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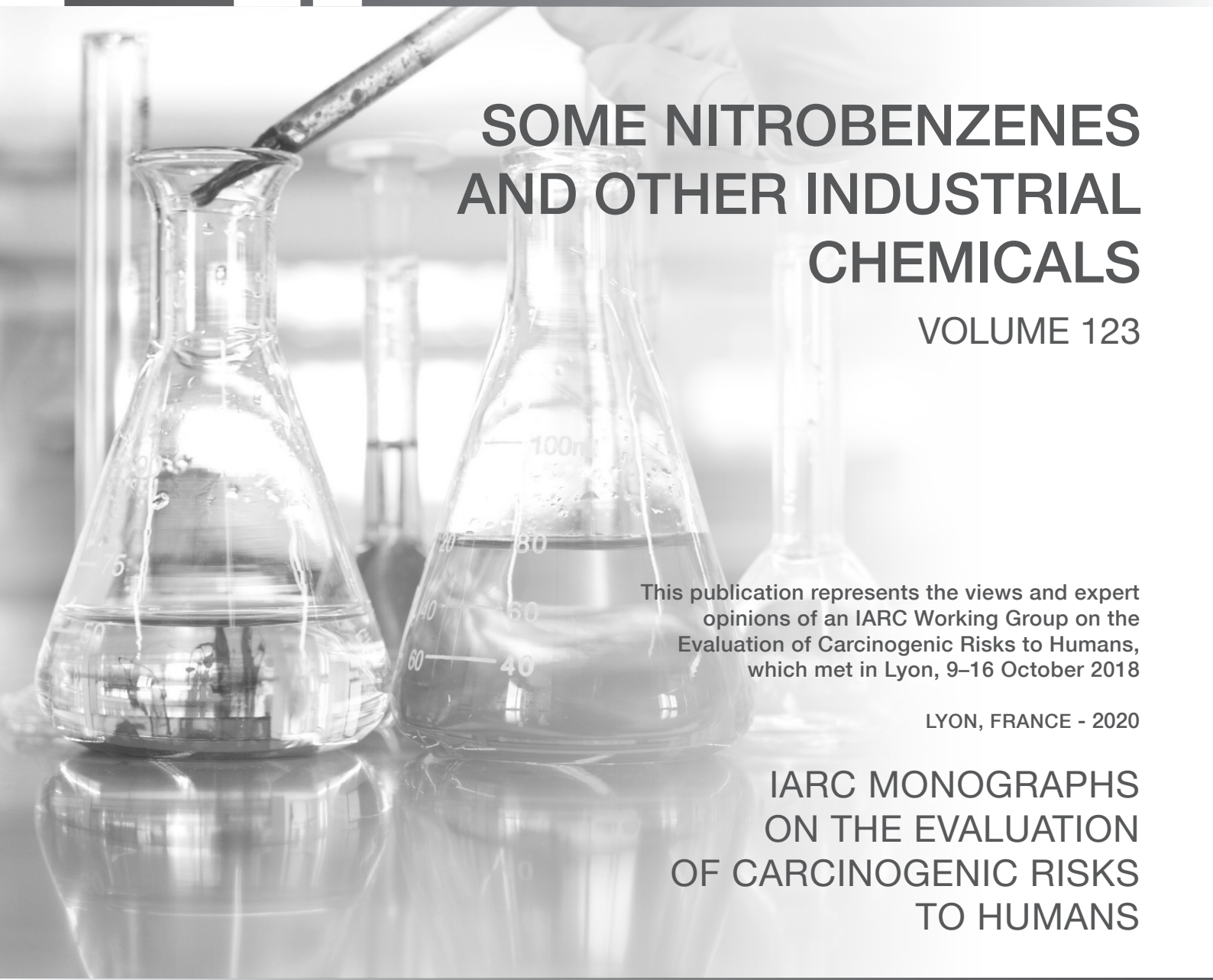

# SOME NITROBENZENES AND OTHER INDUSTRIAL CHEMICALS

VOLUME 123

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IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS

International Agency for Research on Cancer

World Health Organization

# 2-AMINO-4-CHLOROPHENOL

## 1. Exposure Data

### 1.1 Identification of the agent

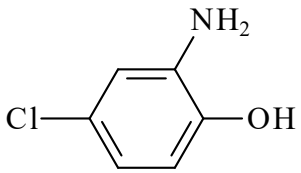
#### *1.1.1 Nomenclature*

*Chem. Abstr. Serv. Reg. No.*: 95-85-2

*Chem. Abstr. Serv. name*: 2-amino-4-chlorophenol

*Synonyms*: 1-amino-2-hydroxy-5-chlorobenzene; 1-hydroxy-2-amino-4-chlorobenzene; 2-amino 4-chloro phenol; phenol, 2-amino-4-chloro-; 5-chloro-2-hydroxyaniline; 4-chloro-2-aminophenol; *para*-chloro-*ortho*-aminophenol.

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




*Molecular formula*: $C_6H_6NOCl$

*Relative molecular mass*: 143.57 (PubChem, 2018).

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

*Description*: brown crystalline powder with characteristic amine-like odour (Merck, 2012; PubChem, 2018)

*Melting point*: 140 °C (PubChem, 2018)

*Volatility*: vapour pressure, 0.18 Pa at 25 °C (Merck, 2012)

*Density*: 1.406 g/cm$^3$ (Emco Dyestuff Pvt. Ltd, 2018)

*Water solubility*: 2.3 g/L at 25 °C (Merck, 2012)

*Octanol/water partition coefficient (P)*: log $K_{ow}$ = 1.24 (PubChem, 2018)

*Conversion factor*: 1 ppm = 5.87 mg/m$^3$

*Relative vapour density (air = 1)*: 5.0 (NIOSH, 2015)

*Stability*: does not burn; decomposes when heated or burnt to form toxic and corrosive emissions, including hydrogen chloride and nitrogen oxides; reacts with oxidizing agents (PubChem, 2018)

*Impurities*: available with a purity of greater than 95% (ThermoFisher Scientific, 2018).

## 1.2 Production and use

### 1.2.1 Production

2-Amino-4-chlorophenol is manufactured by converting 2,5-dichloronitrobenzene to 4-chloro-2-nitrophenol in a reaction with sodium hydroxide, followed by reduction with iron, hydrazine, or hydrogen, with Raney nickel or platinum catalyst (Yamazaki et al., 2009).

### 1.2.2 Production volume

In 2006, the annual production of 2-amino-4-chlorophenol in Japan was reported to be 500 tonnes, and it is currently listed as being produced in volumes of between 1 and 1000 tonnes (Yamazaki et al., 2009; NITE, 2018). 2-Amino-4-chlorophenol is listed as an intermediate with four active producers in Europe; between 1 and 10 tonnes are currently manufactured in or imported into Europe each year (ECHA, 2018). Information on quantities produced and used elsewhere in the world was not available to the Working Group.

### 1.2.3 Use

2-Amino-4-chlorophenol is used as an intermediate in the production of dyes, which in turn are used to colour textiles and clothing fabrics (e.g. mattresses, curtains, carpets, or textile toys), leather (e.g. gloves, shoes, purses, or furniture), and paper chemicals (e.g. tissues, feminine hygiene products, nappies, books, magazines, or wallpaper), and as inks and toners (ECHA, 2018). The compound is not used directly in consumer products, although trace amounts may be present in such products (Corbett, 1999). 2-Amino-4-chlorophenol has also been used in some hair dyes (Corbett, 1999; Anon., 2004). A United States Cosmetics Ingredients Review Expert Panel concluded that it was safe to use 2-amino-4-chlorophenol in oxidative hair dyes, but there was insufficient information to support its safety in nonoxidative (semipermanent) hair dyes (Anon., 2004). 2-Amino-4-chlorophenol is also used in the manufacture of the muscle relaxant chlorzoxazone (Belal et al., 2011).

## 1.3 Methods of measurement and analysis

### 1.3.1 Air

Air samples collected on polytetrafluoroethylene membrane filters with a 5 µm pore can be analysed for 2-amino-4-chlorophenol using high-performance liquid chromatography (HPLC) with ultraviolet detection, based on the United States National Institute for Occupational Safety and Health (NIOSH) analytical method 5013 for dyes (NIOSH, 1994).

### 1.3.2 Other environmental media

Puig & Barcelo (1996) reviewed the methods available for the analysis of phenols in water. An analytical method for measuring 2-amino-4-chlorophenol in water, based on solid-phase extraction followed by HPLC coupled with tandem mass spectrometry and electrospray ionization, was developed by Mourato (2014). The limit of quantification was 2 mg/L.

Dedhiya et al. (2016) described a method to assess the concentration of the 2-amino-4-chlorophenol contaminant in the drug chlorzoxazone. The method uses reversed-phase HPLC with particle size 5 µm, C18 column with 70:30:1% v/v/v water:acetonitrile:acetic acid as isocratic mobile phase, and ultraviolet detection. The limits of detection and quantification for 2-amino-4-chlorophenol were 0.5 mg/L and 2 mg/L, respectively. Similar analytical techniques described by others (Hassib et al., 2007; Belal et al., 2011) include a colorimetric test to identify 2-amino-4-chlorophenol as an impurity in chlorzoxazone powder using the reaction with 4-aminoantipyrine in the presence of alkaline

oxidizing agent, $K_3(Fe(CN)_6)/NH_3$, and measuring the produced red colour at 520 nm. This method reported detection and quantitation limits of 0.2 mg/L and 0.6 mg/L, respectively (Belal et al., 2011).

### 1.3.3 Biomarkers

No methods of measurement and analysis for biomarkers of exposure to 2-amino-4-chlorophenol were available to the Working Group.

## 1.4 Occurrence and exposure

### 1.4.1 Environmental occurrence

If accidentally released to the environment, 2-amino-4-chlorophenol may be found in air, water, or soil. It is also formed from the degradation of other anthropogenic toxic chemicals such as 4-chloro-2-nitrophenol. Degradation in the environment may occur through microbial metabolism, for example (Arora et al., 2012).

### 1.4.2 Exposure in the general population

Consumer exposure to very low concentrations may occur from residues in products where 2-amino-4-chlorophenol has been used as an intermediate (Belal et al., 2011). These exposures could arise from inhalation or ingestion; for example, low concentrations (< 0.0004–0.3200%) of 2-amino-4-chlorophenol have been identified in commercial formulations of the drug chlorzoxazone (Zhang et al., 2013; Dedhiya et al., 2016).

### 1.4.3 Occupational exposure

Occupational exposure to 2-amino-4-chlorophenol mainly occurs in industrial plants where the chemical is synthesized or used in the manufacture of other products (Yamazaki et al., 2009). Primary manufacturing is carried out in enclosed systems [the Working Group noted that this would be expected to minimize worker exposure], but higher levels of exposure are possible during packing, cleaning, or maintenance tasks (Yamazaki et al., 2009).

Exposure to 2-amino-4-chlorophenol in the workplace may also occur by inhalation and inadvertent ingestion (NIOSH, 2015). The primary route of exposure is by inhalation; dermal absorption can also be assumed from reports of skin sensitization of workers using this chemical (Anon., 2004).

## 1.5 Regulations and guidelines

2-Amino-4-chlorophenol is covered by generic occupational health and safety regulations relating to hazardous chemicals in many countries. It is registered under the European Union Registration, Evaluation, Authorisation and Restriction of Chemicals regulations (ECHA, 2018).

According to the Globally Harmonized System of Classification and Labelling of Chemicals, 2-amino-4-chlorophenol is harmful if swallowed (H302, category 4) and may cause skin irritation (H315, category 2). Precautionary measures should therefore include the avoidance of exposure by inhalation (P261) (IFA, 2018).

The use of 2-amino-4-chlorophenol in cosmetic products was banned in 2008 in some south-east Asian countries through the Association of Southeast Asian Nations Cosmetics Directive (Health Sciences Authority, 2007). Its use was also recently banned in the late 2000s: in the European Union under the provision of regulation (European Commission) No. 1223/2009 (European Commission, 2018); in Canada through the Health Canada Cosmetic Ingredient Hotlist; and in New Zealand under the Cosmetic Products Group Standard. 2-Amino-4-chlorophenol is still permitted for use in hair dyes in Australia (NICNAS, 2015), China, and the USA, and in other countries.

No threshold limit values or MAK values (established by the German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, or MAK Commission) have been established for 2-amino-4-chlorophenol (NIOSH, 2015; ACGIH, 2018; DFG, 2018).

## 2. Cancer in Humans

No data were available to the Working Group.

## 3. Cancer in Experimental Animals

See Table 3.1

### 3.1 Mouse

*Oral administration*

In a study that complied with good laboratory practice (GLP), groups of 50 male and 50 female B6D2F$_1$/Crlj mice (age, 6 weeks) were fed diets containing 2-amino-4-chlorophenol (purity, > 99.1%) at a concentration of 0 (control), 512, 1280, or 3200 ppm for 104 weeks (2 years) (JBRC, 2008a). All mice, including those found dead or in a moribund state, as well as those surviving to the end of the 2-year exposure period, underwent complete necropsy. In males and females at 0, 512, 1280, or 3200 ppm, survival was similar to their respective controls; survival rates were 33/50, 34/50, 36/50, and 35/50 for males, and 34/50, 28/50, 28/50, and 30/50 for females. There was no significant difference in final body weight of treated male and female mice compared with their respective controls.

In male mice, the incidence of squamous cell papilloma of the forestomach (0/50, 4/50, 3/50, and 6/50) was significantly ($P$ = 0.0133, Fisher exact test) increased in the group at 3200 ppm, with a significant positive trend ($P$ = 0.0273, Peto trend test). The incidence of squamous cell papilloma of the forestomach in all groups of treated males was higher than the upper bound observed in male mice (incidence, 5/1946; range, 0–2%) in historical control groups in studies from the Japan Bioassay Research Center (JBRC).

In female mice, the incidence of squamous cell papilloma of the forestomach (0/50, 1/50, 1/50, and 3/50) was not significantly increased, but there was a small but significant positive trend ($P$ = 0.0279, Peto trend test). The incidence in all groups was within the range observed for historical controls for JBRC female mice (incidence, 8/1947; range, 0–6%). [The Working Group noted that although all incidences in all groups of female mice were within the range for historical controls, there was also a significant positive trend in the incidence and an increase in the incidence of squamous cell papilloma of the forestomach in male mice.]

There was no treatment-related increase in non-neoplastic lesions in groups of treated males or females. [The Working Group noted that the strengths of this well-conducted GLP study included the use of multiple doses, a large number of mice per group, and testing in males and females.]

### 3.2 Rat

*Oral administration*

In a GLP study, groups of 50 male and 50 female Fischer 344/DuCrlCrlj rats (age, 6 weeks) were fed diet containing 2-amino-4-chlorophenol (purity, > 99.1%) at a concentration of 0 (control), 1280, 3200, or 8000 ppm, equivalent to 0, 56, 144, or 373 mg/kg body weight (bw) per day for males, and 0, 75, 184, or 469 mg/kg bw per day for females, for 104 weeks (JBRC, 2008b; Yamazaki et al., 2009). All rats, including those found dead or in a moribund state, as well as those surviving to the end of the 2-year exposure period, underwent complete necropsy.

## Table 3.1 Studies of carcinogenicity with 2-amino-4-chlorophenol in experimental animals

| Species, strain (sex)<br>Age at start<br>Duration<br>Reference | Route<br>Purity<br>Vehicle<br>Dose(s)<br>No. of animals at start<br>No. of surviving animals | Incidence of tumours | Significance | Comments |
|---|---|---|---|---|
| Mouse, B6D2F$_1$/Crlj (M)<br>6 wk<br>104 wk<br>JBRC (2008a) | Oral<br>> 99.1%<br>Diet<br>0, 512, 1280, 3200 ppm<br>50, 50, 50, 50<br>33, 34, 36, 35 | *Forestomach:* squamous cell papilloma<br>0/50, 4/50 (8%), 3/50 (6%), 6/50 (12%)* | $P = 0.0273$, Peto trend test; $P = 0.0365$, Cochran–Armitage trend test; *$P = 0.0133$, Fisher exact test | Principal strengths: well-conducted GLP study; males and females used; use of multiple doses; adequate number of mice<br>Incidence in historical controls: forestomach squamous cell papilloma, 5/1946 (range, 0–2%) |
| Mouse, B6D2F$_1$/Crlj (F)<br>6 wk<br>104 wk<br>JBRC (2008a) | Oral<br>> 99.1%<br>Diet<br>0, 512, 1280, 3200 ppm<br>50, 50, 50, 50<br>34, 28, 28, 30 | *Forestomach:* squamous cell papilloma<br>0/50, 1/50 (2%), 1/50 (2%), 3/50 (6%) | $P = 0.0279$, Peto trend test | Principal strengths: well-conducted GLP study; males and females used; use of multiple doses; adequate number of mice<br>Incidence in historical controls: forestomach squamous cell papilloma, 8/1947 (range, 0–6%) |
| Rat, F344/DuCrlCrlj (M)<br>6 wk<br>104 wk<br>JBRC (2008b), Yamazaki et al. (2009) | Oral<br>> 99.1%<br>Diet<br>0, 1280, 3200, 8000 ppm (0, 56, 144, 373 mg/kg bw)<br>50, 50, 50, 50<br>33, 38, 39, 39 | *Forestomach*<br>Squamous cell papilloma<br>0/50, 2/50, 11/50*, 39/50**<br>Squamous cell carcinoma<br>0/50, 0/50, 0/50, 12/50*<br>Squamous cell papilloma or carcinoma (combined)<br>0/50, 2/50, 11/50*, 43/50** | $P < 0.0001$, Peto trend test; *$P = 0.0003$, **$P < 0.0001$, Fisher exact test<br>$P < 0.0001$, Peto trend test; *$P = 0.0001$, Fisher exact test<br>$P < 0.0001$, Peto trend test; *$P = 0.0003$, **$P < 0.0001$, Fisher exact test | Principal strengths: well-conducted GLP study; males and females used; use of multiple doses; adequate number of rats<br>Incidence in historical controls: forestomach squamous cell papilloma, 5/2249 (range, 0–2%); forestomach squamous cell carcinoma, 4/2249 (0–2%); urinary bladder transitional cell papilloma, 11/2249 (0–4%); urinary bladder transitional cell carcinoma, 0/2249 |

**Table 3.1 (continued)**

| Species, strain (sex)<br>Age at start<br>Duration<br>Reference | Route<br>Purity<br>Vehicle<br>Dose(s)<br>No. of animals at start<br>No. of surviving animals | Incidence of tumours | Significance | Comments |
|---|---|---|---|---|
| Rat, F344/DuCrlCrlj (M)<br>6 wk<br>104 wk<br>JBRC (2008b), Yamazaki et al. (2009) (cont.) | | *Urinary bladder*<br>Transitional cell papilloma<br>0/50, 0/50, 1/50, 0/50<br>Transitional cell carcinoma<br>0/50, 0/50, 0/50, 7/50*<br>Transitional cell papilloma or carcinoma (combined)<br>0/50, 0/50, 1/50, 7/50* | <br><br>NS<br><br>$P < 0.0001$, Peto trend test; *$P = 0.0062$, Fisher exact test<br><br>$P < 0.0001$, Peto trend test; *$P = 0.0062$, Fisher exact test | |
| Rat, F344/DuCrlCrlj (F)<br>6 wk<br>104 wk<br>JBRC (2008b), Yamazaki et al. (2009) | Oral<br>> 99.1%<br>Diet<br>0, 1280, 3200, 8000 ppm (0, 75, 184, 469 mg/kg bw)<br>50, 50, 50, 50<br>42, 45, 46, 40 | *Forestomach*<br>Squamous cell papilloma<br>1/50, 1/50, 1/50, 25/50*<br>Squamous cell carcinoma<br>0/50, 0/50, 0/50, 2/50 (4%)<br>Squamous cell papilloma or carcinoma (combined)<br>1/50, 1/50, 1/50, 25/50* | <br><br>$P < 0.0001$, Peto trend test; *$P < 0.0001$, Fisher exact test<br><br>NS<br><br>$P < 0.0001$, Peto trend test; *$P < 0.0001$, Fisher exact test | Principal strengths: well-conducted GLP study; males and females used; use of multiple doses; adequate number of rats<br>Incidence in historical controls: forestomach squamous cell papilloma, 5/2097 (range, 0–2%); forestomach squamous cell carcinoma, 0/2097 |

bw, body weight; F, female; GLP, good laboratory practice; M, male; NS, not significant; ppm, parts per million; wk, week

Survival in groups of treated males and females was similar to that in their respective controls; survival rates were 33/50, 38/50, 39/50, and 39/50 in males, and 42/50, 45/50, 46/50, and 40/50 in females. There was a significant decrease in the body weights of females at 3200 and 8000 ppm of 7% and 13%, respectively, compared with female controls.

In male rats, there were significant increases in the incidence of squamous cell papilloma of the forestomach in those exposed at 3200 ppm (11/50; $P = 0.0003$, Fisher exact test) and at 8000 ppm (39/50; $P < 0.0001$, Fisher exact test) compared with controls (0/50), with a significant positive trend ($P < 0.0001$, Peto trend test). There was a significant increase in the incidence of squamous cell carcinoma of the forestomach at the highest dose (12/50, 24%) versus controls (0/50) ($P = 0.0001$, Fisher exact test), with a significant positive trend ($P < 0.0001$, Peto trend test). There was a significant increase in the incidence of squamous cell papilloma or carcinoma (combined) of the forestomach in males at 3200 ppm (11/50; $P = 0.0003$, Fisher exact test) and at 8000 ppm (43/50; $P < 0.0001$, Fisher exact test) compared with controls, with a significant positive trend. As potential pre-neoplastic lesions, the incidence of squamous cell hyperplasia of the forestomach was significantly increased in males at 3200 and 8000 ppm. There was a significant increase in the incidence of transitional cell carcinoma of the urinary bladder in males at 8000 ppm (7/50; $P = 0.0062$, Fisher exact test) compared with controls (0/50), with a significant positive trend ($P < 0.0001$, Peto trend test).

In female rats, there was a significant increase in the incidence of squamous cell papilloma of the forestomach of females at 8000 ppm (25/50; $P < 0.0001$, Fisher exact test) compared with controls (1/50, 2%), with a significant positive trend ($P < 0.0001$, Peto test). The occurrence of squamous cell carcinoma of the forestomach was observed at the highest dose (2/50, 4%) compared with none in 50 controls. Squamous cell carcinoma of the forestomach was not observed in female rats (0/2097) in the JBRC historical control database. [On the basis of comparison with the historical control database, the Working Group concluded that the increase in the incidence of squamous cell carcinoma of the forestomach in females was related to treatment.] There was a significant increase ($P < 0.0001$, Fisher exact test) in the incidence of squamous cell papilloma or carcinoma (combined) of the forestomach at the highest dose (25/50), with a significant positive trend ($P < 0.0001$, Peto trend test). As potential pre-neoplastic lesions, the incidence of squamous cell hyperplasia of the forestomach was significantly increased in females at 8000 ppm. [The Working Group noted that the strengths of this well-conducted GLP study included the use of multiple doses, the large number of rats per group, and testing in males and females.]

# 4. Mechanistic and Other Relevant Data

## 4.1 Absorption, distribution, metabolism, and excretion

### *4.1.1 Humans*

The only available study reported that partially oxidized haemoglobin or methaemoglobin was elevated in circulating erythrocytes in the blood samples of all 21 workers who had handled 2-amino-4-chlorophenol (and other compounds) (Tomoda et al., 1989).

### *4.1.2 Experimental systems*

No data were available to the Working Group.

[The Working Group noted that, on the basis of its hydrophilicity, orally administered 2-amino-4-chlorophenol is expected to be absorbed and eliminated via the kidneys.]

**Table 4.1 Genetic and related effects of 2-amino-4-chlorophenol in non-human mammalian cells in vitro and in non-mammalian experimental systems**

| Test system | End-point | Results[a] | | Concentration (LEC or HIC) | Reference |
|---|---|---|---|---|---|
| | | Without metabolic activation | With metabolic activation | | |
| Chinese hamster lung cells, CHL | Chromosomal aberrations | + | + | NR | JETOC (1997b) |
| *Salmonella typhimurium* TA1535 | Reverse mutation | – | + | 333 µg/plate | Zeiger et al. (1988) |
| *Salmonella typhimurium* TA97, TA98, TA100 | Reverse mutation | – | – | 1000 µg/plate | Zeiger et al. (1988) |
| *Salmonella typhimurium* TA100, TA1537 | Reverse mutation | – | + | NR | JETOC (1997a) |
| *Salmonella typhimurium* TA98, TA1535, WP2*uvr*A | Reverse mutation | – | – | 625 µg/plate | JETOC (1997a) |

HIC, highest ineffective concentration; LEC, lowest effective concentration; NR, not reported

[a] +, positive; –, negative

## 4.2 Mechanisms of carcinogenesis

This section summarizes the available evidence for the key characteristics of carcinogens (Smith et al., 2016), on whether 2-amino-4-chlorophenol: is genotoxic; or alters cell proliferation, cell death, or nutrient supply.

### 4.2.1 Genetic and related effects

See Table 4.1

#### (a) Humans

No data were available to the Working Group.

#### (b) Experimental systems

No data in experimental animals in vivo were available to the Working Group. Exposure to 2-amino-4-chlorophenol gave a positive result in hamster lung cells in vitro, increasing the percentage of cells with structural chromosomal aberrations at some of the tested concentrations (JETOC, 1997b).

2-Amino-4-chlorophenol produced statistically significant mutagenic effects with (but not without) metabolic activation in *Salmonella typhimurium* strains TA100, TA1535, and TA1537, but not in other tested strains (Zeiger et al., 1988; JETOC, 1997a).

Because there is *weak* evidence of genotoxicity, including some positive results in vitro, the human relevance of forestomach tumours observed in rodents could not be ruled out (IARC, 2003).

### 4.2.2 Altered cell proliferation, cell death or nutrient supply

#### (a) Humans

No data were available to the Working Group.

#### (b) Experimental systems

In a 2-year bioassay with 2-amino-4-chlorophenol in rats, forestomach nodules and squamous cell hyperplasia were observed (Yamazaki et al., 2009). Similar effects were not observed in mice (JBRC, 2008a).

In a 13-week test for oral toxicity in rats, 2-amino-4-chlorophenol induced proliferative lesions in the forestomach and urinary bladder (Yamazaki et al., 2009). Simple and papillary and/or nodular types of transitional cell hyperplasia

were observed in the urinary bladder of male rats fed diets containing 2-amino-4-chlorophenol.

## 4.3 Other adverse effects

### *4.3.1 Humans*

As noted in Section 4.1.1 above, partially oxidized haemoglobin or methaemoglobin were elevated in circulating erythrocytes in the blood samples of all 21 workers who handled 2-amino-4-chlorophenol (and other compounds) (Tomoda et al., 1989).

### *4.3.2 Experimental systems*

In a chronic bioassay in rats, 2-amino-4-chlorophenol decreased erythrocyte counts, haemoglobin, and haematocrit, indicating erythrocyte toxicity. Methaemoglobin concentrations and reticulocyte counts were concurrently increased (Yamazaki et al., 2009). In a chronic bioassay in mice, the effects observed included eosinophilic changes in the mouse nasal respiratory epithelium, and clinical chemistry changes indicating renal and hepatic toxicity in males (JBRC, 2008a).

Nephrotoxic effects were observed when male Fischer 344 rats were exposed to 2-amino-4-chlorophenol by intraperitoneal injection, inducing mild effects on renal function and marked proximal tubular damage; hepatotoxicity was not observed (Hong et al., 1996). In vitro, 2-amino-4-chlorophenol affected organic ion accumulation, pyruvate-stimulated gluconeogenesis, and lactate dehydrogenase leakage in a renal cortical slice system (Hong et al., 1996).

## 4.4 Data relevant to comparisons across agents and end-points

See the monograph on 2-chloronitrobenzene in the present volume.

# 5. Summary of Data Reported

## 5.1 Exposure data

2-Amino-4-chlorophenol is manufactured in relatively small quantities in Japan and Europe; information on production elsewhere in the world was unavailable. It is used as an intermediate in the manufacture of dyes used in textiles and other consumer products, and in the manufacture of the muscle relaxant chlorzoxazone. It is also used in some hair dyes, although its use in this way has been banned in several countries.

The compound is not known to occur naturally, but can be released to the environment as a by-product of manufacturing and downstream uses. Quantitative information on levels in the environment was not available.

Some consumer products may contain residues of 2-amino-4-chlorophenol, and low levels have been detected in the drug chlorzoxazone. However, quantitative information on exposure in the general population was not available.

Occupational exposure is expected to occur primarily through inhalation in workplaces where 2-amino-4-chlorophenol is produced or used as an intermediate in the manufacture of other products; exposure may also occur through skin contact or inadvertent ingestion. Quantitative information on exposure in occupational settings was not available.

## 5.2 Cancer in humans

No data were available to the Working Group.

## 5.3 Cancer in experimental animals

2-Amino-4-chlorophenol was tested for carcinogenicity in two well-conducted good laboratory practice (GLP) studies of oral exposure by diet from the same laboratory: one in male and female mice, and one in male and female rats.

In male mice, 2-amino-4-chlorophenol induced a significant positive trend in the incidence and a significant increase in the incidence of squamous cell papilloma of the forestomach.

In female mice, 2-amino-4-chlorophenol induced a significant positive trend in the incidence of squamous cell papilloma of the forestomach.

In male rats, 2-amino-4-chlorophenol induced a significant positive trend in the incidence and a significant increase in the incidence of squamous cell papilloma, squamous cell carcinoma, and squamous cell papilloma or squamous cell carcinoma (combined) of the forestomach. In male rats, 2-amino-4-chlorophenol induced a significant positive trend in the incidence and a significant increase in the incidence of transitional cell carcinoma of the urinary bladder.

In female rats, 2-amino-4-chlorophenol induced a significant positive trend in the incidence and a significant increase in the incidence of squamous cell papilloma, and squamous cell papilloma or carcinoma (combined) of the forestomach. Two animals developed a squamous cell carcinoma of the forestomach at the highest dose tested; this cancer was not observed in the historical database of the laboratory.

## 5.4 Mechanistic and other relevant data

No studies evaluating absorption, distribution, metabolism, or excretion in humans or in experimental animals were available.

Concerning the key characteristics of carcinogens, there is *weak* evidence that 2-amino-4-chlorophenol is genotoxic; available data were scarce and there were inconsistencies in the reported results. No data in humans or experimental animals in vivo were available. In one study, 2-amino-4-chlorophenol induced chromosomal damage in Chinese hamster lung cells in the presence or absence of metabolic activation. In bacteria, 2-amino-4-chlorophenol induced mutations in some strains, but only with metabolic activation.

There is *moderate* evidence that 2-amino-4-chlorophenol alters cell proliferation, cell death, or nutrient supply. Data were available for hyperplasia, but not for other relevant end-points. In 13-week and 2-year studies of oral exposure, hyperplastic lesions in the forestomach were observed in male and female rats; similar results were not seen in mice. Hyperplasia was observed in the urinary bladder of male rats in the 13-week study.

Haematotoxicity, especially methaemoglobin and other erythrocyte effects, was reported in exposed workers and in the rat (but not the mouse) chronic toxicity bioassay. In an acute toxicity study of intraperitoneal exposure in male rats, nephrotoxicity was seen.

Because there is *weak* evidence of genotoxicity, including some positive results in vitro, the human relevance of forestomach tumours observed in rodents could not be ruled out.

# 6. Evaluation

## 6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of 2-amino-4-chlorophenol.

## 6.2 Cancer in experimental animals

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

## 6.3 Overall evaluation

2-Amino-4-chlorophenol is *possibly carcinogenic to humans (Group 2B).*

## References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