Australian Government
Department of Health
Australian Industrial Chemicals Introduction Scheme

Phenol, 2,4-dichloro-

Evaluation statement

14 January 2022

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AICIS Evaluation Statement

Subject of the evaluation

Phenol, 2,4-dichloro-

Chemical in this evaluation

Name	CAS registry number
Phenol, 2,4-dichloro-	120-83-2

Reason for the evaluation

An evaluation is required to provide information on the risks to human health.

Parameters of evaluation

The chemical is listed on the Australian Inventory of Industrial Chemicals (the Inventory). This evaluation is a human health risk assessment for all identified industrial uses of the chemical.

Summary of evaluation

Summary of introduction, use and end use

The chemical has reported use in Australia in the manufacture of other chemicals with an introduction volume between 1000 and 9999 tonnes (NICNAS 2006).

Based on international use information, the chemical has site-limited uses as an intermediate in chemical manufacturing and as a raw material for polyester films. The chemical also has reported non-industrial applications in pesticides and pharmaceuticals.

Human health

Summary of health hazards

The critical health effects for risk characterisation include:

- systemic acute effects from oral and dermal exposure
- local effects (severe skin burns and eye damage).

Information on the toxicokinetics of the chemical is limited. The available information on the chemical indicates that the chemical can be rapidly absorbed via the oral, dermal and inhalation routes of exposure. Following uptake of the chemical into the blood, it is expected to be distributed to plasma, liver, kidney, fat, and brain, and subsequently metabolised to its glucuronate conjugate or into dichloromethoxyphenol and excreted mainly via urine.

Based on available data, the chemical has low to moderate acute oral toxicity (LD50 ranges from 580 to 4500 mg/kg bw) and moderate dermal toxicity (LD50 of 780 mg/kg bw) in mice and/or rats. There is insufficient information to conclude a finding on acute inhalation exposure.

The chemical is considered corrosive to skin based on a non-guideline skin and a Test Guideline (TG) acute dermal toxicity study. A non-guideline study also suggests that the chemical will also cause irreversible eye damage.

There are no skin sensitisation data available for the chemical.

Following repeated oral exposure, the chemical is not expected to be toxic to specific organs. Based on the combined information from in vitro and in vivo genotoxicity tests, the chemical is not genotoxic. Carcinogenicity data from subchronic and chronic studies in rat and mice did not indicate any potential for the chemical to induce tumours. Based on the available data, the chemical is not expected to cause specific adverse effects on fertility and sexual function after oral exposure; however, studies on developmental toxicity suggest that this cannot be ruled out. Available hormone disruption data related to the chemical suggests that there may be endocrine activity in vitro associated with the use of the chemical. In vivo hormone disruption assays were negative.

Health hazard classification

The chemical satisfies the criteria for the classification according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) (UNECE 2017) for hazard classes relevant for work health and safety as follows. This does not consider classification of physical hazards and environmental hazards. These are the current classifications in the Hazardous Chemicals Information System (HCIS) (Safe Work Australia).

Health hazards	Hazard category	Hazard statement
Acute toxicity	Acute Tox. 4	H302: Harmful if swallowed
Acute toxicity	Acute Tox. 3	H311: Toxic in contact with skin
Corrosion/irritation	Skin Corr. 1B	H314: Causes severe skin burns and eye damage

Summary of health risk

Public

Based on the available use information it is unlikely that the public will be exposed to the chemical. Therefore, there are no identified risks to the public that require management.

Workers

During chemical manufacturing and product formulation, dermal, ocular and inhalation exposure may occur, particularly where manual or open processes are used. These could include transfer and blending activities, quality control analysis, and cleaning and maintaining equipment. Worker exposure to the chemical at lower concentrations could also occur while using formulated products containing the chemical. The level and route of exposure will vary

depending on the method of application and work practices employed. Good hygiene practices to minimise incidental oral exposure are expected to be in place.

Given the critical health effects (acute and local health effects), the chemical could pose a risk to workers. Control measures to minimise dermal, ocular and inhalation exposure are needed to manage the risk to workers (refer to **Recommendation** section). Control measures implemented due to the corrosivity classification are expected to be sufficient to protect workers from any potential developmental effects.

Conclusions

The conclusions of this evaluation are based on the information described in this statement. Obligations to report additional information about hazards under section 100 of the *Industrial Chemicals Act 2019* apply.

The Executive Director is satisfied that the identified human health risks can be managed within existing risk management frameworks provided all requirements are met under environmental, workplace health and safety and poisons legislation as adopted by the relevant state or territory. The proposed means of managing the risks identified during this evaluation are set out in the **Recommendations** section.

Recommendations

Workers

Information on managing identified risks

The information in this report, including hazard classifications, should be used by persons conducting a business or undertaking at the workplace (such as an employer) to determine the appropriate controls under the Model Work Health and Safety Regulations.

Control measures that could be implemented to manage the risk arising from occupational exposure to the chemical include, but are not limited to:

- using closed systems or isolating operations
- using local exhaust ventilation to prevent the chemical from entering the breathing zone of any worker
- minimising manual processes and work tasks through automating processes
- adopting work procedures that minimise splashes and spills
- cleaning equipment and work areas regularly
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

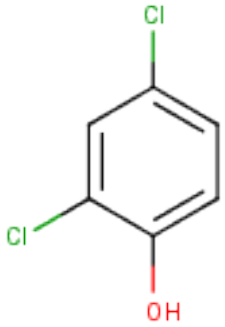
Measures required to eliminate, or manage risks arising from storing, handling and using a hazardous chemical depend on the physical form and how the chemical is used.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Model codes of practice, available from the Safe Work Australia website, provide information on how to manage the risks of hazardous chemicals in the workplace, prepare an SDS and label containers of hazardous chemical.

Supporting information

Chemical identity

Chemical Name	Phenol, 2,4-dichloro-
CAS No.	120-83-2
Synonyms	2,4-dichlorophenol (ACI) 1,3-dichloro-4-hydroxybenzene 2,4-DCP 2,4-dichlorophenic acid DCP
Structural formula	
Molecular formula	C6H4Cl2O
Molecular weight (g/mol)	163
SMILES	ClC1=CC=C(O)C(Cl)=C1
Chemical description	-

Relevant physical and chemical properties

Physical form	White solid
Melting point	42-45 °C
Boiling point	207–210 °C at 1013 hPa
Vapour pressure	0.16 hPa at 25 °C; 1.33 hPa at 53 °C
Water solubility	4.5 g/L at 20 °C
Henry's law constant	3.16×10^{-6} atm-m^3/mole

pKa	7.89
log K_{ow}	3.21–3.25 at 20 °C

Introduction and use

Australia

The total volume introduced into Australia reported under previous mandatory and/or voluntary calls for information was between 1000 and 9999 tonnes. The industry selected use category was manufacture of other chemicals (NICNAS High Volume Chemical List 2006).

International

The following international uses have been identified through the:

- Galleria Chemical (Chemwatch)
- eChemPortal (OECD)
- US National Library of Medicine's Hazardous Substances Data Bank (NCBI)
- European Union Registration, Evaluation, Authorisation and Restriction of Chemicals dossiers (REACH);
- Substances and Preparations in Nordic countries database (SPIN)
- OECD High Production Volume chemical program (OECD 2004)
- US EPA Chemical Data Reporting (CDR) database (US EPA 2016).

Uses were also identified in various international assessments including the:

- OECD Screening Information Dataset Initial Assessment Report (OECD 2006)
- National Institute for Public Health and the Environment report (RIVM 2009)
- European Commission Study on the Scientific Evaluation of 12 substances in the context of Endocrine Disruptor Priority List of Actions (EC 2002)
- International Agency for Research on Cancer (IARC 1999) and National Toxicology Program (NTP 1989) on 2,4-dichlorophenol.

No specific domestic or commercial uses were identified for the chemical.

The chemical has reported the following site-limited use as an intermediate in chemical manufacturing (OECD 2006) and as a raw material for polyester films (EC 2002).

The chemical has reported non-industrial uses including:

- the synthesis of phenoxy acid herbicides (such as 2,4-dichlorophenoxyacetic acid)
- the synthesis of anthelmintics (NCBI)
- as an intermediate in the manufacturing of miticides, germicides, algicides, fungicides, mothproofing agents, seed disinfectants, antiseptics and wood preservatives (NTP 1989; EC 2002; RIVM 2009; NCBI)
- in pharmaceuticals (RIVM 2009).

Existing Australian regulatory controls

AICIS

No specific controls are currently available for the chemical.

Public

This chemical is not specifically listed in the Poisons Standard: The Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP). However, the chemical falls under the scope of the following Schedule 6 group entry (SUSMP 2021):

‘PHENOL, including cresols and xylenols and any other homologue of phenol boiling below 220°C, except:

(a) when separately specified in these Schedules; or

(b) in preparations containing 1 per cent or less of phenols, and in preparations b) containing 3 per cent or less of cresols and xylenols and other homologues of phenol.

Schedule 6 chemicals are labelled with 'Poison'. These are substances with a moderate potential for causing harm, the extent of which can be reduced by using distinctive packaging with strong warnings and safety directions on the label.’

Phenol is also listed in schedules 2, 4 and 5 for non-industrial uses. The Schedule 5 entry relates to use in animal feed.

Workers

The chemical is classified as hazardous with the following risk phrases for human health in the HCIS (Safe Work Australia):

- Acute toxicity – Category 4; H302 (Harmful if swallowed)
- Acute toxicity – Category 3; H311 (Toxic in contact with skin)
- Skin corrosion – Category 1B; H314 (Causes severe skin burns and eye damage)

No exposure standards are available for this chemical in Australia (Safe Work Australia).

International regulatory status

Exposure standards

The following exposure standards are identified (Galleria Chemica):

- An exposure limit (OEL), TWA of 0.5 mg/m^3 and short-term exposure limits (STEL) of 1.5 mg/m^3 in countries such as Estonia, Iceland and Sweden.
- An exposure limit of 1 ppm time weighted average (TWA) workplace environmental exposure level (WEEL) was reported by the US Toxicology Excellence for Risk Assessment (TERA).

Health hazard information

Toxicokinetics

There is limited available information on the absorption, distribution, metabolism, and excretion (ADME) of the chemical.

Two metabolism studies using the chemical have been reported (EC 2002). In a metabolism study conducted in isolated perfused whole rat liver, 2,4-dichlorophenol was reported to undergo conjugation into its glucuronide conjugate or metabolise into dichloromethoxyphenol. In an in vitro study focusing on human P450 3A4-mediated metabolism of 2,4-dichlorophenol, the following metabolites were detected using thin layer chromatography: 2-chloro-1,4-hydroquinone, 2-chloro-1,4-benzoquinone and 1,2,4-trihydroxybenzene (EC 2002).

Following a single intravenous injection in male Sprague Dawley (SD) rats at 10 mg/kg, 2,4-dichlorophenol was rapidly distributed to the kidneys, liver, brain, fat and plasma of rats, and metabolised to its glucuronate conjugate, which was the major metabolite detected in all distributed organs (except fat). Small amounts of other unspecified conjugates and dichloromethoxyphenols were also detected. Elimination of the chemical and its metabolites from plasma, liver, kidneys, fat, and brain was rapid, with half-life values ranging between 4 and 30 minutes (NTP 1989; EC 2002; OECD 2006). At 1 hour after administration, tissue to plasma concentration ratios of 2,4-dichlorophenol and total conjugates were the highest in kidneys (116.8: 9.96) followed by the liver (30.0: 0.38), fat (5.75: 0.03), and brain (0.25: 0.00) (NTP 1989). Excretion of the chemical and its conjugates was reported to mainly occur via the urine and an unspecified bile pathway after conjugation with sulfate or glucuronic acid (OECD 2006).

Data reported on rabbit excretion suggests that majority of 2,4-dichlorophenol is excreted as the glucuronide conjugate, with less than or equal to 16% excreted as sulfate via urine. Additional information from calves showed that the total administered amount of 2,4-dichlorophenol (20 g) was excreted within 24 hours of administration (EC 2002; NCBI).

Available information on 2,4-dichlorophenol suggests the chemical can be absorbed via the gastrointestinal tract, skin and respiratory tract (ICPS 1989; EC 2002).

Acute toxicity

Oral

The chemical is classified as hazardous in the HCIS (Safe Work Australia) as ‘Acute toxicity (Oral) – Category 4; H302 (Harmful if swallowed)’. The available data support this classification.

In an acute oral toxicity study similar to the Organisation for Economic Co-operation and Development (OECD) Test Guideline (TG) 401, CD-1 mice (8/sex/dose) were administered the chemical via oral gavage. The median lethal doses (LD50) were 1276 and 1352 mg/kg body weight (bw) for males and females, respectively. Reported signs of toxicity included ataxia, loss of righting reflex, slights tremors, salivation, laboured breathing and depression, which occurred shortly after administration. Mortalities occurred 6–24 hours after administration. No gross abnormalities were noted during necropsy. No other findings were reported (NTP 1989; OECD 2006; REACH).

The following LD50 values have also been reported for the chemical from studies conducted similarly to OECD TG 401: 2830 mg/kg bw in male SD rats and 1630 mg/kg bw in male CF-1 mice. No clinical signs or other findings were reported for both studies (EC 2002; OECD 2006).

Several other oral LD50 values in the range 580–4500 mg/kg were reported in various studies in rats (NTP 1989; EC 2002).

Dermal

The chemical is classified as hazardous in the HCIS (Safe Work Australia) as 'Acute toxicity (Dermal) – Category 3; H311 (Toxic in contact with skin)'. The available data support this classification.

In an acute dermal toxicity study conducted according to OECD TG 402, liquid 2,4-dichlorophenol melted at 40°C was applied to the skin of SD rats (5/sex/dose) at doses of 0, 200, 300, 1400 or 2000 mg/kg bw in males and 200 or 2000 mg/kg bw in females. The median lethal dose (LD50) was 780 mg/kg bw. Mortalities occurred within 6 days of application, with 4/5 mortalities occurring for both sexes in the 2000 mg/kg bw group. Reported sub-lethal signs of toxicity included decreases in motor activity and respiratory impairment in the lowest to middle dose groups (200–1400 mg/kg bw), coma, soft faeces and blood-like colouration in urine at the highest dose (2000 mg/kg bw). Marked to severe skin irritation occurred in all dose groups at the application site. Irreversible skin necrosis was observed at the patch site within 2 weeks after application. Necropsy revealed the presence of a black liquid in the urinary bladder of one male and one female in the 2000 mg/kg bw group (OECD 2006; REACH).

Inhalation

The available information on the chemical is insufficient to conclude any findings on acute inhalation toxicity due to the lack of information on the purity of 2,4-dichlorophenol, the particulate size distribution, the temperature of the inhaled substance and lack of control groups used in the study.

In an acute inhalation study conducted similarly to OECD TG 403, SD rats (5/sex/dose) were exposed to aerosolised 2,4-dichlorophenol (melted at 55°C to form a liquid) (inhalation route not specified) for 4 hours at concentrations between 0.77–1.13 mg/L, corresponding to inhaled doses between 105–155.5 mg/kg). A median lethal concentration (LC50) of 0.97 mg/L was reported. Observed sub-lethal signs of toxicity included restlessness, eye irritation, nasal mucosa irritation, salivation, head/neck/trunk tremor, swelling of the extremities, dyspnoea, polypnoea, low reactivity to sound stimuli, slight spasms and prone posturing. At lethal concentrations, severity of spasms increased. In addition, early loss of righting reflex and cyanosis before death were noted. At necropsy, red spots on the lungs were observed at all doses and this was considered treatment related by the authors (OECD 2006).

Observation in humans

Mortalities following dermal exposure to 2,4-dichlorophenol has been reported. Following skin contact, absorption is very rapid, and signs and symptoms develop rapidly (within 20–90 minutes). Death can occur within 20 minutes to several hours. Reported signs of toxicity include:

- chemical burns

- swollen, red, sloughed mucosa of the larynx, trachea, and bronchi
- focal haemorrhage and considerable haemorrhagic fluid in the lungs (with fluid extruding through the mouth and nostrils)
- blue/tan swollen oesophageal mucosa
- reddened mucosa and turbid haemorrhagic fluid in the stomach (OECD 2006; NCBI).

Reported sub-lethal signs include:

- seizures
- burning sensations and white necrotic lesions at the exposure site
- abdominal pain
- vomiting
- bloody diarrhoea
- headaches
- dizziness
- sweating
- tinnitus
- shock
- weak irregular pulse
- hypotension
- shallow respiration
- cyanosis
- pallor
- decreases in body temperature
- noisy and laboured breathing
- mucous rales
- rhonchi (low pitch sound that resembles snoring)
- frothing at nose and mouth
- pulmonary oedema
- dark-coloured urine
- moderate to severe renal insufficiency and mortality from respiratory, circulatory or cardiac failure.

Ingestion of the chemical is reported to cause methaemoglobinemia, Heinz body haemolytic anaemia and hyperbilirubinemia (REACH; NCBI).

Corrosion/Irritation

Skin irritation

The chemical is classified as hazardous in the Hazardous Chemical Information System (HCIS) (Safe Work Australia) as 'Skin Corrosion – Category 1B; H314 (Causes severe skin burns and eye damage)'. The available data support this classification.

In a non-guideline skin irritation study, application of 80% 2,4-dichlorophenol in water to the skin of rabbits for 1 minute, 5 minutes, 15 minutes or 20 hours resulted in the development of persistent strong necrosis, oedema and reddening of the skin in the 15 minutes to 20 hour exposure period. Necrosis was, by definition, irreversible. No further details were provided (OECD 2006; REACH).

The chemical is also reported to be a moderate to severe skin irritant in an acute animal study (see **Acute toxicity – dermal**).

Based on the available data, this chemical is considered corrosive to the skin.

Eye irritation

The chemical is classified as hazardous in the HCIS (Safe Work Australia) as 'Skin Corrosion – Category 1B; H314 (Causes severe skin burns and eye damage)'. The available data support this classification.

In a non-guideline eye irritation study, direct application of a single 0.1 mL dose of neat 2,4-dichlorophenol to the eye for 30 seconds caused severe corneal damage in rabbits. Rinsing of the chemical from the eye after exposure did not prevent damage to the cornea. No other details were provided (OECD 2006; REACH).

Sensitisation

Skin sensitisation

No data are available to evaluate skin sensitisation. However, it has been reported that human exposure to a chemical mixture of chlorophenols containing 2,4-dichlorophenol causes chloracne. No other details were provided (OECD 2006; REACH).

Repeat dose toxicity

Oral

Based on the available data, the chemical is not expected to cause serious systemic health effects following repeated oral exposure.

In a subchronic toxicity study conducted similarly to the OECD TG 408, CD-1 mice (20/sex/dose) were administered 2,4-dichlorophenol in drinking water containing 10% emulphor (a polyethoxylated vegetable oil used as a vehicle) at 0, 50, 143 or 491 mg/kg bw/day for females and 0, 40, 114 or 383 mg/kg bw/day for males for 7 days/week. No dose-related effects were observed. This study reported no observed adverse effect levels (NOAELs) of ≥383 mg/kg bw/day and >491 mg/kg bw/day for males and females, respectively (OECD 2006; NCBI).

In a non-guideline 14 day oral repeat dose toxicity study, CD-1 mice (12/sex/dose) were administered 2,4-dichlorophenol via oral gavage at 0, 64, 128 or 638 mg/kg bw/day for 7 days/week for 2 weeks. No treatment related effects were observed. A NOAEL of ≥638 mg/kg bw/day was determined based on this study (OECD 2006).

In a non-guideline combined 14 day and 90 day study, Fischer 344 rats (5/sex/dose and 10/sex/dose, respectively) were administered 2,4-dichlorophenol in feed at 0, 2500, 5000, 10000, 20000, or 40000 ppm (equivalent to 0, 200, 400, 800, 1500 and 3000 mg/kg bw/day) for 7 days/week. The NOAEL was reported to be 400 mg/kg bw/day in females and 800 mg/kg bw/day in males for 2,4-dichlorophenol for the 90 day study based on adverse effects such as bone marrow degeneration in female and male rats (in the 800 mg/kg bw/day and 1500 mg/kg bw/day dose groups, respectively). Changes in general appearance (hunched posture, rough hair coats and/or dehydrated appearance) in the highest dose group and significant decreases in body weight was also reported; however, the authors suggested that the cause of the latter may be due to the palatability of the compound. No other adverse effects were reported (NTP 1989; IARC 1999; OECD 2006).

In a non-guideline combined 14 day and 90 day study, B6C3F1 mice (5/sex/dose and 10/sex/dose, respectively) were administered 2,4-dichlorophenol in feed at 0, 2500, 5000, 10000, 20000 or 40000 ppm (equivalent to 0, 750, 1500, 3000, 6000 and 12000 mg/kg bw/day) for 7 days/week. An NOAEL could not derived in this study. The lowest observed adverse effect level (LOAEL) was reported to be 750 mg/kg bw/day for male mice. Effects observed in the 90 day study included:

- treatment related increases in liver damage (observed as an increase in hepatocellular necrosis) in all dose groups
- an increase in the incidence of multi-nucleated hepatocytes in the male mice of the 10000 and 20000 ppm dose groups
- kidney damage (observed as renal tubular epithelial necrosis) in 8/9 male mice and 3/10 female mice of the 40000 ppm dose group and
- decreases in mean body weight gain in the male and female mice from the 20 000 ppm group.

One mortality was reported in the 40000 ppm group before the completion of the 14 day study; however, by the third week of the 90 day study, all mice in this dose group were found dead. Necropsy revealed that the mice had kidney damage (NTP 1989; IARC 1999; OECD 2006).

In a 103 week combined chronic toxicity/carcinogenicity study (see **Carcinogenicity** section) conducted in accordance with OECD TG 453, Fischer 344 rats (50/sex/dose) received the chemical in feed at 0, 120 or 250 mg/kg bw/day in females or 0, 210 or 440 mg/kg bw/day in males, for 7 days/week. An increased incidence of mild degenerative changes in the mucosal lining of the nose was observed in males at both doses. NOAELs of >440 mg/kg bw/day for males and >250 mg/kg bw/day for females were reported (NTP 1989; OECD 2006).

In a 103 week combined chronic toxicity/carcinogenicity study (see **Carcinogenicity** section) conducted in accordance with OECD TG 453, B6C3F1 mice (50/sex/dose) received the chemical in feed at 0, 430 or 820 mg/kg bw/day in females, and at 0, 800 or 1300 mg/kg bw/day in males for 7 days/week. Mild liver changes (increase in hepatocytes containing multinucleated cells) were observed in males at all doses. LOAELs of 430 and 800 mg/ kg bw/day were reported in female and male mice, respectively. An NOAEL of <430 mg/kg bw/day for females was reported (NTP 1989; OECD 2006).

In a 2 generation reproduction toxicity study (see **Reproductive and development toxicity** section) conducted in accordance with OECD 416, Wistar Hannover rats (24/sex/dose) were administered the chemical daily in feed at 0, 500, 2000 or 8000 ppm (equivalent to 0, 33.4, 134, and 543 mg/kg/day in males and 0, 49.1, 194, and 768 mg/kg/day in females). Exposure started from 5 weeks of age throughout mating (10–12 weeks), gestation (3 weeks) and lactation (3 weeks) for a total of 18 weeks in the F0 and F1 generation. The following effects were reported:

- Significant decreases in terminal body weight and significant increases in relative brain weight in the 8000 ppm F0 and F1 animals except for F0 males.
- A statistically significant increase in food consumption in the F0 males of the 500 ppm group.
- Decreases in food consumption and body weight gain in all the F0 and F1 parental animals at 2000 ppm and 8000 ppm.
- Increases in staining of the lower abdomen hair in F0 and F1 animals at all doses.
- Increases in relative kidney weight and frequency of the dilatation of renal pelvis in the F0 and F1 males of the 8000 ppm group.
- Transient mammary swelling after weaning in the F0 and F1 females at all doses.

No mortalities occurred during the study in the F0 and F1 parental groups. An NOAEL of 2000 ppm (543 mg/kg bw/day for males and 768 mg/kg bw/day for females) is reported for parental and offspring general toxicity (OECD 2006).

In a 15 week and 2 year combined developmental toxicity (see **Reproductive and development toxicity** section) and carcinogenicity study (see **Carcinogenicity** section) conducted similarly to OECD TG 415 and OECD TG 451, respectively, SD rats (24–32/sex/group) were administered 2,4-dichlorophenol in drinking water at 0, 3, 30 and 300 ppm (estimated to be 0.3, 3 and 30 mg/kg bw/day. However, there are discrepancies between the reported equivalents and actual doses received [OECD 2006, RIVM 2009, US EPA IRIS, NCBI, ASTDR], the primary data are unavailable) for 7 days/week. Dams (12–14/group) were treated with the chemical from 3 weeks of age through to parturition and lactation. Progeny (24–28/group) were treated after weaning at 3 weeks until 15 weeks or 24 months. Other than reproductive effects, no notable effects were reported in the F0 generation. A NOAEL of >30 mg/kg bw/day was reported for the F1 generation (OECD 2006). The following effects were reported (OECD 2006; IARC 1999; US EPA IRIS):

- Significant decreases in markers of cell-mediated immunity (measured as a decrease in delayed-type hypersensitivity responses to bovine serum albumin) in the middle and highest dose groups.
- Enhanced markers of humoral immunity (measured by an increase in serum antibody levels to keyhole limpet haemocyanin) in the highest dose group.
- Significant increases in liver and spleen weights in the highest dose group after 14 weeks of prenatal and/or post-natal exposure to the chemical.
- Significant increases in the number of red blood cells and haemoglobin levels in the highest dose group after 24 months of exposure.

Based on the effects reported in this study, an NOEL of 3 ppm and a minimal risk level (MRL), an oral reference dose (RfD) and tolerable daily intake (TDI) value of 0.003 mg/kg-day were derived for 2,4-dichlorophenol (ATSDR 1999; RIVM 2009; US EPA IRIS).

Dermal

No data are available for the chemical.

Inhalation

No data are available for the chemical.

Genotoxicity

Based on the weight of evidence from the available genotoxicity studies, the chemical is not genotoxic. Positive results were seen in some in vitro studies but in vivo mutagenicity and clastogenicity studies were negative.

In vitro

Negative results were reported in the following in vitro genotoxicity tests (NTP 1989; OECD 2006; REACH):

- In a bacterial reverse mutation assay (OECD TG 471) in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 with and without metabolic activation at concentrations up to 500 µg/plate.
- In a bacterial reverse mutation assay (equivalent or similar to OECD TG 471) in *S. typhimurium* strains G46, TA1535, TA100, C3076, TA1537,D3052, TA1538 and TA98 and *Escherichia Coli* strains WP2 and WP2 uvrA-negative with and without metabolic activation at concentrations up to 1000 µg/plate.

- In a non-guideline bacterial reverse mutation assay in *S. typhimurium* strains TA98, TA100, YG1021, YG1024, YG1026 and YG 1029 with and without metabolic activation at concentrations up to 500 µg/plate.
- In a non-guideline bacterial reverse mutation assay in *S. typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 with and without metabolic activation at concentrations up to 5 mg/plate.
- In a mammalian chromosomal aberration test (OECD TG 473) in Chinese hamster ovary (CHO) cells with and without metabolic activation at concentrations up to 463 µM and 1079 µM, respectively.
- In a mammalian chromosomal aberration test (OECD TG 473) in CHO cells (clone WBL) with and without metabolic activation at concentrations up to 1.4 µM.
- In a mammalian chromosomal aberration test (OECD TG 473) in TK6 human lymphoblasts (WI-L2-NS cells) without metabolic activation at concentrations up to 1.2 µM; however, this test was considered invalid since the cell line used had no established optimal sampling time.
- In a mammalian cell gene mutation assay (similar to OECD TG 476) in the hypoxanthine-guanine phosphoribosyl transferase (hprt) locus in Chinese hamster lung V79 cells without metabolic activation at concentrations up to 306 µM.
- In an unscheduled DNA synthesis (UDS) assay (similar to OECD TG 482) in rat hepatocytes without metabolic activation at concentrations to 1000 mM.
- In a non-guideline DNA damage and repair assay measuring the development of double strand breaks in rat hepatocytes without metabolic activation at concentrations up to equivalent to 0.8 mM.
- In a cytogenetic assay involving the activation of the human hsp70 gene in HeLa cells without metabolic activation at concentrations up to 500 µM.

Unclear results were reported in the following in vitro genotoxicity tests (OECD 2006):

- In a bacterial reverse mutation assay (equivalent or similar to OECD TG 471; using a pre-incubation procedure) in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 with and without metabolic activation at concentrations up to 333 µg/plate. A weak but non-significant positive result was observed at the 333 µg/plate concentration in the TA1535 strain.
- In a bacterial reverse mutation assay (equivalent or similar to OECD TG 471) in *S. typhimurium* strains TA98, TA100, TA1535 and TA1537 with and without metabolic activation at concentrations up to 333 µg/plate. An ambiguous result was observed at the 333 µg/plate concentration in the TA1535 strain with metabolic activation.

Positive results were reported in the following in vitro genotoxicity studies (OECD 2006):

- In a mammalian cell gene mutation assay (OECD TG 476) in the hprt locus of L5178Y mouse lymphoma cells without metabolic activation at concentrations up to 368 µM.
- In a mammalian cell gene mutation assay (similar to OECD TG 476) in the hprt locus of Chinese hamster lung cells V79 without metabolic activation at concentrations up to 24 µM. However, the test was considered invalid as the mutants used in the study are those not recommended by the OECD guidelines.
- In a sister chromatid exchange assay (OECD TG 479) in CHO cells with and without metabolic activation at concentrations up to 77 µM and 981 µM, respectively
- In a mammalian chromosomal aberration test (OECD TG 473) in CHO cells (clone WBL) without metabolic activation at concentrations up to 1.6 mM.
- In a mammalian chromosomal aberration test (equivalent or similar to OECD TG 473) in V79 Chinese hamster lung cells without metabolic activation at concentrations up

to 1.6 mM; however, the test was considered invalid due to the lack of positive controls, no duplication of cultures and no testing with metabolic activation.
- In a non-guideline micronucleus test in human lymphocytes without metabolic activation at concentrations up to 613.5 µM. However, the test was considered invalid due to the lack of positive control, the use of a single culture to record the number of micronuclei and no record of the cytotoxicity concentration.

In vivo

In a non-GLP compliant micronucleus test conducted in accordance with OECD TG 474, Swiss male mice (10 mice/dose) were treated with the chemical in peanut oil twice by gavage at doses of 0, 160 or 800 mg/kg bw/day. Severe prostration was observed in animals at the 800 mg/kg bw/day dose (OECD 2006).

In a UDS test similar to OECD TG 486, a single dose of the chemical was administered via gavage to male B6C3F1 mice (4–5 mice/group) at doses of 0, 300 or 600 mg/kg bw. The substance did not induce DNA damage in liver cells at any of the dose tested. However, it should be noted that no positive control was used in the study and the hepatocytes was prepared at 24, 39 or 48 hours rather than 12–16 hours after treatment as stated in the test guideline (OECD 2006).

In 2 non-guideline sister chromatid exchange assays, the chemical was administered to CD-1 mice daily via gavage in corn oil (12 mice/sex/dose) or drinking water (20 mice/sex/dose) for 14 or 90 days at doses up to 638 mg/kg bw/day or 500 mg/kg bw/day, respectively. The rate of sister chromatid exchanges did not exceed background rates in the bone marrow of mice (OECD 2006).

Carcinogenicity

Based on the weight of evidence from the available carcinogenicity studies, the chemical is not expected to be carcinogenic.

The International Agency for Research on Cancer (IARC) has evaluated and concluded that polychlorophenols and their sodium salts are classifiable as ‘Possibly carcinogenic to humans’. However, based on their report there is evidence suggesting lack of carcinogenicity in experimental animals for 2,4-dichlorophenol (IARC 1999). The US National Toxicology Program (NTP) concluded that 2,4-dichlorophenol presented no evidence of carcinogenicity Fischer 344 rats or B6C3F1 mice following oral exposure (NTP 1989).

The results from the 103-week NTP bioassays in the two species (see **Repeat Dose Toxicity – Oral** section) are detailed as follows:

- In a 103 week study, Fischer 344 rats (50/sex/dose) received 2,4-dichlorophenol via their diet. The incidence of tumours was not significantly increased in any treatment group in comparison to the controls (NTP 1989; IARC 1999).
- In a 103 week study, B6C3F1 mice (50/sex/dose) received 2,4-dichlorophenol via their diet. The incidence of tumours was not significantly increased in any treatment group in comparison to the controls (NTP 1989; IARC 1999).

The chemical was also negative in the following study:

- In a 15 week and 2 year combined developmental toxicity and carcinogenicity study (see **Repeat Dose Toxicity** and **Reproductive and development toxicity** section) conducted similarly to OECD TG 415 and OECD TG 451, respectively, dams (n = 13–14/group) and their progeny (n = 24–32/group) received 2,4-dichlorophenol via drinking water with or without the initiator, ethyl-nitroso-urea (ENU), in the form of its precursor, ethyl urea (EU) at 0.15% on GD 14–21. The incidence of tumours was not significantly increased in any treatment group (IARC 1999; OECD 2006).

The chemical was positive in the following study:

- In a non-guideline carcinogenicity study, female Stutter mice (23–33/group) were dermally treated with 5 mg 2,4-dichlorophenol in 20% benzene for 2 days/week following a single application of the initiator, 0.3% dimethylbenzanthracene (DMBA), for 15 or 24 weeks. An increase incidence of papillomas (48%) and carcinomas (11%) in the surviving mice of the treatment group (27/33) after 15 weeks of exposure was reported. Increased incidence of papillomas (75%) and carcinomas (6%) was also reported in surviving mice exposed to the chemical for 24 weeks (16/23). Despite the positive result, the study was considered invalid due to the use of the chemical in conjunction with DMBA and benzene during application (OECD 2006).

Reproductive and development toxicity

Based on the available data, the chemical is not expected to cause specific adverse effects on fertility and sexual function after oral exposure. However, the chemical may cause specific adverse effects to the development of foetuses after maternal oral exposure. While the available data is not sufficient for classification, developmental toxicity cannot be ruled out.

In a 2 generation reproductive toxicity study conducted in accordance with OECD 416, Wistar Hannover rats (24/sex/dose) were administered the chemical daily in feed at 0, 500, 2000 or 8000 ppm (equivalent to 0, 33.4, 134, or 543 mg/kg bw/day in males and 0, 49.1, 194, or 768 mg/kg bw/day in females). Exposure started from 5 weeks of age throughout mating (10–12 weeks), gestation (3 weeks) and lactation (3 weeks) for a total of 18 weeks in the F0 and F1 generation. Fertility effects observed included decreases in mean litter size and mean numbers of implantations in F0 and F1 females in the 2000 ppm and 8000 ppm groups with statistically significance in the highest dose group; slight early onset of sexual maturation (vaginal opening) in F1 females as well as delays in sexual development (preputial separation) and increase in relative testis weight in the F1 males in the 8000 ppm group. Developmental effects observed included significant growth delays and slower eye opening in the pups of the F1 and F2 generation at 8000 ppm and significant increases in the absolute and relative uterine weights in the F1 and F2 generation of the 2000 ppm and/or 8000 ppm groups. Histopathological examination of pups revealed increased height of the epithelial cells in the uterine horn in the F2 females of the high dose group. Changes in relative weight of the brain in F1 females, the relative and absolute weight of the brain in F2 males and the absolute weight of the thymus and spleen in both F2 males and F2 female rats were also observed. However, the authors suggested that this was due to the decreases in body weight of the pups. NOAELs of 500 ppm (33.4 mg/kg bw/day for males and 49.1 mg/kg bw/day for females) and 2000 ppm (543 mg/kg bw/day for males and 768 mg/kg bw/day for females) were reported for fertility and development, respectively (OECD 2006).

In a prenatal developmental toxicity study conducted in accordance with OECD TG 414, pregnant Fischer 344 rats (34/group) were administered the chemical in corn oil by gavage once daily at 0, 200, 375 or 750 mg/kg bw/day on gestational days (GD) 6 to 15. Dams were sacrificed on GD20 and the foetuses examined. Maternal effects observed included urogenital staining of fur and decreases in body weight gain at all doses as well as alopecia,

respiratory rales and porphyrin accumulation around the area around the eyes, the opening of the nostrils and mouth of rats in the highest dose group. Mortalities were also observed in 4/34 animals at the highest dose. Foetal effects observed included delayed foetal development (ossification of sternebrae and vertebral arches), increased early embryonic death and decreased foetal weight at the 750 mg/kg bw/day dose. As no teratogenic effects were observed, an NOAEL of 750 mg/kg bw/day was reported for teratogenicity (IARC 1999; OECD 2006; REACH). An NOAEL of 375 mg/kg bw/day was reported for foetal toxicity, while maternal toxicity was seen at the lowest dose of 200 mg/kg bw/day (OECD 2006).

In a 15 week and 2 year combined developmental toxicity and carcinogenicity study (see **Repeat Dose Toxicity** and **Carcinogenicity** section) conducted similarly to OECD TG 415 and OECD TG 451, respectively, female SD rats received 2,4-dichlorophenol in drinking water. Decreases in litter size and an increase in the birth of stillborn pups were reported. However, it should be noted that a dose-response relationship could not be quantified due to issues in the statistical analysis used in the study (OECD 2006).

In a non-guideline one generation toxicity study, CD-1 mice (10/sex/dose) were administered the chemical in drinking water (containing 21% emulphor as a vehicle) twice a week at 0, 50, 150 or 500 mg/kg bw/day for 108 days. Exposure started 90 days prior to mating and then for another 18 days during the mating and gestation period. An NOAEL of 500 mg/kg bw was established for the parental and F1 generation by the study authors. No further details were provided (EC 2002; OECD 2006).

In a non-guideline in vitro and in vivo reproductive toxicity study, CD-1 mice were administered the chemical in drinking water at 0, 50, 150 or 500 mg/kg bw/day for 90 days. No effects on the penetration of sperm into mouse ova were observed. An NOAEL of 500 mg/kg bw was established. No further details were provided (OECD 2006).

In a non-guideline in vitro reproductive toxicity study, male CD-1 mice and female B6C3F1 mice were administered the chemical in drinking water at 0, 50, 150 or 500 mg/kg bw/day for 90 days. No adverse effects on the sperm penetration, sperm motility or acrosome integrity were observed. An NOAEL of 500 mg/kg bw was established. No further details were provided (OECD 2006).

Endocrine effects

Based on the weight of evidence from the available in vitro assays, the chemical may have endocrine activity in vitro. In vivo hormone disruption assays were negative.

In vitro

Negative results were reported in the following in vitro endocrine activity assays (EC 2002; OECD 2006):

- In two cell proliferation assays using MCF-7 cells at concentrations up to 0.1 mM.
- In a competitive binding assay using human and calf cytosolic oestrogen receptor (ER) and radiolabelled 17B oestradiol at concentrations up to 5 mM.
- In a reporter gene assay using cultured recombinant cells that measured the induction of ERE- (oestrogen response element) – dependent gene transcription activation at concentrations up to 0.1 mM.
- In a mammalian cell growth assay using the human breast cancer cell line, ZR-75, at concentrations up to 0.1 mM.

- In a recombinant yeast assay measuring the modulation of the human progesterone receptor activity in a modified DY150 yeast strain containing the human progesterone receptor – progesterone response element (hPR-PRE) at 1 µM. However, this test was considered invalid due to lack of information on other tested concentrations and the fact that oestrogenic potency was measured directly.

Positive results were reported in the following in vitro endocrine activity assays (OECD 2006):

- In a yeast two hybrid study investigating the interaction between a hormone receptor (oestrogen receptor alpha) and a coactivator (TIF2). However, the study was considered invalid due to the lack of information on the purity of the chemical used and the number of replicates conducted (OECD 2006).

In vivo

In a uterotrophic bioassay (method not specified), ovariectomised 8 week old Wistar Hannover rats were orally administered 2,4-dichlorophenol alone, at doses of 0, 100, 200 or 400 mg/kg/day, or in combination with 17 alpha-ethynyloestradiol subcutaneously at 0.5 µg/kg/day for 3 days to detect oestrogenic and anti-oestrogenic effects, respectively. No treatment-related changes were observed in the uterine weight in either group (OECD 2006).

In a Hershberger bioassay (similar or equivalent to OECD TG 441), castrated 8 week old Wistar Hannover rats were orally administered 2,4-dichlorophenol alone, at doses of 0, 50, 100 or 200 mg/kg/day, or in combination with testosterone propionate subcutaneously at 0.4 mg/kg/day for 10 days. No treatment-related changes were observed in the weights of any male accessory reproductive organs in either group (OECD 2006).

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