(b) (4)

Phenylacetaldehyde

Toxicity monograph (with existing HCVs)

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INTRODUCTION

(b) (4) was asked to produce a toxicity monograph of phenylacetaldehyde (CAS RN[1] 122-78-1), focusing on the inhalation route of exposure. Data on the inhalation of tobacco smoke containing the ingredient (if available) have not been included in this monograph.

EXPERTISE

(b)) was founded[2] in 1961 to provide independent, high-quality research, information and advice on chemical toxicology to industry and governmental departments. Its risk assessors have been working together for many years (more than 40 years in some instances) and have a record of objectivity and scientific excellence. All senior and principal scientists in the current team are accredited and listed in the European (Eurotox) and UK Royal Society of Biology/British Toxicology Society Registers of Toxicologists and are thus bound by their specific codes of conduct.

TOXICITY DATA SEARCH CRITERIA

(b) (4) access to a wide-range of data sources, including the unique (b) (4) databank (see the Appendix for details), PubMed, the TOXNET system of databases and databanks (which includes Toxline (the toxicity subset of Medline), HSDB, GENETOX, DART, CCRIS, IRIS, ITER and CPDB), eChemPortal and RTECS. All searches were conducted in June 2016 using the CAS RN and (in PubMed only) name identified below.

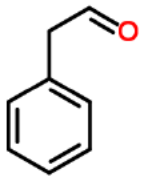
The data summarised in this report refers to the unheated form unless otherwise stated.

IDENTIFICATION, REACH STATUS AND EU CLASSIFICATION

Identifier / status	
Name	Phenylacetaldehyde
Synonym(s)	Benzeneacetaldehyde 2-Phenylethanal
CAS RN	122-78-1
FEMA	2874

[1] Chemical Abstracts Service Registry Number.

[2] (b) (4)

EC number	204-574-5
REACH registration number	Not REACH registered
Molecular formula	C_8H_8O
Molecular weight	120.2
Structure	
Classification, according to EU CLP (EU 1272/2008)	**Harmonised classification** None available
	REACH joint registrants None available

ADME

Phenylacetaldehyde is oxidised to phenylacetic acid *in vivo*, which is conjugated and excreted primarily in the urine (Williams, 1959).

TOXICOLOGY

LOCAL EFFECTS

Respiratory tract irritation

No substance-specific data were identified.

Skin irritation

Human

Skin irritation reactions were observed in 2/25 subjects following application of phenylacetaldehyde (2% in petrolatum) under an occluded patch for 48 hours (Kligman, 1971). [See also Skin sensitisation section.]

No irritation was observed in two panels [different from that tested by Kligman (1971), as described above] of 25 and 23 subjects who were treated with 48-hour occluded patches of phenylacetaldehyde (2% in petrolatum) (Epstein, 1973; Kligman, 1971). [See also Skin sensitisation section.]

Non-human

No substance-specific data were identified.

Eye irritation

No substance-specific data were identified.

Other local effects

No substance-specific data were identified.

SENSITISATION AND INTOLERANCE

Respiratory tract sensitisation

No substance-specific data were identified.

Skin sensitisation

Human

Four maximisation tests[3] were conducted on four separate panels with 2% phenylacetaldehyde in petrolatum. 11/25, 4/25, 12/23 and 2/25 sensitisation reactions were observed in each of the panels, respectively. In the panel of 23, seven of the twelve who reacted were re-tested 4 months later with a fresh sample, confirming the initial sensitisation reaction (Epstein, 1973; Kligman, 1971; Maibach, 1971). [See also Skin irritation section.]

No sensitisation reactions were observed in repeated-insult patch tests on 56 subjects using eleven 24-hour exposures with 2% phenylacetaldehyde (Maibach, 1971), or on 50 subjects using fifteen 24-hour exposures with the same concentration (Shelanski, 1971).

When a 0.5% solution of phenylacetaldehyde was applied to the skin of 275 patients under a 48-hour occluded patch (and scored 24 hours after patch removal), four patients had a positive reaction at 24 hours, and a further two reported a flare-up after 8 or 12 days. The latter patients were re-tested at lower concentrations and reacted to 0.01% but not 0.001% phenylacetaldehyde (Fregert, 1970).

1.1% of 182 patients reportedly displayed a positive patch-test reaction to phenylacetaldehyde (2% in petrolatum) (Malten *et al.*, 1984).

A man was accidentally splashed with pure phenylacetaldehyde on the face, trunk and arms at his workplace, resulting in erythema with papules and pruiginous [itchy] plaques which later spread to other parts of his body. Three months later he was patch tested with phenylacetaldehyde (0.5, 1 and 2% in petrolatum), resulting in severe sensitisation reactions to the 1 and 2% solutions; a moderate reaction to the 0.5% concentration (Sanchez-Politta *et al.*, 2007).

Non-human

In a LLNA[4], phenylacetaldehyde (25 µL; 0, 1, 2.5, 5, 10 or 25% in acetone/olive oil) was applied to the dorsum of both ears of CBA/Ca mice (4/group) on three consecutive days and, five days after the initial exposure, [^{3}H]methyl thymidine was intravenously injected into a tail vein. After five hours, the auricular lymph node cells were isolated, pooled for each group and the radioisotope uptake into cells was counted as a measure of cell proliferation. The SI[5]

[3] The maximisation test procedure typically involves an initial induction phase of five 48-hour covered patch tests, followed 10-14 days later by a 48-hour covered challenge patch.
[4] Local lymph node assay.
[5] Stimulation index.

was determined to be 0.73, 1.76, 7.84, 8.76 and 18.96 at 1, 2.5, 5, 10 and 25%, respectively. An EC3 value[6] of 3% was subsequently calculated, indicating that phenylacetaldehyde is a moderate skin sensitiser (Basketter *et al.*, 2001).

In another LLNA (analogous to the methods described above), phenylacetaldehyde at concentrations of 25, 50 or 100% was applied to the ears of CBA/J mice (4/group). The SI was 15.5, 23.8 and 24.1 and 25, 50 and 100%, respectively. An EC3 value of 8.8% was calculated, indicating moderate skin sensitisation (Ryan *et al.*, 2000).

An EC3 value of 4.7% was calculated from the results of another LLNA with CBA/Ca mice, therefore phenylacetaldehyde caused moderate sensitisation (Basketter *et al.*, 2002). [No further detail given in the original source, but presumably the assay was conducted to the same protocol as described above.]

Positive reactions for skin sensitisation were reported in a Buehler test[7] with phenylacetaldehyde in Vaseline (5% induction; 1% challenge) in guinea pigs (Majeti and Suskind, 1976/1977).

Other

According to the ECHA Annex III Inventory[8], phenylacetaldehyde is a "suspected skin sensitiser" as "protein binding alerts for skin sensitisation by OASIS v1.3 gives an alert for skin sensitisation", and using (Q)SAR[9] information from the VEGA CAESAR skin sensitisation model (experimental value) (ECHA, 2016a).

Oral allergy/intolerance

No substance-specific data were identified.

INHALATION TOXICITY STUDIES

Single dose toxicity

Human

No substance-specific data were identified.

[6] OECD test guideline 429 defines stimulation index (SI) as the ratio of lymphocyte proliferation in a treated group to that in the vehicle control group. An SI of ≥3 is considered positive and the estimated concentration three (EC3) is the estimated concentration of a test substance needed to produce an SI of 3. ECETOC definitions of potency are: extreme sensitizer (EC3 value <0.1); strong sensitizer (EC3 >0.1 - ≤1); moderate sensitizer (EC3 value >1 - <10; and weak sensitizer (EC3 value >10).

[7] The Buehler test usually involves application of an irritant dose to the shaved skin on days 0, 6-8 and 13-15 under an occluded patch, followed on day 27-29 by the application of a non-irritant challenge dose, with scoring at 30 and 56 hours after patch removal.

[8] ECHA has compiled "an inventory of substances likely to meet the criteria of Annex III to the REACH regulation". These are a) substances predicted (i.e. by the use of QSARs or other evidence) to likely meet criteria for CMR category 1A or 1B or Annex XIII criteria (i.e. PBT and vPvB); b) substances with dispersive or diffuse use(s) AND predicted to likely meet criteria for any health or environmental hazard classes or differentiations under CLP Regulation" (ECHA, 2016b).

[9] (Quantitative) Structure-Activity Relationship.

Non-human

An LC_{50} value[10] of 2000 mg/m³ and a TCLo[11] of 100 mg/m³ have been reported in the mouse [duration of exposure not stated], the associated toxic effects being reduced activity and behavioural changes (Anon., 1995).

Repeated dose toxicity

No substance-specific data were identified.

TOXICITY STUDIES – OTHER EXPOSURE ROUTES

Single dose toxicity

Human

No substance-specific data were identified.

Non-human

The oral LD_{50} value[12] in the rat has been reported as 1550 mg/kg bw (Moreno, 1977) and in rats, mice and guinea pigs the LD_{50} was determined to be 3890 mg/kg bw after the rodents were dosed with a 20-40% solution of phenylacetaldehyde in sunflower-seed oil by oral gavage [no further details given in citing source] (Zaitsev and Rakhmanina, 1974).

Up to 5000 mg/kg bw phenylacetaldehyde was applied to the skin of rabbits, the dermal LD_{50} reported as >5000 mg/kg bw [no further details given in citing source] (Moreno, 1977).

Repeated dose toxicity

No substance-specific data were identified.

GENOTOXICITY

Mammals (*in vivo*)

No substance-specific data were identified.

Mammalian cells (*in vitro*)

No substance-specific data were identified.

Micro-organisms

In a limited bacterial reverse mutation (Ames) assay, conducted according to the spot-method, *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537 were exposed to 3 µmol/plate [0.36 mg/plate], both in the presence and absence of S9[13]. A negative result for mutagenicity was reported, although the substance was seen to precipitate [which could have made it difficult to evaluate the results] (Florin *et al.*, 1980).

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[10] Lethal Concentration 50, i.e. the concentration that is lethal to 50% of the exposed group.

[11] Toxic Concentration Low, i.e. "the lowest concentration of a substance in air to which humans or animals have been exposed for any given period of time that has produced any toxic effect in humans or animals, or produced tumorigenic, reproductive, or multiple dose effects in animals".

[12] Lethal Dose 50, i.e. the dose that is lethal to 50% of the exposed group.

[13] Induced mammalian liver post-mitochondrial fraction used for metabolic activation.

In another limited Ames test, conducted according to the pre-incubation method, no mutagenicity was observed when *S. typhimurium* (strains TA98, TA100 and TA104) and *Escherichia coli* (stain WP2uvrA/pKM101) were exposed to unspecified concentrations of phenylacetaldehyde, with and without S9 (Kato *et al.*, 1989). [No further details were specified in the brief abstract. Only three strains of *S. typhimurium* were used; current guidelines recommend the use of 4 or 5 strains.]

Other
No substance-specific data were identified.

CARCINOGENICITY

Human
No substance-specific data were identified.

Non-human
No substance-specific data were identified.

Other
According to the ECHA Annex III Inventory, phenylacetaldehyde is a "suspected carcinogen" using (Q)SAR information from the ISS VEGA carcinogenicity model[14] (moderate reliability) (ECHA, 2016a).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Human
No substance-specific data were identified.

Non-human
No substance-specific data were identified.

Other
According to the ECHA Annex III Inventory, phenylacetaldehyde is "suspected toxic to reproduction" using the Toolbox profiler DART scheme v.1.0[15] which gives a structural alert for toxicity to reproduction (ECHA, 2016a).

[14] The VEGA ISS model "provides a qualitative prediction of carcinogenicity potency according to specific requirements of Chemical regulation. The model has been built as a set of rules, taken from the work of Benigni and Bossa (ISS) as implemented in the software ToxTree version 2.6. The model implement[s] all the rules related to carcinogenicity and does not implement the full decision tree used by ToxTree. If at least one carcinogen rule is matching with the given compound, a "carcinogen" prediction is given; otherwise, a "non-carcinogen" prediction is given. The training set for the model has been extracted from ToxTree, and consists of 797 compounds" (ECHA, 2016b).

[15] "Extracted from the OECD QSAR Toolbox" (ECHA, 2016b).

CARDIOPULMONARY EFFECTS[16]

Phenylacetaldehyde was classified as a depressor on the basis of its effects on the blood pressure of dogs given single doses of 3.4-40 mg/kg bw. An initial large, rapid fall in blood pressure followed by a smaller, longer rise was typically observed (Wingard *et al.*, 1955). Additionally, the substance was reported to have decreased blood pressure by 8 mm [Hg] for 40 s in one dog (Romano *et al.*, 1954).

EXISTING HEALTH CRITERIA VALUES (HCVs)

No existing HCVs were identified.

JECFA has concluded that its use as a food flavouring is of "no safety concern" at current estimated intakes of 40 and 60 µg/day in the US and Europe, respectively (JECFA, 2003). In a more recent assessment, EFSA concurred with JECFA's conclusion of "no safety concern" of phenylacetaldehyde when used as a food flavour at the estimated level of intake of 37 and 60 µg/day in the US and Europe, respectively (EFSA, 2009).

Phenylacetaldehyde was determined to be generally recognised as safe (GRAS) by the FEMA[17] Expert Panel in 1993, when they assessed phenethyl alcohol, aldehyde, acid and related acetals and esters as flavour ingredients (Adams *et al.*, 2005). Their judgement was based on the groups self-limiting properties in food, rapid absorption, metabolic detoxication and excretion by humans and other mammals, and the Panel noted that there was a wide margin of safety between their conservative estimates of intake (56 µg/capita/day for phenylacetaldehyde) and the NOAELs[18] from (sub)chronic studies as well as a lack of mutagenic potential for all of the assessed substances (Adams *et al.*, 2005).

REFERENCES

Adams TB, Cohen SM, Doull J, Feron VJ, Goodman JI, Marnett LJ, Munro IC, Portoghese PS, Smith RL, Waddell WJ and Wagner BM (2005). The FEMA GRAS assessment of phenethyl alcohol, aldehyde, acid, and related acetals and esters used as flavor ingredients. Food and Chemical Toxicology 43, 1179-1206.

Anon. (1995). Toksikologicheskii Vestnik. 36 [no further bibliographic details; cited in RTECS, 2015.]

Basketter DA, Wright ZM, Warbrick EV, Dearman RJ, Kimber I, Ryan CA, Gerberick GF and White IR (2001). Human potency predictions for aldehydes using the local lymph node assay. Contact Dermatitis 45, 89-94.

Basketter DA, Evans P, Gerberick GF and Kimber IA (2002). Factors affecting thresholds in allergic contact dermatitis: safety and regulatory considerations. Contact Dermatitis 47, 1-6.

[16] Potential effects on the heart, blood vessels and/or respiratory tract.
[17] Flavor and Extract Manufacturers Association
[18] No observed adverse effect levels.

ECHA (2016a). European Chemicals Agency. Annex III Inventory. Last updated 18 May 2016. Accessed 14 June 2016. http://echa.europa.eu/information-on-chemicals/annex-iii-inventory

ECHA (2016b). European Chemicals Agency. Preparation of an inventory of substances suspected to meet REACH Annex III criteria. Technical documentation. 18 May 2016. http://echa.europa.eu/documents/10162/22332820/annex_iii_preparation_inventory_en.pdf

EFSA (2009). European Food Safety Authority. Scientific Opinion of the Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF). Flavouring Group Evaluation 53, Revision 1 (FGE.53Rev1): Consideration of phenethyl alcohol, aldehyde, acid and related acetals and esters evaluated by JECFA (59th meeting) and structurally related to phenethyl alcohol, aldehyde, esters and related phenylacetic acid esters evaluated by EFSA in FGE.14Rev1 (2009) and one phenoxyethyl ester evaluated in FGE.23Rev1 (2008). EFSA Journal 1024, 1-42. http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/1024.pdf

Epstein WL (1973). Report to RIFM, 29 June and 9 October [cited in Opdyke, 1979].

Florin I, Rutberg L, Curvall M and Enzell CR (1980). Screening of tobacco smoke constituents for mutagenicity using Ames' test. Toxicology 15, 219-232.

Fregert S (1970). Sensitization to phenylacetaldehyde. Dermatologica 141, 1-14.

JECFA (2003). Safety evaluation of certain food additives. Phenylethyl Alcohol, Aldehyde, Acid and Related Acetals and Esters and Related Substances. Prepared by the fifty-ninth meeting of the Joint FAO/WHO Expert Committee on Food Additives. WHO Food Additives Series 50. World Health Organization, Geneva. http://www.inchem.org/documents/jecfa/jecmono/v50je11.htm

Kato F, Araki A, Nozaki K and Matsushima T (1989). Mutagenicity of aldehydes and diketones. Mutation Research 216, 366-367.

Kligman AM (1971). Reports to RIFM, 20 April and 9 June [cited in Opdyke, 1979].

Maibach HI (1971). Report to RIFM, September [cited in Opdyke, 1979].

Majeti VA and Suskind RR (1976/1977). The sensitisation activity of three aroma aldehydes and inhibition by specific chemical agents. Reports to RIFM, 16 January 1976, 7 January 1977 and 1 November 1977 [cited in Opdyke, 1979].

Malten KE, van Ketel WG, Nater JP and Liem DH (1984). Reactions in selected patients to 22 fragrance materials. Contact Dermatitis 11, 1-10 [cited in SCCS, 2012].

Moreno OM (1977). Report to RIFM, 7 February [cited in Opdyke, 1979].

Opdyke DLJ (1979). Monographs on Fragrance Raw Materials: Phenylacetaldehyde. Food and Cosmetics Toxicology 17, 377.

Registry of Toxic Effects of Chemical Substances, established by NIOSH (US National Institute for Occupational Safety and Health), 2015.

Romano C, Meyers FH and Anderson HH (1954). Pharmacological relationship between aldehydes and arterenol. Archives Internationales de Pharmacodynamie et de Thérapie 99, 378-398 [cited in JECFA, 2003].

Ryan CA, Gerberick GF, Cruse LW, Basketter DA, Lea L, Blaikie L, Dearman RJ, Warbrick EV and Kimber I (2000). Activity of human contact allergens in the murine local lymph node assay. Contact Dermatitis 43, 95-102.

Sanchez-Politta S, Campanelli A, Pashe-Koo F, Saurat JH and Piletta P (2007). Allergic contact dermatitis to phenylacetaldehyde: a forgotten allergen? Contact Dermatitis 56, 171-172.

SCCS (2012). Scientific Committee on Consumer Safety. Opinion on fragrance allergens in cosmetic products. Opinion adopted by the SCCS at its 15th plenary meeting of 26-27 June 2012. European Commission, SCCS/1459/11. http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_102.pdf

Shelanski MV (1971). Report to RIFM, 30 August [cited in Opdyke, 1979].

Williams RT (1959). Detoxication Mechanisms—The Metabolism and Detoxication of Drugs, Toxic Substances and Other Organic Compounds, 2nd Ed., London, Chapman & Hall [cited in JECFA, 2003].

Wingard C, Hitchcock P and Teague RS (1955). A survey of aldehydes with respect to their action on the blood pressure. Archives Internationales de Pharmacodynamie et de Thérapie 102, 65-84 [cited in JECFA, 2003].

Zaitsev AN and Rakhmanina NL (1974). Toxic properties of phenylethanol and cinnamic alcohol derivatives. Voprosy Pitaniia 5, 48-53 [cited in Opdyke, 1979].

APPENDIX: The(b) (4) database and databank

(b) (4)

(b) (4) includes information from peer-reviewed toxicology and nutrition journals as well as secondary sources and websites. In addition to primary literature on the health effects of chemicals, ((b) covers official publications and evaluations issued by authoritative groups including:

- WHO/IPCS reports and evaluations (including CICADs and EHCs, and IARC, JECFA and JMPR monographs), and the WHO Air Quality and Drinking-Water Quality Guidelines
- OECD SIDS dossiers/SIARS
- IUCLID data sets
- EU Risk Assessment Reports
- EU expert committee opinions (including EU scientific committees, and EFSA scientific panels) and other reports from EU agencies and institutes etc (including ECHA, ECVAM, EMA and CPS&Q)
- ECETOC, HERA, Council of Europe and other pan-European programmes
- UK government agency (including Defra, EA, FSA, DoH, HSE, HPA, PSD and VMD) and advisory committee (e.g. COT, COM, COC, ACNFP, SACN, ACP, ACAF, VPC, VRC and ACRE) reports and evaluations
- Opinions from other UK organisations such as the Royal Society
- US agency reports and evaluations (EPA, ATSDR, FDA, NTP, OSHA, NCEA, CFSAN, CERHR, NIEHS, CDC, OEHHA and ACGIH)
- Health Canada evaluations
- BUA, DFG, BG Chemie and BfR reports and monographs
- Gezondheidsraad opinions, including those from its various committees such as DECOS
- RIVM reports
- Danish EPA reviews
- Reports and other information provided by Swedish governmental organisations, including the National Food Administration and the Swedish Chemicals Agency
- Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals
- Australian agency reviews including NICNAS Priority Existing Chemical Assessments, APMVA reports and (jointly with New Zealand) FSANZ assessments
- Japanese Chemical Industry Ecology-Toxicology & Information Center reports
- CIR, RIFM and other specialist industry groups
- (b) Toxicity Profiles