

## PHTHALIC ANHYDRIDE

**CAS number:** 85-44-9

**Synonyms:** 1,3-Isobenzofurandione, phthalic acid anhydride, PAN

**Chemical formula:**  $C_8H_4O_3$

**Structural formula:** —

### Workplace exposure standard (amended)

**TWA:** 0.002 mg/m<sup>3</sup> (0.0003 ppm)

**STEL:** —

**Peak limitation:** —

**Notations:** Sk., DSEN, RSEN

**IDLH:** 60 mg/m<sup>3</sup>

**Sampling and analysis:** There is uncertainty regarding quantification of the recommended value with available sampling and/or analysis techniques.

### Recommendation and basis for workplace exposure standard

A TWA of 0.002 mg/m<sup>3</sup> (0.0003 ppm) is recommended to protect for induction of respiratory sensitisation and asthma in exposed workers.

### Discussion and conclusions

Phthalic anhydride (PAN) is used in organic synthesis for the manufacture of alkyd and epoxy resins, unsaturated polyesters, dyes, pharmaceuticals, plasticisers and fungicides.

Critical effects of exposure are respiratory sensitisation, asthma and possible irritation. Exposure to PAN in humans can cause or is associated with sensitisation, elevated immunoglobulin E (IgE) and Immunoglobulin G (IgG), occupational asthma, rhinitis, conjunctivitis, chronic bronchitis, respiratory irritation and contact urticaria. Sensitisation in workers rarely results following an average exposure below 0.01 mg/m<sup>3</sup>. At these concentration, rhinitis, conjunctivitis and rhinoconjunctivitis occur in a substantial proportion of workers exposed. However, no cases of asthma are found (ACGIH, 2018; SCOEL, 2011). In a study of workers with average full-day exposures at 0.4 mg/m<sup>3</sup> combined with peak exposures of up to 13 mg/m<sup>3</sup>, 24 percent workers had work-related rhinitis, 18 percent had asthma and 11 percent developed chronic bronchitis (HCOTN, 2010). A LOAEL of 0.5 mg/m<sup>3</sup> in guinea pigs is reported for sensitised animals and production of allergic antibodies (ACGIH, 2018).

A TWA of 0.002 mg/m<sup>3</sup> (0.0003 ppm) by ACGIH (2018) is recommended. This TWA is expected to protect for respiratory sensitisation, asthma and possible irritation in exposed workers.

Insufficient data are available to recommend a STEL.

### Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Classified as a skin sensitiser and respiratory sensitiser according to the GHS.

A skin notation is recommended due to evidence of dermal absorption and contribution to adverse systemic effects.

DRAFT

## APPENDIX

### Primary sources with reports

Source	Year set	Standard
<b>SWA</b>	<b>1991</b>	<b>TWA: 1 ppm (6.1 mg/m<sup>3</sup>)</b>
<b>ACGIH</b>	<b>2017</b>	<b>TLV-TWA: 0.0003 ppm (0.002 mg/m<sup>3</sup>); TLV-STEL: 0.0009 ppm (0.005 mg/m<sup>3</sup>)</b>
<p>TLV-TWA is recommended to protect against the induction of sensitisation.</p> <p>TLV-STEL is recommended to keep exposures below short-term exposures found in studies with high asthma prevalence.</p> <p>Summary of data:</p> <ul style="list-style-type: none"> <li>Respiratory tract irritant and sensitiser associated with asthma, conjunctivitis, rhinitis, chronic bronchitis, urticaria and allergic dermatitis</li> <li>The TLV–TWA intended to protect against the induction of sensitisation and is based on worker studies that indicate average exposures below 0.01 mg/m<sup>3</sup> rarely result in sensitisation; may not necessarily protect against an allergic reaction in previously sensitised individuals.</li> </ul> <p>Human data:</p> <ul style="list-style-type: none"> <li>Human studies identified exposure can cause or is associated with sensitisation, elevated IgE and IgG, occupational asthma (immediate, late or both), rhinitis, conjunctivitis, chronic bronchitis, respiratory irritation and contact urticaria</li> <li>A cohort study involving 285 past and present workers from 3 factories (# 1,3 &amp; 4); mixed exposure to PAN, maleic anhydride (MA) and trimellitic anhydride (TMA); based on production and work areas, more PAN exposure than MA &amp; TMA; respirators worn when manually loading MA &amp; TA; no respirators loading PAN; following are PAN concentrations: <ul style="list-style-type: none"> <li>exposure at time of study was TWA of 0.009–0.062 mg/m<sup>3</sup>; at current levels, low risk for developing sensitisation (measured by skin prick test); may be some risk of developing respiratory symptoms</li> <li>past exposures range from 0.0004–2.5 mg/m<sup>3</sup></li> <li>geometric mean exposures for the three factories were 2.2; 4.5; and 5.5 µg/m<sup>3</sup></li> <li>124 workers from factory #1 exposure at time of study was TWA of 0.009 mg/m<sup>3</sup>; past exposure 0.0004–2.5 mg/m<sup>3</sup>; 0% immediate skin prick reaction to AA-HAS; 5.0% work-related respiratory symptoms</li> <li>69 workers from factory #2 exposure at time of study was TWA of 0.062 mg/m<sup>3</sup>; past exposure 0.002–0.14 mg/m<sup>3</sup>; 1.6% immediate skin prick reaction to AA-HAS (none currently exposed); 7.8% work-related respiratory symptoms</li> <li>92 workers from factory #2 exposure at time of study was TWA of 0.012 mg/m<sup>3</sup>; past exposure 0.002–0.06 mg/m<sup>3</sup> (none currently exposed); 3.5% immediate skin prick reaction to AA-HAS; 11.6% work-related respiratory symptoms</li> <li>evidence of increased respiratory symptoms</li> <li>34 (85) identified respiratory symptoms occurred after starting work in acid anhydride area; 21 of which in mixed exposure</li> <li>8/12 workers who were sensitised worked in the factory with TMA exposures only; not currently exposed, but likely exposed to higher levels in the past</li> <li>PAM is a weaker sensitiser than TMA</li> </ul> </li> </ul>		



Source	Year set	Standard
		<ul style="list-style-type: none"> <li>Cohort of 60 workers in 2 plants exposed to PAN for 5–30 min up to twice a day; average concentration 6.6 mg/m<sup>3</sup> (n= 24) per event; corresponds to 8 h TWA of 0.4 mg/m<sup>3</sup> (heavily exposed group); &lt;0.1 mg/m<sup>3</sup> for other tasks (slightly exposed group): <ul style="list-style-type: none"> <li>35 workers in heavily exposed group; 13 yr exposure</li> <li>25 workers in slightly exposed group; 12 yr exposure</li> <li>controls from other facilities with no exposure</li> <li>symptoms of rhinitis and/or conjunctivitis were frequently reported by heavily exposed workers (69%); 0% reported in non-exposed workers</li> <li>6 (17%) workers with chronic bronchitis among the highly exposed group; 1 (4%) among the slightly exposed group</li> <li>no difference between the two exposure groups regarding total serum level of IgE, IgG, and IgM; or PAN specific IgE and IgM</li> <li>subjects with symptoms did not differ from subjects without symptoms in total serum IgE, IgM, IgA, or specific IgE and IgM; 1 worker with asthma had an increased specific IgE level</li> </ul> </li> <li>Case report of 1 chemical worker experienced rhinorrhoea, postnasal drip, and wheezing that began several months after beginning work involving PA use; symptoms increased with severity over time but disappeared on weekends and on vacation; positive in scratch tests with PA; bronchial challenge testing resulted in significant, immediate, decrease in Vmax<sub>50</sub></li> <li>Contact urticaria; urticaria and skin irritation have been reported in human studies</li> <li>3 urticaria cases; exposures: 1. to powder form; 2. welding on painted pipes releasing PAN, and 3. mixing PAN and MA in polyester production; all 3 workers diagnosed with anhydride rhinitis; the packer (first case) diagnosed with anhydride asthma</li> <li>Case reports of allergic dermatitis reported with cosmetics containing PAN; individuals patch tested responded positively to PAN; results were confounded by the presence of TMA.</li> </ul> <p>Animal data:</p> <ul style="list-style-type: none"> <li>Acute LD<sub>50</sub>: 800–1,600 mg/kg (rat, oral)</li> <li>Mediates the induction of respiratory sensitisation through a Th2 type response as demonstrated in laboratory animals</li> <li>Closed patch test in guinea pigs and mouse ear swelling test demonstrated PAN as a moderate sensitizer causing delayed (Type IV) allergic contact dermatitis</li> <li>LOAEL of 0.5 mg/m<sup>3</sup> in guinea pigs; sensitised animals and produce allergic antibodies; no further information</li> <li>Female guinea pigs exposed at 0, 0.5, 1.0 and 5.0 mg/m<sup>3</sup> for 3 h/d for 5 d; 2 wk after last exposure, groups challenged with 2.0 mg/m<sup>3</sup> (phthalic anhydride-guinea pig serum albumin [PA-GPSA]) or 5.0 mg/m<sup>3</sup> dust for 30 min: <ul style="list-style-type: none"> <li>no significant differences were found in the respiratory rate or respiratory pressure in animals challenged with PA dust</li> <li>animals challenged with PA-GPSA; 1 animal in the 0.5 mg/m<sup>3</sup> exposed group (n= 8) and 4 animals in the 5 mg/m<sup>3</sup> exposed group (n= 8) experienced significant increases in respiratory rate compared to controls</li> <li>respiratory pressure was significantly increased in 1 animal in the 0.5 mg/m<sup>3</sup> group, 1 animal in the 1.0 mg/m<sup>3</sup> group and 3 animals in the 5 mg/m<sup>3</sup> exposed group</li> </ul> </li> <li>No indication of carcinogenicity in animal studies.</li> </ul>

Source	Year set	Standard
<b>DFG</b>	<b>1995</b>	<b>Not assigned</b>
<p>Insufficient information to establish MAK.</p> <p>Summary of additional information:</p> <ul style="list-style-type: none"> <li>• Previous MAK value of 1 mg/m<sup>3</sup> recommended to reduce the extent of sensitisation</li> <li>• Sensitising and irritating effects in the respiratory passages cannot always be differentiated</li> <li>• Inadequately documented animal study; exposure at 0.5 mg/m<sup>3</sup> caused effects in the lungs which were interpreted to be allergenic to the respiratory tract.</li> </ul>		
<b>SCOEL</b>	<b>2011</b>	<b>Not assigned</b>
<p>Summary of additional data:</p> <ul style="list-style-type: none"> <li>• No reason provided for no TWA assigned; assumed lack of enough data</li> <li>• Considers allergic respiratory effects being persistent, as the most severe effects</li> <li>• IgE-mediated asthma and rhinitis has been proven, but other unknown mechanisms may be involved</li> <li>• Experimental animal studies have demonstrated a weak skin sensitising effect; skin sensitisation has been reported in humans</li> <li>• Rhinitis, conjunctivitis and rhinoconjunctivitis occurred in a substantial proportion of workers exposed at &lt;0.1 mg/m<sup>3</sup> (TWA) (cited by ACGIH, 2018); no cases of asthma were found</li> <li>• Considers human dose-response data as poor</li> <li>• Studies available do not indicate genotoxic or carcinogenic effects.</li> </ul>		
<b>OARS/AIHA</b>	<b>NA</b>	<b>NA</b>
No report.		
<b>HCOTN</b>	<b>2010</b>	<b>NA</b>
<p>Summary of additional data:</p> <ul style="list-style-type: none"> <li>• Evaluation of data for group of cyclic acid anhydrides including PAN; considers the available data not suitable for deriving a health-based recommended OEL or reference value for PAN</li> <li>• 118 workers in 4 plants; 24% had work-related rhinitis, 18% asthma, and 11% chronic bronchitis; latency period before the onset of symptoms varied between 1 mo and 16 yr; work-related respiratory symptoms reported at average full-day exposure to 0.4 mg/m<sup>3</sup> combined with peak exposures to up to 13 mg/m<sup>3</sup></li> <li>• Considers available data not suitable for deriving a health-based recommended OEL (HBROEL) or reference value for PAN.</li> </ul>		

## Secondary source reports relied upon

Source	Year	Additional information
ECHA	✓ 2019	<ul style="list-style-type: none"> <li>• No additional data available.</li> </ul>

## Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic?

No

**The chemical is not a non-threshold based genotoxic carcinogen.**

## Notations

Source	Notations
SWA	Sen
HCIS	Skin sensitisation – category 1, Respiratory sensitisation – category 1
NICNAS	Skin sensitisation, Respiratory sensitisation
EU Annex	NA
ECHA	Resp. Sens. 1, Skin Sens. 1
ACGIH	Skin, DSEN, RSEN, Carcinogenicity – A4
DFG	Sa (respiratory sensitiser)
SCOEL	Sensitisation (dermal), Sensitisation (respiratory)
HCOTN	—
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 <sub>50</sub> ≤ 1000 mg/kg:	
Dermal repeat-dose NOAEL ≤ 200 mg/kg:	
Dermal LD <sub>50</sub> /Inhalation LD <sub>50</sub> < 10:	
<i>In vivo</i> dermal absorption rate > 10%:	
Estimated dermal exposure at WES > 10%:	
<b>a skin notation is warranted</b>	

## IDLH

Is there a suitable IDLH value available?

Yes

## Additional information

Molecular weight:	148.10
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 6.05 mg/m <sup>3</sup> ; 1 mg/m <sup>3</sup> = 0.17 ppm
This chemical is used as a pesticide:	<input type="checkbox"/>
This chemical is a biological product:	<input type="checkbox"/>
This chemical is a by-product of a process:	<input type="checkbox"/>
A biological exposure index has been recommended by these agencies:	<input type="checkbox"/> ACGIH <input type="checkbox"/> DFG <input type="checkbox"/> SCOEL

## Workplace exposure standard history

Year	Standard
Click here to enter year	

## References

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

Deutsche Forschungsgemeinschaft (DFG) (2009) phthalic anhydride – MAK value documentation.

European Chemicals Agency (ECHA) (2019) phthalic anhydride – REACH assessment.

EU Scientific Committee on Occupational Exposure Limits (SCOEL) (2011) Recommendation from the Scientific Committee on Occupational Exposure Limits for phthalic anhydride. SCOEL/SUM/152.

Health Council of the Netherlands (HCOTN) (2010) cyclic acid anhydrides. Health-based calculated occupational cancer risk values. The Hague: Health Council of the Netherlands; publication no. 2010/02OSH.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2013) 1,3-Isobenzofurandione: Human health tier II assessment – IMAF report.

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – phthalic anhydride.