PENTACHLOROPHENOL

CAS number: 87-86-5

Synonyms: Dowicide EC-7, PCP, penchlorol, penta, santophen 20

Chemical formula: C_6HCl_5O

Structural formula: —

Workplace exposure standard (interim)

TWA: **0.5 mg/m^3**

STEL: **—**

Peak limitation: **—**

Notations: **Carc. 2, Sk.**

IDLH: **2.5 mg/m^3**

Sampling and analysis: The recommended value is quantifiable through available sampling and analysis techniques.

Recommendation and basis for workplace exposure standard

An interim TWA of 0.5 mg/m^3 is recommended to protect for irritation of the upper respiratory tract and eyes and reduce the risk of cancer in exposed workers.

Given the limited data available from the primary sources, it is recommended that a review of additional sources be conducted at the next scheduled review to investigate carcinogenic effects.

Discussion and conclusions

Pentachlorophenol (PCP) is a herbicide, fungicide and an insecticide used to control termites. It is also used to preserve wood. Commercial or technical PCP contains approximately 10% contaminants, primarily polychlorinated phenols, polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans and hexachlorobenzene (ACGIH, 2018).

The critical effects of exposure are cancer and irritation of the upper respiratory tract and eyes.

IARC (2019) reported an elevated risk of non-Hodgkin lymphoma (NHL) after exposure to PCP in four occupational cohort studies and in three independent case-control studies. The increased risks for the most highly exposed workers were statistically significant and at least two-fold higher (IARC, 2019). Evidence for mutagenicity is inconclusive and therefore, it is unclear if a non-threshold mechanism for cancer is a critical effect in recommending a TWA.

Irritation to eyes and nose reported in occupational studies at concentrations greater than 1 mg/m^3 with irritation to respiratory tract occurring at 0.3 mg/m^3. Accustomed workers can tolerate up to 2.4 mg/m^3. No further exposure information is provided (ACGIH, 2018). Exposure at 3 mg/m^3 and 30 mg/m^3 in rats and rabbits for four hours a day for four months resulted in only slight changes in liver function, cholinesterase (ChE) activity and blood sugar level (DFG, 1992; ACGIH, 2018; DFG, 1992; NTP, 2014). It is noted that most human exposures relate to technical grade products containing impurities. Comparison studies between technical grade and the pure chemical in animals demonstrate greater toxicity due to the technical grade compound, likely due to impurities (DFG,

1992). For example, a LOAEL of 1.5 mg/kg/day (technical grade) is reported in a one-year study in dogs based on increased liver weight, increased incidence and severity of hepatocellular pigmentation, cytoplasmic vacuolation and chronic inflammation (US EPA, 2010). In comparison, a LOAEL of 10 mg/kg/day (purified) based on liver and kidney pathology in female rats is reported in a two-year study.

The presence of impurities raises concerns regarding interpretation of the data and outcomes of hazard assessment (DFG, 1992). The current SWA TWA of 0.5 mg/m^3 is recommended to be retained in the interim. Insufficient evidence exists to recommend a STEL.

Noting there are inconclusive data regarding genotoxicity and mechanism of carcinogenic action and limits to the exposure data and NHL outcomes. It is recommended that an investigation of additional data sources is undertaken at the next scheduled review to confirm the relevance of carcinogenic effects.

Recommendation for notations

Classified as a category 2 carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). A review of this classification is recommended based on evidence in workers and risk of NHL.

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

A skin notation is recommended as evidence indicates rapid absorption through the skin and reports of acute poisonings in the workplace.

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 0.5 mg/m^3***
ACGIH	***2014***	***TLV-TWA: 0.05 ppm (0.5 mg/m^3) (Inhalable fraction and vapour); TLV-STEL: 0.1 ppm (1 mg/m^3) (Inhalable fraction and vapour)***

TLV-TWA recommended to minimise upper respiratory tract and eye irritation and CNS and cardiac system impairment in exposed workers.

Summary of data:

- TLV-TWA based on nose and eye irritation in workers exposed to >1 mg/m^3
- TLV-STEL is an additional factor to prevent irritation; no specific evidence used.

Human data:

- Rapidly and completely absorbed following oral administration
- Symptoms reported following acute and longer-term inhalation and/or dermal exposure include:
  - increased body temperature, increased respiration and heart rate, progressive neuromuscular weakness, convulsions and possible death from cardiac failure
- Irritation (mainly to eyes and nose) at concentrations >1 mg/m^3; some irritation to respiratory tract (no further information provided but presumably upper respiratory tract) occurred at 0.3 mg/m^3:
  - accustomed workers tolerate up to 2.4 mg/m^3
- Dermal absorption can lead to systemic toxicity and death:
  - numerous cases of death occurring in workers following application of the chemical to wood without wearing gloves
- Conflicting results related to immunological impairment, allergic responses and neurological impairment in workers
- Suggestive but inconsistent evidence of increased risk of lymphohematopoietic cancers or soft tissue sarcoma (from cohort and case-control studies):
  - concurrent exposure to other contaminants and lack of exposure levels confounds results
- No evidence of SCE and/or chromosomal aberrations in studies of workers at wood treatment plants exposed at 1–180 mg/m^3, 3–34 y duration:
  - one study did report a significant increase in peripheral lymphocyte chromosomal aberration in exposed workers.

Animal data:

- LD_{50}: 150–200 mg/kg (rats, oral)
- LD_{50}: 96–330 mg/kg (rats, dermal)
- Calculated dose associated with systemic poisoning by inhalation is 11.7 mg/kg (following 10–20 min exposure to ≈900 mg/m^3 of the sodium salt in aerosol form)
- No dermal sensitisation observed
- No evidence of carcinogenicity in rats fed 200, 400 or 600 ppm in the diet for 2 yr
- Liver is main target organ for toxicity in sub-chronic oral studies:

Source	Year set	Standard
		o increased hepatocyte degeneration in rats at ≥400 ppm (dose range 200–3,200 ppm, 28 d) o liver toxicity in mice at ≥500 ppm (dose range 20–12,500 ppm, 30 d); at 50 ppm (dose 50 or 500 ppm, 90 d) o hepatocellular hypertrophy and vacuolisation in rats at ≥50 ppm (doses 25, 50 or 200 ppm, 90 d) • No sub-chronic or chronic inhalational studies • Evidence of clastogenicity (after metabolic activation) and no evidence of mutagenicity • Positive result in mouse spot test, caused increase in point mutation rate of P53 gene of zebrafish liver cells and tetrachlorohydroquinone metabolite was mutagenic in cultured hamster V79 cells and CHO cells • Genotoxicity not observed in other *in vivo* studies. A skin notation is assigned but insufficient data to recommend a DSEN or RSEN. IARC concluded there is sufficient evidence in animals for carcinogenicity and limited evidence in humans.
DFG	***1992***	***Not assigned***
		MAK is withdrawn due to carcinogenic effects in mice. Summary of additional data: • Technical products containing impurities such as pentachlorodibenzo-*p*-dioxin and hexachlorodibenzo-*p*-dioxin can cause chloracne • Technical grade and pure chemical shown to be embryotoxic or teratogenic • Estimated acute oral lethal dose in humans is ≈30 mg/kg • Clear majority of human exposures relate to technical grade products containing impurities • No unequivocal evidence of chromosome damage in studies of workers involved in production or processing • Comparison studies between technical grade and the pure chemical in animals demonstrate greater toxicity in the technical grade due to impurities • Exposure at 3 mg/m^3 and 30 mg/m^3 in rats and rabbits (4 h/d, 4 mo): o increased liver weights, slight changes in ChE and blood sugar at 3 mg/m^3 o anaemia, leucocytosis, hyperglycaemia, dystrophy of liver cells and some deaths at 30 mg/m^3 • 2 y study with male and female rats, doses of 0, 1, 3, 10 or 30 mg/kg/d (purified technical grade): o NOEL of 10 mg/kg/d (males) and 3 mg/kg/d (females); changes in erythrocyte or leukocyte count, in haemoglobin level or haematocrit, nor were there any detectable changes in organ weights • Technical grade of the chemical; carcinogenic in mice (increased incidence of liver tumours).
SCOEL	***NA***	***NA***
No report.		
OARS/AIHA	***NA***	***NA***
No report.		

Source	Year set	Standard
HCOTN	***NA***	***NA***
No report.		

Secondary source reports relied upon

Source		Year	Additional information
NICNAS	✓	2019	• No industrial uses in Australia; agricultural uses excluded from assessment • No additional information.
IARC	✓	2019	• There is sufficient evidence in humans for the carcinogenicity of pentachlorophenol. • Pentachlorophenol causes NHL • Evaluation of human carcinogenicity data is complicated by contamination with dioxin and furans and other chlorophenols, however, IARC attributed the cancers observed in studies in humans and experimental animals to exposure to pentachlorophenol and not to impurities in pentachlorophenol • An elevated risk of NHL after exposure to pentachlorophenol was reported in four occupational cohort studies and in three independent case– control studies; the increased risks for the most highly exposed workers were statistically significant and at least 2-fold • Sufficient evidence of carcinogenicity in animals • Induces oxidative stress and genotoxicity that can operate in humans • Caused DNA strand breaks in multiple human cell types • Did not induce reverse mutations in the Ames test • Studies in acellular systems reported DNA damage and/or adducts caused by pentachlorophenol in the presence of metabolic activation • Overall evaluation is carcinogenic to humans (Group 1).
NTP	✓	2014	• Observed carcinogenicity in animal studies is not explained by presence of by-products alone; plausible that some by-products contribute to tumour formation • Mechanisms of carcinogenic effects not completely understood but associated with multiple mechanisms of carcinogenesis: metabolism to genotoxic metabolites, oxidative damage, inflammation, cytotoxicity and sustained cell proliferation, inhibition of apoptosis and immunosuppression • Credible evidence of causal relationship between exposure and NHL • Preliminary listing recommendation: reasonably anticipated to be a human carcinogen.

Source		Year	Additional information
US EPA	✓	2010	• Inadequate data to derive inhalation unit risk factor (no sub-chronic or chronic animal inhalation studies) • NOAEL: 3 mg/kg/d and LOAEL: 10 mg/kg/d (based on liver and kidney pathology in female rats; study cited in DFG) • LOAEL: 1.5 mg/kg/d (lowest dose tested, technical grade) (dogs, 1 yr); doses 0, 1.5, 3.5 or 6.5 mg/kg/d; based on increased liver weight, increase in incidence and severity of hepatocellular pigmentation, cytoplasmic vacuolation and chronic inflammation • Considered likely to be human carcinogen, by all routes of exposure.
US NIOSH	✓	2007	• REL =0.5 mg/m^3.

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic?	Insufficient data
Is the chemical carcinogenic with a mutagenic mechanism of action?	Insufficient data

Insufficient data are available to determine if the chemical is a non-threshold based genotoxic carcinogen.

Notations

Source	Notations
SWA	NA
HCIS	Carcinogenicity – category 2
NICNAS	NA
EU Annex	NA
ECHA	NA
ACGIH	Carcinogenicity – A3, Skin
DFG	Carcinogenicity – 2, H (skin)
SCOEL	NA
HCOTN	NA
IARC	NA
US NIOSH	NA

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

Skin notation assessment

Calculation	
Adverse effects in human case study:	yes

Dermal LD_{50} ≤1000 mg/kg:	yes
Dermal repeat-dose NOAEL ≤200 mg/kg:	
Dermal LD_{50}/Inhalation LD_{50} <10:	
In vivo dermal absorption rate >10%:	
Estimated dermal exposure at WES >10%:	
	a skin notation is warranted

IDLH

Is there a suitable IDLH value available?	Yes

Additional information

Molecular weight:	266.35
Conversion factors at 25°C and 101.3 kPa:	1 ppm = Number mg/m^3; 1 mg/m^3 = Number ppm
This chemical is used as a pesticide:	✓
This chemical is a biological product:	☐
This chemical is a by-product of a process:	☐
A biological exposure index has been recommended by these agencies:	✓ ACGIH ✓ DFG ☐ SCOEL

Workplace exposure standard history

Year	Standard
Click here to enter year	

References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the *TLVs® and BEIs® Guidelines section* on the ACGIH website.

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National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2019) Phenol, pentachloro-: Human health tier I assessment – IMAP report.

National Toxicology Program (NTP) (2014) NTP - RoC Monograph on Pentachlorophenol: Cancer Evaluation.

US Environmental Protection Authority (US EPA) (2010) Integrated Risk Information System (IRIS) Chemical Assessment Summary – Pentachlorophenol.

US National Institute for Occupational Safety and Health (NIOSH) (2007) NIOSH Pocket Guide To Chemical Hazards – Pentachlorophenol.