiolar adenoma): 7/50, 26/51, 24/50	$P < 0.001$ (10 000 ppm) $P < 0.001$ (20 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0, 10 000, 20 000 ppm): Lung (alveolar/bronchiolar adenoma): 0/10, 3/9, 5/10[b]	

Table 3.1 (continued)

Species, strain (sex) Duration	Dosing regimen, Animals/group at start	Incidence of tumours at the end of 2-year exposure (103–104 weeks)	Significance (logistic regression test)	Tumours at interim evaluations (significance by the Fisher exact test)	Comments
Mouse, $B6C3F_1$ (M) (contd)		Lung (alveolar/bronchiolar carcinoma): 3/50 (6%), 4/51 (8%), 1/50 (2%)			
		Lung (alveolar/bronchiolar adenoma or carcinoma): 10/50, 28/51, 25/50	$P < 0.001$ (10 000 ppm) $P = 0.002$ (20 000 ppm) $P < 0.001$ (trend)		Historical incidence for 2-yr feed studies with untreated control groups (mean ± SD): 265/1469 (18.0 ± 7.6%); range, 4–32%
Mouse, B6C3F1 (F) 2 yr	0, 10 000 or 20 000 ppm [approximately 0, 1950 or 4350 mg/kg bw/d] 60 animals/group	Liver (hepatocellular adenoma): 6/50, 45/50, 49/50	$P < 0.001$ (10 000 ppm) $P < 0.001$ (20 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0, 10 000, 20 000 ppm): Liver (hepatocellular adenoma): 0/10, 2/10, 7/10[a]	
		Liver (hepatocellular carcinoma): 0/50, 23/50, 27/50	$P < 0.001$ (10 000 ppm) $P < 0.001$ (20 000 ppm) $P < 0.001$ (trend)		
		Liver (hepatocellular adenoma or carcinoma): 6/50, 46/50, 50/50	$P < 0.001$ (10 000 ppm) $P < 0.001$ (20 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0, 10 000, 20 000 ppm): Liver (hepatocellular adenoma or carcinoma): 0/10, 2/10, 8/10[a]	Historical incidence for 2-yr feed studies with untreated control groups (mean ± SD): 247/1462 (16.9 ± 10.7%); range, 3–42%
		Forestomach (squamous-cell papilloma): 2/50, 16/50, 27/50	$P < 0.001$ (10 000 ppm) $P < 0.001$ (20 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0, 10 000, 20 000 ppm): Forestomach (squamous-cell papilloma): 0/10, 4/10[b], 2/10	
		Forestomach (squamous-cell carcinoma): 0/50, 12/50, 11/50	$P < 0.001$ (10 000 ppm) $P < 0.001$ (20 000 ppm) $P = 0.002$ (trend)		
		Forestomach (squamous-cell papilloma or carcinoma): 2/50, 25/50, 34/50	$P < 0.001$ (10 000 ppm) $P < 0.001$ (20 000 ppm) $P < 0.001$ (trend)		Historical incidence for 2-yr feed studies with untreated control groups (mean ± SD): 33/1470 (2.2 ± 3.1%); range, 0–14%

Table 3.1 (continued)

Species, strain (sex) Duration	Dosing regimen, Animals/group at start	Incidence of tumours at the end of 2-year exposure (103–104 weeks)	Significance (logistic regression test)	Tumours at interim evaluations (significance by the Fisher exact test)	Comments
Mouse, B6C3F$_1$ (F) (contd)		Lung (alveolar/bronchiolar adenoma): 4/50, 17/50, 13/49	$P < 0.001$ (10 000 ppm) $P < 0.001$ (20 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0, 10 000, 20 000 ppm): Lung (alveolar/bronchiolar adenoma): 0/10, 3/10, 2/10	
		Lung (alveolar/bronchiolar adenoma or carcinoma): 4/50, 17/50, 15/49	$P = 0.005$ (10 000 ppm) $P = 0.001$ (20 000 ppm) $P = 0.006$ (trend)		Historical incidence for 2-yr feed studies with untreated control groups (mean ± SD): 110/1469 (7.5 ± 5.0%); range, 2–26%
		Large intestine, colon (adenomatous polyp (adenoma)): 0/50, 1/40, 1/59, 3/50	NS (2000 ppm) NS (5000 ppm) $P = 0.081$ (10 000 ppm) $P = 0.027$ (trend)	Groups at 15-mo evaluation (0 or 10 000 ppm): Large intestine, rectum (adenomatous polyp (adenoma)): 0/10, 6/10[a]	
Rat, F344/N (M) 2 yr	0, 2000, 5000 or 10 000 ppm [approximately 0, 90, 240 or 490 mg/kg bw/d] 50–70 animals/group	Liver (hepatocellular adenoma): 1/50, 2/40, 40/59, 34/50	$P < 0.001$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0 or 10 000 ppm): Liver (hepatocellular adenoma): 0/10, 2/10	
		Liver (hepatocellular carcinoma): 1/50, 12/40, 55/59, 46/50	$P < 0.001$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0 or 10 000 ppm): Liver (hepatocellular carcinoma): 0/10, 7/10[a]	
		Liver (hepatocholangiocarcinoma): 0/5, 0/40, 6/59, 2/50	$P < 0.05$ (5000 ppm)		
		Liver (hepatocellular adenoma or carcinoma): 2/50, 25/40, 57/59, 47/50	$P < 0.001$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0 or 10 000 ppm): Liver (hepatocellular adenoma or carcinoma): 0/10, 10/10[a]	Historical incidence for 2-yr feed studies with untreated control groups (mean ± SD): 450/1350 (3.3 ± 3.6%); range, 0–10%

Table 3.1 (continued)

Species, strain (sex) Duration	Dosing regimen, Animals/group at start	Incidence of tumours at the end of 2-year exposure (103–104 weeks)	Significance (logistic regression test)	Tumours at interim evaluations (significance by the Fisher exact test)	Comments
Rat, F344/N (M) (contd)		Large intestine, colon (adenomatous polyp (adenoma)): 0/50, 1/40, 1/59, 3/50	NS (2000 ppm) NS (5000 ppm) $P = 0.081$ (10 000 ppm) $P = 0.027$ (trend)	Groups at 15-mo evaluation (0 or 10 000 ppm): Large intestine, rectum (adenomatous polyp (adenoma)): 0/10, 6/10[a]	
		Large intestine, colon (carcinoma): 0/50, 0/40, 1/59, 4/50	NS (2000 ppm) NS (5000 ppm) $P = 0.046$ (10 000 ppm) $P = 0.003$ (trend)		Historical incidence for 2-yr feed studies with untreated control groups (mean ± SD): 1/1353 (0.1 ± 0.4%); range, 0–2% (includes all carcinomas of the large intestine)
		Large intestine, rectum (adenomatous polyp (adenoma)): 0/50, 13/40, 51/59, 40/50	$P < 0.001$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)		
		Large intestine, rectum (carcinoma): 0/50, 1/40, 10/59, 15/50	$P = 0.48$ (2000 ppm) $P < 0.003$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)		
		Large intestine, all sites (adenomatous polyp (adenoma)): 0/50, 13/40, 51/59, 40/50	$P < 0.001$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)		
		Large intestine, all sites (carcinoma): 0/50, 1/40, 11/59, 17/50	$P < 0.444$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)		
		Kidney (renal tubule adenoma): 2/50, 10/40, 11/59, 14/50	$P < 0.007$ (2000 ppm) $P < 0.014$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0 or 10 000 ppm): Kidney (renal tumour adenoma): 0/10, 2/10	
		Kidney (renal tubule carcinoma): 0/50, 0/40, 2/59, 1/50	NS		

Table 3.1 (continued)

Species, strain (sex) Duration	Dosing regimen, Animals/group at start	Incidence of tumours at the end of 2-year exposure (103–104 weeks)	Significance (logistic regression test)	Tumours at interim evaluations (significance by the Fisher exact test)	Comments
Rat, F344/N (M) (contd)		Kidney (renal tubule adenoma or carcinoma): 2/50, 10/40, 13/59, 15/50	$P = 0.007$ (2000 ppm) $P < 0.005$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)		Historical incidence for 2-yr feed studies with untreated control groups (mean ± SD): 15/1350 (1.1 ± 1.7%); range, 0–6%
		Urinary bladder (transitional-cell papilloma): 0/50, 1/38, 2/58, 8/50	$P = 0.459$ (2000 ppm) $P = 0.192$ (5000 ppm) $P < 0.004$ (10 000 ppm) $P < 0.001$ (trend)		
		Urinary bladder (transitional-cell carcinoma): 0/50, 0/38, 1/58, 4/50	NS (2000 ppm) $P = 0.491$ (5000 ppm) $P < 0.022$ (10 000 ppm) $P < 0.001$ (trend)		
		Urinary bladder (transitional cell papilloma or carcinoma): 0/50, 1/38, 3/58, 12/50	$P = 0.459$ (2000 ppm) $P < 0.096$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)		Historical incidence for 2-yr feed studies with untreated control groups (mean ± SD): 3/1329 (0.2 ± 0.6%); range, 0–2%
Rat, F344/N (F) 2 yr	0, 2000, 5000 or 10 000 ppm [approximately 0, 110, 285 or 600 mg/kg bw/d] 50–70 animals/group	Liver (hepatocellular adenoma): 0/50, 28/40, 47/60, 29/48	$P < 0.001$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0 or 10 000 ppm): Liver (hepatocellular adenoma): 0/10, 5/10[b]	
		Liver (hepatocellular carcinoma): 0/50, 12/40, 57/60, 45/48	$P < 0.001$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0 or 10 000 ppm): Liver (hepatocellular carcinoma): 0/10, 6/10[a]	
		Liver (hepatocholangiocarcinoma): 0/50, 0/40, 11/60[a], 13/48[a]	[Only Fisher exact test given for this tumour in the report]		
		Liver (hepatocellular adenoma or carcinoma): 0/50, 33/40, 59/60, 45/48	$P < 0.001$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0 or 10 000 ppm): Liver (hepatocellular adenoma or carcinoma): 0/10, 9/10[a]	Historical incidence for 2-yr feed studies with untreated control groups (mean ± SD): 9/1351 (0.7 ± 1.5%); range, 0–6%

Table 3.1 (continued)

Species, strain (sex) Duration	Dosing regimen, Animals/group at start	Incidence of tumours at the end of 2-year exposure (103–104 weeks)	Significance (logistic regression test)	Tumours at interim evaluations (significance by the Fisher exact test)	Comments
Rat, F344/N (F) (contd)		Large intestine, colon (adenomatous polyp [adenoma]): 0/50, 1/40, 2/60, 2/49 (carcinoma): 0/50, 1/40, 2/60, 1/49	NS NS		
		Large intestine, rectum (adenomatous polyp [adenoma]): 0/50, 27/40, 53/60, 43/49	$P < 0.001$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0 or 10 000 ppm): Large intestine, rectum (adenomatous polyp (adenoma)): 0/10, 2/10	
		Large intestine, rectum (carcinoma): 0/50, 1/40, 19/60, 7/49	$P = 0.466$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)		Historical incidence for 2-yr feed studies with untreated control groups: 0/1351 (includes all carcinomas of the large intestine)
		Large intestine, all sites (adenomatous polyp [adenoma]): 0/50, 28/40, 53/60, 43/49	$P < 0.001$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)		
		Large intestine, all sites (carcinoma): 0/50, 2/40, 21/60, 8/49	$P = 0.201$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)		
		Kidney (renal tubule adenoma): 0/50, 3/40, 16/60, 16/48	$P = 0.049$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)		
		Kidney (renal tubule carcinoma): 0/50, 0/40, 0/60, 2/48	NS		
		Kidney (renal tubule adenoma or carcinoma): 0/50, 3/40, 16/60, 16/48	$P = 0.049$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)		Historical incidence for 2-yr feed studies with untreated control groups (mean ± SD): 1/1348 (0.1 ± 0.4%); range, 0–2%

Table 3.1 (continued)

Species, strain (sex) Duration	Dosing regimen, Animals/group at start	Incidence of tumours at the end of 2-year exposure (103–104 weeks)	Significance (logistic regression test)	Tumours at interim evaluations (significance by the Fisher exact test)	Comments
Rat, F344/N (F) (contd)		Urinary bladder (transitional-cell papilloma): 0/50, 2/40, 7/60, 9/46	$P = 0.201$ (2000 ppm) $P = 0.012$ (5000 ppm) $P = 0.003$ (10 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0 or 10 000 ppm): Urinary bladder (transitional-cell papilloma): 0/10, 1/10	
		Urinary bladder (transitional-cell carcinoma): 0/50, 0/40, 8/60, 16/46	NS (2000 ppm) $P = 0.008$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0 or 10 000 ppm): Urinary bladder (transitional-cell carcinoma): 0/10, 2/10	
		Urinary bladder (transitional-cell papilloma or carcinoma, overall rate): 0/50, 2/40, 17/60, 26/46	$P = 0.201$ (2000 ppm) $P < 0.001$ (5000 ppm) $P < 0.001$ (10 000 ppm) $P < 0.001$ (trend)	Groups at 15-mo evaluation (0 or 10 000 ppm): Urinary bladder (squamous-cell carcinoma): 0/10, 2/10	Historical incidence for 2-yr feed studies with untreated control groups (mean ± SD): 3/1334 (0.2 ± 0.6%); range, 0–2%

[a] $P < 0.01$

[b] $P < 0.05$

bw, body weight; d, day or days; F, female; M, male; mo, month or months; NS, not significant; SD, standard deviation; yr, year or years

From NTP (1996)

Table 3.2 Carcinogenicity studies of oral administration of 1-amino-2,4-dibromoanthraquinone in the diet to rats: 9-month stop-exposure group and evaluations at 9 or 15 months

Species, strain (sex) Duration	Dosing regimen, Animals/group at start	Incidence of tumours (significance by the Fisher exact test)	Comments
Group 1: Rat, F344/N (M) 9 mo	0, 20 000 ppm 10 animals/group	Liver (hepatocellular adenoma or carcinoma): 0/10, 2/10	
Group 2: Rat, F344/N (M) 9-mo stop exposure then no treatment until 15 mo	0, 20 000 ppm 10 animals/group	Liver (hepatocellular adenoma or carcinoma): 0/10, 9/10[a] Large intestine (adenomatous polyp [adenoma]): 0/10, 3/10 Kidney (renal tubule adenoma): 0/10, 3/10	
Group 3: Rat, F344/N (M) 15 mo	0, 20 000 ppm 20 animals/group	Liver (hepatocellular adenoma or carcinoma): 0/10, 20/20[a] Large intestine (adenomatous polyp [adenoma]): 0/10, 7/20[b] Urinary bladder (transitional-cell papilloma): 0/10, 3/19; (transitional-cell carcinoma): 0/10, 1/19; (squamous-cell carcinoma): 0/10, 1/19 Kidney (renal tubule adenoma): 0/10, 1/20	Controls were the same as those for Group 1
Group 1: Rat, F344/N (F) 9 mo	0, 20 000 ppm 10 animals/group	Liver (hepatocellular adenoma or carcinoma): 0/10, 2/10	
Group 2: Rat, F344/N (F) 9-mo stop exposure then no treatment until 15 mo	0, 20 000 ppm 10 animals/group	Liver (hepatocellular adenoma or carcinoma): 0/10 8/10[a] Large intestine (adenomatous polyp [adenoma]): 0/10, 5/10[b] Kidney (renal tubule adenoma): 0/10, 3/10	
Group 3: Rat, F344/N (F) 15 mo	0, 20 000 ppm 20 animals/group	Liver (hepatocellular adenoma or carcinoma): 0/10, 16/18[a] Large intestine (adenomatous polyp [adenoma]): 0/10, 3/17 Kidney (renal tubule adenoma): 0/10, 2/17 Urinary bladder (transitional-cell papilloma): 0/10, 1/18; (transitional-cell carcinoma): 0/10, 1/18; (squamous-cell papilloma): 0/10, 1/18; (squamous-cell carcinoma): 0/10, 4/18	Controls were the same as those for Group 1

[a] $P < 0.01$

[b] $P < 0.05$

F, female; M, male; mo, month or months

From NTP (1996)

(b) Stop exposure

See Table 3.2

Groups of 40 male and 40 female F344/N rats were fed 20 000 ppm 1-amino-2,4-dibromoanthraquinone in the diet for 9 or 15 months. After 9 months of exposure, 10 males and 10 females were evaluated histopathologically (9-month interim evaluation groups). At the same time, 10 males and 10 females were fed control diet until the end of the 15-month evaluation (9-month stop exposure), and 20 males and 20 females continued to receive 20 000 ppm 1-amino-2,4-dibromoanthraquinone for the 15-month period (15-month exposure groups). The approximate daily consumption of 1-amino-2,4-dibromoanthraquinone was 1335 and 1790 mg/kg bw for males and females in the 9-month stop exposure groups and 1115 and 1435 mg/kg bw for males and females in the 15-month exposure groups, respectively. After 9 months of exposure, hepatocellular adenoma or carcinoma (combined) occurred in treated males and females. In males, rare neoplasms at other sites included one adenomatous polyp (adenoma) in the large intestine and one transitional-cell papilloma in the urinary bladder. In the 9-month stop exposure and 15-month exposure groups, hepatocellular adenoma or carcinoma (combined) occurred in most treated males and females. Adenomatous polyp (adenoma) of the rectum occurred in 3/10 males and 5/10 females in the 9-month stop exposure group, and in 7/20 males and 3/17 females in the 15-month exposure group. Renal tubule adenoma occurred in 3/10 males and 3/10 females in the 9-month stop exposure group and 1/20 males and 2/17 females in the 15-month exposure group. Transitional-cell papilloma (3/19 males, 1/18 females) or carcinoma (1/19 males, 1/18 females) of the urinary bladder developed in the 15-month exposure group. In addition, squamous-cell carcinoma of the urinary bladder occurred in 1/10 males and 4/10 females in the 15-month exposure group (NTP, 1996).

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

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

4.1.1 Humans

Human exposure to 1-amino-2,4-dibromoanthraquinone occurs primarily through dermal contact. Specific data on possible oral exposure to 1-amino-2,4-dibromoanthraquinone in humans were not available to the Working Group. Inhalation exposure to 1-amino-2,4-dibromoanthraquinone is considered to be highly unlikely because of its very low vapour pressure, but dye-contaminated dust particles could be inhaled (NTP, 1996).

4.1.2 Experimental systems

In rats, a single oral dose of 2, 23, 118, 814 or 1473 mg/kg bw [^{14}C]-labelled 1-amino-2,4-dibromoanthraquinone was readily absorbed from the gastrointestinal tract and distributed to most soft tissues (NTP, 1996). The percentage of the oral dose that was absorbed was inversely proportional to the dose level administered: 90% of the lowest dose (2 mg/kg) but only 2% of the high dose (814 mg/kg) was absorbed (NTP, 1996). A single intravenous dose of [^{14}C]-labelled 1-amino-2,4-dibromoanthraquinone administered to rats was rapidly and widely distributed to all tissues, and the highest concentrations of radioactivity were found in the lungs, kidneys, small intestine, liver, adipose tissue and adrenal glands, but no quantitative data on tissue distribution of radioactivity were reported (NTP, 1996). The

majority of 1-amino-2,4-dibromoanthraquinone was metabolized within 2 h after administration because only a small amount (less than 3%) of ^{14}C attributed to the parent compound was recovered from either the blood or urine. Adipose tissue contained primarily unmetabolized 1-amino-2,4-dibromoanthraquinone after 24 h, but other tissues, such as the liver, muscle and skin, contained mostly 1-amino-2,4-dibromoanthraquinone metabolites. However, 1-amino-2,4-dibromoanthraquinone metabolites, excreted primarily in the faeces and urine, have not been identified or characterized (NTP, 1996).

4.2 Genetic and related effects

4.2.1 Humans

No data were available to the Working Group.

4.2.2 Experimental systems

Limited data are available on the genetic and related effects of 1-amino-2,4-dibromoanthraquinone in experimental systems, because their evaluation has been hindered by the insolubility of this compound in water (NTP, 2005). No data on the mammalian genotoxicity of 1-amino-2,4-dibromoanthraquinone *in vivo* were available to the Working Group.

(a) Salmonella *reverse mutation assay*

1-Amino-2,4-dibromoanthraquinone (100–10 000 µg/plate) was tested for its induction of gene mutations in several strains of *S. typhimurium* using a preincubation protocol in the presence and absence of metabolic activation (NTP, 1996). *Salmonella* strains included those that revert by base-pair substitutions (TA100 and TA1535) and those that revert by frameshift mutations (TA98 and TA1537). 1-Amino-2,4-dibromoanthraquinone was mutagenic in the absence of microsomal metabolic activation in strains TA98 and TA1537, and, in the presence of metabolic activation, reverse mutation was not induced in strain TA98, whereas strain TA1537 yielded an equivocal response (Haworth *et al.*, 1983; NTP, 1996). It was weakly mutagenic in strain TA100 (in the presence and absence of metabolic activation) and non-mutagenic in strain TA1535 (in the presence and absence of metabolic activation). The variability of the test results may be due to the tendency of 1-amino-2,4-dibromoanthraquinone to precipitate at concentrations of 100 µg/plate and above (NTP, 1996).

(b) Chromosomal aberrations and sister chromatid exchange

1-Amino-2,4-dibromoanthraquinone was tested in cultured Chinese hamster ovary cells for its induction of chromosomal aberrations in the presence and absence of metabolic activation (Loveday *et al.*, 1990; NTP, 1996). Two separate trials conducted without metabolic activation (Loveday *et al.*, 1990) yielded equivocal results. In one trial, exposure to 1-amino-2,4-dibromoanthraquinone at 3.02 or 10.10 µg/mL significantly increased the percentage of chromosomal aberrations ($P < 0.05$), but, in the second trial, there was no significant increase. However, in the presence of metabolic activation, 1-amino-2,4-dibromoanthraquinone failed to increase the incidence of chromosomal aberrations (Loveday *et al.*, 1990; NTP, 1996).

1-Amino-2,4-dibromoanthraquinone induced sister chromatid exchange in Chinese hamster ovary cells in a dose-dependent manner in the presence or absence of metabolic activation. In the absence of metabolic activation, it induced a ≥ 20% increase in sister chromatid exchange compared with controls at a concentration of 10 µg/mL, but not at lower concentrations (Loveday *et al.* 1990; NTP, 1996).

(c) Mouse lymphoma L5178Y/Tk$^{+/-}$ cells

1-Amino-2,4-dibromoanthraquinone did not induce mutations at the thymidine kinase (*Tk*$^{+/-}$) locus in mouse lymphoma cells in the absence or presence of metabolic activation at a concentration of 25 μg/mL. Micronucleus formation was not assessed because of the limited solubility of 1-amino-2,4-dibromoanthraquinone in culture medium (Harrington-Brock *et al.*, 1991).

(d) Toxicity in Daphnia magna

In the *Daphnia magna* immobilization assay, 1-amino-2,4-dibromoanthraquinone was shown to be highly toxic under visible light and simulated solar radiation (Wang *et al.*, 2009). Increased levels of reactive oxygen species *in vivo* were detected by fluorescence of 2′,7′-dichlorofluorescein in the presence of both simulated solar radiation and 1-amino-2,4-dibromoanthraquinone, suggesting that toxicity to *D. magna* is due to the induction of oxidative stress and subsequent damage to biological macromolecules such as proteins, DNA, carbohydrates and polyunsaturated fatty acids. However, the specific nature of the macromolecular alterations has not been reported. The photo-induced oxidative damage to *D. magna* was reduced by antioxidants, including vitamin C, vitamin E and β-carotene (Wang *et al.*, 2009). These observations demonstrated that photosensitization reactions that resulted in the generation of superoxide anion and singlet oxygen species contributed to the photo-induced toxicity of 1-amino-2,4-dibromoanthraquinone and imply an ecological risk of dyes and their intermediates under natural sunlight (Wang *et al.*, 2009).

(e) Photo-excitation-related DNA damage in vitro

Some anthraquinones undergo photomodification or photosensitization reactions in aqueous or organic solutions (Brinson *et al.*, 2005). Anthraquinones can serve as an electron acceptor chromophore to initiate DNA oxidation on photoexcitation with ultraviolet light (Abou-Elkhair *et al.*, 2009). Photoexcitation of anthraquinone dyes in association with DNA *in vitro* has been shown to cause DNA damage, mainly at guanine residues (Abou-Elkhair *et al.*, 2009). It is also known that thymine residues form oxidation products in preference to adenine, suggesting a significantly higher reactivity of the thymine radical cation compared with that of the adenine radial cation (Abou-Elkhair *et al.*, 2009). Specific data on guanine or adenine oxidation in DNA with 1-amino-2,4-dibromoanthraquinone were not available to the Working Group.

(f) Alterations in oncogenes and suppressor genes in tumours

Hayashi *et al.* (2001) examined 1-amino-2,4-dibromoanthraquinone-induced tumours in B6C3F$_1$ mice for mutations in the H-*ras* or K-*ras* genes. The tumours examined included squamous-cell papillomas and carcinomas of the forestomach, and alveolar/bronchiolar adenomas and carcinomas of the lung. Point mutations in the *ras* proto-oncogene were analysed in DNA isolated from paraffin-embedded mouse forestomach and lung tumours induced by diets containing 10 000 or 20 000 ppm 1-amino-2,4-dibromoanthraquinone for 2 years. The predominant types of mutation observed at a higher frequency were A to T transversions and A to G transitions in codon 61 of K-*ras* (lung tumours) or H-*ras* (forestomach tumours), suggesting that 1-amino-2,4-dibromoanthraquinone or its metabolites target adenine bases in the *ras* proto-oncogene (Hayashi *et al.*, 2001). No A to T transversions at the second base of CAA (codon 61) were detected in tumours from control animals. These mutations may play a role in multi-organ carcinogenesis.

4.3 Other mechanistic considerations

Despite the widespread use and potential for significant human exposure, available data on the biological effects of 1-amino-2,4-dibromoanthraquinone are limited.

4.3.1 Liver toxicity

Fleischman *et al.* (1986) studied toxicity in male and female F344/N rats and B6C3F$_1$ mice fed a diet containing 0, 0.25, 0.50, 1.00, 2.50 and 5.00% 1-amino-2,4-dibromoanthraquinone for 13 weeks. Lethargy and emaciation were noted in both sexes of rats at the 2.50% and 5.00% dose levels. The liver was the main target organ in both species, and the liver/bw ratio increased at all doses. 1-Amino-2,4-dibromoanthraquinone-treated rats developed chronic toxic hepatitis with hepatocytomegaly, centrilobular vacuolar degeneration and necrosis. Serum markers of liver injury were elevated in male and female rats at doses as low as 0.5% (w/w) and were consistently elevated at doses of 2.5% and 5.0%, and regenerative nodules were observed in the liver of rats fed 5.00%. The kidneys exhibited hyaline droplet degeneration of the proximal tubules. Uterine atrophy was noted in female rats at dose levels of 1.00% and higher. In this 13-week study, 1-amino-2,4-dibromoanthraquinone was considered to be markedly toxic in rats and minimally toxic in mice.

4.3.2 Altered hepatocellular foci

Lilja *et al.* (1985) fed female Fischer rats 1% or 2% 1-amino-2,4-dibromoanthraquinone in the diet for up to 15 months and noted an increase in γ-glutamyltransferase-positive hepatocellular foci at 9 and 15 months in the 2% group, and at 15 months in the 1% group. [The Working Group noted that γ-glutamyltransferase is a marker for preneoplastic foci induced by genotoxic chemicals, but is generally not expressed in tissues treated with chemicals that induce tumours by a receptor-mediated mechanism.]

1-Amino-2,4-dibromoanthraquinone was tested in a neonatal rat liver focus model for its potential both as an initiator and promoter (Maronpot *et al.*, 1989). In the test for initiation potential, newborn (< 24 hour old) rats were injected intraperitoneally with 0.07 mg/g bw 1-amino-2,4-dibromoanthraquinone and, at 21 days, were weaned and fed a diet containing phenobarbital (500 ppm) as a promoting agent for either 75 or 300 days. Based on altered hepatocyte foci and liver tumour incidence, no initiating activity of 1-amino-2,4-dibromoanthraquinone was found. To test for liver tumour promoting activity, neonatal rats were initiated with a subcarcinogenic dose of the initiator *N*-nitrosodiethylamine (4 µg/g bw) and then fed 1-amino-2,4-dibromoanthraquinone at concentrations of 5000 and 10 000 ppm in the diet for 75–300 days, at which time they were killed. In low-dose females, 1-amino-2,4-dibromoanthraquinone caused a significant ($P < 0.05$) reduction in the number of altered hepatocellular foci at 75 days but a significant ($P < 0.01$) increase at 300 days. In low-dose and high-dose males, no significant changes in the number of altered foci were noted at 75 and 300 days. However, in male rats, the mean focus volume was significantly increased in the low-dose group at 75 days and in the high-dose group at 300 days. No significant difference in the incidence of grossly visible liver tumours was noted. The authors attributed the equivocal trends to the unpalatability of the feed containing 1-amino-2,4-dibromoanthraquinone.

5. Summary of Data Reported

5.1 Exposure data

1-Amino-2,4-dibromoanthraquinone is widely used as an intermediate for the manufacture of dyes for fibres and textiles. Workers may be exposed by inhalation of dust or by dermal contact. 1-Amino-2,4-dibromoanthraquinone may be released into the environment via wastewater streams during its production and use.

5.2 Human carcinogenicity data

No human cancer studies were identified that evaluated exposure to 1-amino-2,4-dibromoanthraquinone.

5.3 Animal carcinogenicity data

In one feeding study, administration of 1-amino-2,4-dibromoanthraquinone for 2 years caused an increased incidence of lung adenoma, and benign and malignant neoplasms of the liver (including hepatoblastomas) and of the forestomach in male and female mice. In male and female rats, it caused an increased incidence of benign and malignant neoplasms of the liver (including cholangiocarcinomas), large intestine, kidney and urinary bladder, In the same study, groups of rats were killed at 15 months (including rats exposed for 9 months followed by 6 months without treatment or rats exposed continuously for 15 months). At this time-point, tumours of the large intestine, kidney and urinary bladder and benign and malignant liver tumours were observed in treated male and female rats. There was consistency in the tumour sites observed between the 15-month and 2-year experiments.

Tumours of the kidney, urinary bladder, and large intestine in male and female rats, and tumours of the forestomach and hepatoblastomas in experimental animals are rare spontaneous neoplasms.

5.4 Other relevant data

Although 1-amino-2,4-dibromoanthraquinone is metabolically degraded *in vivo* relatively rapidly, no data on the structure of its metabolites were available.

Few studies on the genetic and biological effects of 1-amino-2,4-dibromoanthraquinone have been published, partly due to its poor insolubility in water. 1-Amino-2,4-dibromoanthraquinone was mutagenic in the absence of microsomal metabolic activation in bacteria, but did not induce mutations in rodent cells when tested at lower concentrations. It induced chromosomal aberrations and sister chromatid exchange in mammalian cells *in vitro* but the results were inconsistent. The compound was cytotoxic to the liver *in vivo* in a 13-week feeding study in rats at doses comparable with those tested in the 2-year carcinogenesis bioassay. Analyses of forestomach and lung tumours that developed in 1-amino-2,4-dibromoanthraquinone-treated mice revealed point mutations in the *ras* proto-oncogene. The predominant types of mutation were A to T transversions and A to G transitions, suggesting that 1-amino-2,4-dibromoanthraquinone or its metabolites target adenine bases in the *ras* proto-oncogene.

Based on the available data, there is moderate evidence of a genotoxic mechanism in the carcinogenicity of 1-amino-2,4-dibromoanthraquinone in rats and mice. 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 1-amino-2,4-dibromoanthraquinone.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of 1-amino-2,4-dibromoanthraquinone.

6.3 Overall evaluation

1-Amino-2,4-dibromoanthraquinone is *possibly carcinogenic to humans (Group 2B).*

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