European Commission

Recommendation from the Scientific Committee on Occupational Exposure Limits for 2-Phenylpropane (Cumene)

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Employment,
Social Affairs
and Inclusion

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8-hour TWA:	10 ppm (50 mg/m^3)
STEL (15-min):	50 ppm (250 mg/m^3)
BLV:	7 mg 2-phenyl-2-propanol/g creatinine *(sampled within 2 hours post shift)*
Additional categorisation:	SCOEL carcinogen group D (non-genotoxic carcinogen)
Notation:	Skin

This evaluation is an update of an earlier assessment by this committee from 1993 and is based on ACGIH (2001), ECB (2000 and 2001), EPA (1997), Gardner (1994), Greim (1996), NTP (2009 and 2012a,b), WHO (1999), the references cited in these reviews and a literature survey by SCOEL performed in 2012.

1. Substance identification, physico-chemical properties

Chemical name: 2-Phenylpropane
Synonyms: Cumene; propylbenzene; isopropylbenzene; (1-methylethyl)benzene
Molecular formula: C_9H_{12}
Structural formula:
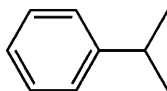
EC No.: 202-704-5
CAS No.: 98-82-8
Index No.: 601-024-00-X
Molecular weight: 120.19 g/mol
Boiling point: 152.7 °C
Melting point: -96.0 °C
Vapour pressure (20 °C): 4 hPa
Conversion factors: 1 ppm = 5 mg/m^3
(20 °C, 101.3kPa) 1 mg/m^3 = 0.2 ppm

EU classification:

Flam. Liq. 3	H226	Flammable liquid and vapour
Asp. Tox. 1	H304	May be fatal if swallowed and enters airways
STOT SE 3	H335	May cause respiratory irritation
Aquatic Chronic 2	H411	Toxic to aquatic life with long lasting effects

2-Phenylpropane is a clear, colourless liquid with a strong aromatic odour. The boiling point of the substance is 152.7 °C and the vapour pressure is 4.96 hPa at 20 °C. 2-Phenylpropane is almost insoluble in water, but is soluble in most organic solvents. The log P_{OW} is 3.55. The substance has a flash point of 39 °C (closed cup) and a density of 0.86 g/cm^3 at 20 °C (ACGIH 2001, ECB 2000).

2. Occurrence/use and occupational exposure

2-Phenylpropane is found in crude oil, gasoline, solvents, plants (essential oils), food and cigarette smoke. Other sources include vulcanisation of rubber, jet engine exhaust, outboard motor operation, solvent use, paint, iron and steel manufacturing, pharmaceutical production, textile plants, paving and roofing, mining, organics and plastics manufacturing, electroplating, and pulp and paper production (HSDB 2005).

2-Phenylpropane is used for the synthesis of acetone and phenol, and is also used as a catalyst for acrylic polyester resins and as a solvent in the automobile and printing industries. It has been recommended as a substitute for benzene for many industrial applications (NTP 2009). In the atmosphere, 2-phenylpropane exists as a vapour and is primarily degraded by reactions with hydroxyl radicals; it is not readily susceptible to photolysis or ozone oxidation. 2-Phenylpropane adsorbs strongly to soils and is unlikely to leach to groundwater. It will volatilise from dry soil surfaces or undergo aerobic biodegradation within the soil. In water, 2-phenylpropane will undergo volatilisation from the surface or bind to sediment and undergo aerobic biodegradation. There is a potential for 2-phenylpropane to bio-accumulate in fish (ECB 2001).

2-Phenylpropane is mainly used as an intermediate in the production of phenol and acetone (95 %). Other uses include the synthesis of α-methylstyrene, acetophenone and detergents, synthesis of di-isopropylbenzene and catalyst for acrylic polyester-type resins.

With regard to analysis, standard methods for solvents can be applied.

3. Health significance

3.1. Toxicokinetics

3.1.1. Human data

2-Phenylpropane is well absorbed through the respiratory tract. Ten healthy subjects (5 per sex) were exposed once for 8 hours to 2-phenylpropane vapour concentrations of 240, 480 and 720 mg/m^3 (48, 96 and 144 ppm), including two breaks of 30 min. Pulmonary retention was about 64 % at the beginning of the exposure and diminished to about 45 % at the end of the exposure (Senczuk and Litewka 1976). Investigation of non-occupationally exposed hospital (n = 58) and chemical workers (n = 28) revealed pulmonary retentions of 70.4 and 77.8 %, respectively (Brugnone *et al* 1989).

Though no adequate human study is available, it can be assumed that 2-phenylpropane is also well absorbed through the gastro-intestinal tract and through the skin because of its structural and physico-chemical analogy with toluene and xylene (ECB 2001).

Based on the physico-chemical properties of 2-phenylpropane, Fiserova-Bergerova *et al* (1990) calculated a human skin penetration rate of about 0.34 mg/cm^2 per hour for a saturated aqueous solution (see also Chapter 4).

2-Phenylpropane is a highly lipophilic substance, which is well distributed in the whole body with partition coefficients of 1.44 (water/air), 37 (blood/air) and 6 215 (oil/air) (Sato and Nakajima 1979). These data also indicate possible accumulation of 2-phenylpropane in adipose tissue.

2-Phenylpropane is metabolised to 2-phenyl-2-propanol (40 %) and to 2-phenyl-1-propanol (25 %), which is further transformed into 2-phenylpropionic acid. About 5 % of 2-phenylpropane is exhaled. Half of the metabolite 2-phenyl-2-propanol is excreted within 9.5 hours. 2-Phenylpropionic acid is eliminated with a biological half-life of 10.8 ± 2.3 hours (Greim and Lehnert 2001).

3.1.2. Animal data

As shown in different animal studies, 2-phenylpropane is well absorbed through the respiratory tract and the gastrointestinal tract (see below). No pharmacokinetic data were available for dermal absorption. Two older studies did not clearly indicate skin absorption (Valette and Cavier 1954, Wolf *et al* 1956). However, topically applied 2-phenylpropane caused severe systemic damages in rabbits (Monsanto Co. 1978; see Section 3.2.2). Thus, it is at least partly absorbed by the skin. ^{14}C-Labelled 2-phenylpropane was readily absorbed by rats after inhalation exposure (nose-only, 6 hours) and after a single oral administration (Research Triangle Institute 1989). Blood levels increased in a concentration-dependent manner. Some radioactivity was still observed in several tissues after 72 hours, mostly in the liver (liver/blood ratio = 5) and in fat (fat/blood ratio = 4.5) indicating the high lipophilicity of this substance.

Inhalation exposure of rats to 509 ppm (2 545 mg/m^3) 2-phenylpropane for 10–150 days (8 hours/day) resulted in high amounts of this compound in the central nervous system (CNS), endocrine glands, bone marrow, spleen and liver (Fabre *et al* 1955). A large fraction (85 %) of the substance in blood was bound to proteins (Greim and Lehnert 2001). Tissue levels of 2-phenylpropane decreased slowly during an observation period of 48 hours after the end of exposure. Identified metabolites in the urine were 2-phenylpropane-2-ol and its glucuronide or sulphate conjugates, 2-propane-1,2-diol, 2-phenylpropionic acid and phenolic compounds (not further specified). These metabolites were also detected after administration of ^{14}C-2-phenylpropane to rats either orally or by inhalation (Research Triangle Institute 1989). Within 72 hours, about 90 % of the ^{14}C-labelled compounds were excreted in the urine and about 5 % were exhaled or excreted in the faeces. Significant amounts of radioactivity were still measured in different organs, with highest quantities in adipose tissue (see above). The exhaled ^{14}C-fraction was unchanged 2-phenylpropane, the relative amount increasing with increasing dose. About 50 % of the renally excreted radioactive compounds was 2-phenylpropan-2-ol (free or conjugated as glucuronide or sulphate) (Research Triangle Institute 1989).

Similar to inhalation exposure, about 90 % of the radiolabelled compounds were eliminated within 72 hours after oral administration, a minimum of 70 % being excreted in the urine and only 3 % in the faeces. The amount of exhaled radioactivity increased at higher doses (5 % at 33 mg/kg and 13 % at 1 323 mg/kg). The elimination half-life of 2-phenylpropane was calculated to be 7.3–8.6 hours (ECB 2001).

Furthermore, the absorption, distribution, metabolism and excretion of ^{14}C-2-phenyl-propane was studied in male rats and mice of both sexes after oral or intravenous administration (Chen *et al* 2011). In both species and sexes, urine accounted for the majority of the excretion (typically ≥ 70 %) by oral and intravenous administration. Enterohepatic circulation of 2-phenylpropane and/or its metabolites was indicated because 37 % of the total dose was excreted in bile in bile duct-cannulated rats with little excreted in normal rats. The highest tissue ^{14}C-levels in rats were observed in adipose tissue, liver and kidney with no accumulation observed after repeat dosing up to 7 days. In contrast, mice contained the highest concentrations of ^{14}C at 24 hours after dosing in the liver, kidney and lung, with repeat dosing accumulation of ^{14}C observed in these tissues as well as in the blood, brain, heart, muscle and spleen. The

metabolites in the expired air, urine, bile and microsomes were characterised with 16 metabolites identified. The volatile organics in the expired air comprised mainly 2-phenylpropane and up to 4 % α-methylstyrene. The major urinary and biliary metabolite was 2-phenyl-2-propanol glucuronide, which corresponded with the main microsomal metabolite being 2-phenyl-2-propanol.

The different distribution patterns of metabolites in the lungs between rats and mice are ascribed to differential local metabolism. There are more Clara cells in mice than in rats containing ring-oxidising CYP2E1 and CYP2F (CYP2F2 in mice, CYP2F4 in rats). Moreover, the human CYP2F1 is much less prevalent in these tissues and therefore much less effective at metabolising 2-phelypropane, compared to the situation in rodents (Chen *et al* 2011, Cruzan *et al* 2009 and 2012).

3.1.3. Biological monitoring

Eighteen persons were exposed by inhalation to 2-phenylpropane for 8 hours at concentrations ranging from 15 to 50 ppm. There was a moderate bicycle exercise of 75 W for 10 min every hour. 2-Phenylpropane was measured in exhaled breath and in blood. 2-Phenyl-1-propanol, 2-phenyl-2-propanol and 2-phenylpropionic acid were measured in urine. The major urinary metabolite was 2-phenyl-2-propanol. The experiment was published in abridged form of a congress report by Knecht and Ulshöfer (1996). Additional data of this experiment were later retrieved by Greim and Lehnert (2001), based on the original experimental data set. The measured parameters provided good correlations with the airborne 2-phenylpropane concentrations.

In this experiment, the highest airborne concentration tested of 45–50 ppm 2-phenylpropane corresponded to 35.8 ± 13.2 mg 2-phenyl-2-propanol/g creatinine (n = 20). At 35–40 ppm 32.8 ± 14.2 mg/g (n = 12), at 25–30 ppm 20.1 ± 4.3 mg/g (n = 9) and at 15 ppm 7.5 ± 2 mg/g (n = 5) were found. 2-Phenylpropane blood concentrations at the end of shift were 1.54 ± 0.33 mg/l at 45–50 ppm 2-phenylpropane in air, 0.79 ± 0.26 mg/l at 35–40 ppm, 0.64 ± 0.14 mg/l at 25–30 and 0.59 ± 0.06 mg/l at 15 ppm. Because of the rapid metabolite excretion (Section 3.1.1) urine sampling for biological monitoring should not be later than two hours after shift. No correlation between health effects and concentrations of 2-phenyl-2-propanol in urine or 2-phenylpropane in blood has been established.

Taking these values, the mean urinary excretion levels of the main metabolite 2-phenyl-2-propanol, immediately after experimental exposure to 2-phenylpropane, are shown in Figure 1. As there is no physiological background excretion of 2-phenyl-2-propanol, the curve in this figure is forced through the origin. Overall, the data suggest a urinary excretion of 7 mg 2-phenyl-2-propanol/g creatinine as a plausible biological equivalent to an 8-hour TWA exposure to 2-phenylpropene of 10 ppm (see Chapter 4).

For analysis of 2-phenyl-2-propanol, after addition of internal standard, 2-(4-fluorophenyl)ethanol, the urine is subjected to hydrolysis using hydrochloric acid. The analyte is enriched using liquid-liquid-extraction and simultaneously separated from matrix components. After separation by capillary gas chromatography, quantitation is done using flame ionisation detection (Knecht 2013).
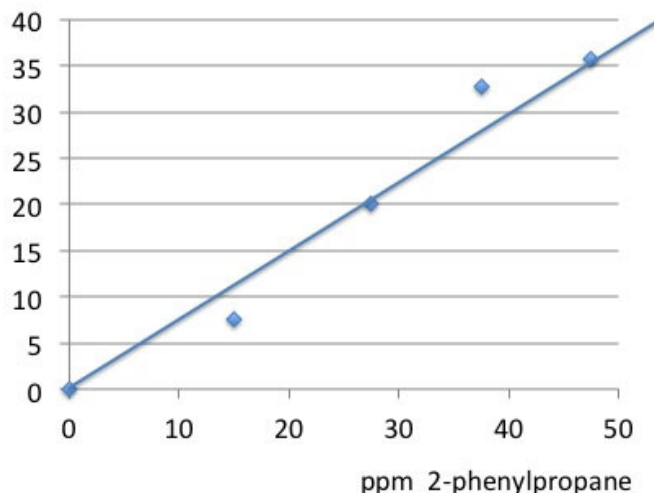
mg 2-phenyl-2-propanol/g creatinine

Figure 1. Mean 2-phenyl-2-propanol after experimental human exposure to 2-phenylpropane (experiment of Knecht and Ulshöfer 1996; linear function forced through the origin.

3.2. Acute toxicity

3.2.1. Human data

According to the US EPA, inhalation exposure of humans to 2-phenylpropane can cause headaches, dizziness, drowsiness, slight ataxia and unconsciousness (EPA 2000) (no further details given).

3.2.2. Animal data

Inhalation exposure of rats to 2-phenylpropane resulted in LC_{50} values of 8 000 ppm (40 000 mg/m^3)/4 hours (Smyth 1951) and > 3 520 ppm (17 600 mg/m^3)/6 hours (Monsanto Co. 1985), while LC_{50} values in mice were 5 000 ppm (25 000 mg/m^3)/2 hours (Solomin 1971) and 2 000 ppm/7 hours (10 000 mg/m^3; unpublished report, Huels AG 1994).

Exposure-related behavioural changes, indicating CNS depression, occurred in CFW mice after single exposures to 2 000–8 000 ppm (10 000–40 000 mg/m³) 2-phenylpropane for 20 min (Tegeris and Balster 1994). Histopathological investigations of rats after inhalation exposure to 2 000 and 5 000 ppm (10 000 and 25 000 mg/m³) for 5 consecutive days (6 hours/day) revealed congestion of many tissues, red fluid filled bladders, abnormal contents in the intestine as well as excessive ocular and nasal accumulations (Gulf Oil Corp. 1985a). A single inhalation exposure of F344 rats to 100, 500 and 1 200 ppm (500, 2 500 and 6 000 mg/m^3; 6 hours) led to lowering of the rectal temperature and changes in a functional observational battery (at 500 ppm), which disappeared after 24 hours (Cushman *et al* 1995, Bushy Run Research Center 1989). The NOAEC for CNS effects was 100 ppm.

Acute toxic symptoms observed in mice were unconsciousness, ataxia, loss of reflexes and depression of the breathing frequency finally leading to death (Gardner and Delic 1994). Steatosis in liver and kidney as well as phagocytosis in the reticular cells of the

follicles of the spleen occurred. 2-Phenylpropane caused sensory irritation of the respiratory mucosa in mice (for details, see Section 3.3.2).

Oral LD_{50} values of 1 400–8 620 mg/kg have been reported in different rat strains (Wolf *et al* 1956, Smyth *et al* 1951, Monsanto Co. 1978, Gerarde 1959). Clinical signs after oral application of 2-phenylpropane were sluggishness, prostration and narcosis. Autopsy of the rats revealed pneumonitis, pulmonary oedema, haemorrhage, inflammation of the gastrointestinal tract and liver discoloration (Monsanto Co. 1978).

The dermal LD_{50} values ranged from > 3 160 mg/kg up to 10 600 mg/kg in rabbits (ECB 2001, Smyth *et al* 1951). Signs of toxicity included weakness, weight loss and collapse. Furthermore, discoloration of liver, kidney and spleen as well as inflammation of the gastrointestinal tract and lung haemorrhage occurred (Monsanto Co. 1978).

3.3. Irritancy and corrosivity

3.3.1. Human data

An odour threshold limit value of 0.088 ppm (0.43 mg/m^3) was reported by Amoore and Hautula (1983).

Experience in handling 2-phenylpropane indicates that painful irritation of the eyes and the respiratory tract occurs at concentrations of approximately 300–400 ppm (1 500–2 000 mg/m^3) (ECB 2001). No further details were given.

3.3.2. Animal data

Skin

Open or semi-occlusive application of unspecified doses of 2-phenylpropane to the shaved skin of the inner ear and on the shaved abdomen of rabbits for 2–4 weeks (once per day) caused slight necrosis, erythema and exfoliation of the skin (Wolf *et al* 1956). According to the authors, there was no indication that 2-phenylpropane was well absorbed through the skin. The effects observed after topical application of pure 2-phenylpropane persisted for 21 days, while the effects produced by a 10 % aqueous solution applied daily over a period of 9 days completely disappeared within 21 days (Dow Chemical Company 1985).

Dermal exposure of New Zealand rabbits to 0.5 ml 2-phenylpropane for 24 hours resulted in slight defatting and flaking of the skin (Monsanto Co. 1978).

Application of 10 ml 2-phenylpropane to shaved strips on the back of calves produced severe cracking or sloughing of the skin (Turner *et al* 1962).

Eyes

Instillation of two drops of undiluted 2-phenylpropane into the rabbit eye caused only slight conjunctival irritation but no corneal injury (Wolf *et al* 1956). Only minor reactions were observed in several other studies (Smyth *et al* 1951, Monsanto Co. 1985, Union Carbide Corporation 1985, Huntingdon Research Center 1979).

Respiratory tract

The RD_{50} (concentration causing a 50 % depression of the respiratory rate due to sensory irritation of the respiratory tract) of 2-phenylpropane was 2 490 ppm (12 450 mg/m³) in Swiss-Webster mice (Nielsen and Alarie 1982) and 2 058 ppm (10 290 mg/m^3) in CF1 mice (Kristiansen *et al* 1986).

3.4. Sensitisation

3.4.1. Human data

No data were available.

3.4.2. Animal data

2-Phenylpropane was not sensitising in a guinea pig maximisation test performed according to OECD guideline 406 (unpublished report; Huels AG 1988).

3.5. Repeated dose toxicity

3.5.1. Human data

No data were available.

3.5.2. Animal data

Inhalation

Cushman *et al* (1995) performed two 13-week inhalation studies with 2-phenylpropane in F344 rats. In the first study, rats (n = 21 per sex and group) were exposed to concentrations of 0, 100, 500 and 1 200 ppm (0, 500, 2 500 and 6 000 mg/m^3) 2-phenylpropane (6 hours/day, 5 days/week). The second study was a repeat of the first study (n = 15 per sex and group) with the exception that one group of animals exposed to 50 ppm (250 mg/m^3) was added and all animals of this second study were allowed to recover for 4 weeks subsequently to exposure.

No exposure-related changes in the functional observational battery occurred in any of the experiments. In the first study at 500 ppm, total motor activity was decreased at week 13 and ambulatory activity was statistically decreased at weeks 4, 9 and 13. These findings were not replicated in the second study. The development of cataracts in the eyes of both control and exposed animals, also occurring only in the first experiment, was not interpretable because of the high incidence in the control group.

Measurement of the auditory brain stem response revealed no changes in the auditory function indicating that 2-phenylpropane is not ototoxic. Haematological examinations revealed exposure-related increases in total leukocytes, lymphocytes and platelets at 500 ppm (both sexes). Furthermore, 2-phenylpropane caused increases in total protein, albumin, globulin, calcium and phosphorous levels in rats of both sexes (500 ppm) and lower serum glucose levels in female rats (1 200 ppm).

The organ weights of liver, kidney and adrenal gland were significantly increased at 500 ppm in both male and female rats of either study. The persistence of the increases of organ weights after 4 weeks of recovery in the second study indicated limited reversibility of this effect. In male rats, the incidences of hypertrophy and hyperplasia of the proximal tubules and interstitial nephritis were increased at 500 ppm due to a greater amount of hyaline droplets. However, this effect was closely linked to the male rat specific nephropathy. No such effect occurred at 100 ppm. Kidney and liver weights were not affected at 50 and 100 ppm in either study, on an absolute and relative basis. At 500 ppm, liver weights increased in females (abs 7 %, rel 11 %) and males (abs 20 %, rel 17 %) in the first study. In the second study (including the post-exposure period) liver weights increased in females (abs 13 %, rel 11 %) and males (only abs 11 %); relative kidney weights in males increased by 6 %. No pathological changes were reported in nasal tissues. Clinical chemistry parameters were not affected at 100 ppm. A NOAEC of 100 ppm was derived from these studies (Cushman *et al* 1995; full reports: Bushy Run Research Center 1989 and 1991).

A 4-week study on rats (0, 100, 300 and 600 ppm = 0, 500, 1 500 and 3 000 mg/m^3) performed by Monsanto Company (1986) revealed similar effects. Renal changes occurred only in male rats and were related to the male rat specific nephropathy. A LOAEC of 100 ppm was established on the basis of cage-side observations of head tilt and head movements, which were associated with CNS perturbation. However, the authors noted that these head movements were not observed in several other studies.

Continuous inhalation exposure of rats, guinea pigs, dogs and monkeys to 3.7 and 30 ppm (18.5 and 150 mg/m^3) 2-phenylpropane for 90 days did not cause any exposure-related effects (Jenkins *et al* 1970, cited in ECB 2001 and HSE 2001). The body weights of the animals were within the normal range and the limited histopathological and haematological examinations performed did not reveal any changes. Also, inhalation exposure (8 hours/day, 5 days/week) of the same animal species to 244 ppm (1 220 mg/m^3) 2-phenylpropane for 6 weeks did not produce histopathological and haematological changes. The only effect observed was a marked reduction in the body weight gain of guinea pigs.

The effect of acute and subacute exposure of 2-phenylpropane on expressions of synaptophysin and glial fibrillary acidic protein (GFAP) in the hippocampi was investigated by Lee *et al* (2009). Sprague-Dawley male rats were exposed to 2-phenylpropane (0, 8, 80 and 800 ppm) by inhalation for 1, 14, 28 and 90 days. In Western blot analysis, the expression levels of synaptophysin in the hippocampi were significantly increased at 800 ppm on day 14 and significantly decreased at 8 ppm on day 28. Levels of GFAP were significantly increased in hippocampi at 1, 14 and 28 days after 2-phenylpropane exposure when compared to the control group. 2-Phenylpropane inhalation changed the expression of synaptophysin and GFAP in hippocampus, even at a dose of 8 ppm. It is not clear whether this represents an adverse health effect or a physiological adaptive response.

In a recent study (NTP 2009), 2-phenylpropane was studied with the primary intention to determine if it caused cancer in rats or mice. Male and female F344/N rats and B6C3F1 mice were exposed to 2-phenylpropane (greater than 99.9 % pure) by inhalation for 2 weeks, 3 months, or 2 years. In the following, a summary of the results from the shorter range-finding studies is given. The 2-year carcinogenicity study is reported in Section 3.7.2.

Groups of 5 male and 5 female rats were exposed to 2-phenylpropane vapour at concentrations of 0, 250, 500, 1 000, 2 000 or 4 000 ppm, 6 hours per day, 5 days per week for 16 days. All rats exposed to 4 000 ppm died on day 1, and 2 male and 3 female rats exposed to 2 000 ppm died by day 4. Mean body weights of 2 000 ppm rats were significantly less than those of the chamber controls. Rats exposed to 2 000 ppm that died early were severely lethargic following daily exposure. Liver and kidney weights of all exposed groups were increased. Accumulation of minimal to mild hyaline droplets was observed in the renal tubular cortex of males exposed to concentrations of 250 to 2 000 ppm.

Groups of 5 male and 5 female mice were exposed to 2-phenylpropane vapour at concentrations of 0, 250, 500, 1 000, 2 000 or 4 000 ppm, 6 hours per day, 5 days per week for 17 days. All mice exposed to 4 000 ppm died on day 1; all mice exposed to 2 000 ppm died on day 2, and 4 female mice exposed to 1 000 ppm died by day 4. Mean body weights of all exposed groups were similar to those of the chamber controls. Mice exposed to 2 000 ppm were severely lethargic after the first exposure. The 4 female mice exposed to 1 000 ppm that died early exhibited signs of lethargy and ataxia. Liver weights, both relative and absolute, were increased in all groups of surviving males and in 250- and 500-ppm female groups.

Groups of 10 male and 10 female rats were exposed to 2-phenylpropane vapour at concentrations of 0, 62.5, 125, 250, 500 or 1 000 ppm, 6 hours per day, 5 days per week for 14 weeks. Additional clinical pathology groups of 10 male and 10 female rats were exposed to the same concentrations for 23 days. All rats survived to the end of the study, and mean body weights of all exposed groups were similar to those of the chamber controls. Kidney and liver weights of 250-ppm or greater males and liver weights of 1 000-ppm females were significantly greater than those of the chamber controls. There were significant differences between exposed and chamber control females in the relative length of time spent in the oestrous stages. The amount of $\alpha2_\mu$-globulin in the right kidneys was significantly increased in male rats exposed to 125 ppm or greater. The incidences of medullary granular casts in males exposed to 250 ppm or greater were significantly increased. The severities of renal tubule cortex hyaline droplet accumulation and regeneration increased with increasing exposure concentration in male rats.

Groups of 10 male and 10 female mice were exposed to 2-phenylpropane vapour at concentrations of 0, 62.5, 125, 250, 500 or 1 000 ppm, 6 hours per day, 5 days per week for 14 weeks. Eight 1 000-ppm females died during week 1 of the study. Mean body weights of males exposed to 500 or 1 000 ppm were significantly less than those of the chamber controls. The eight 1 000-ppm female mice that died during the first week of the study exhibited clinical signs of acute toxicity, including lethargy or ataxia. Liver weights of mice exposed to 500 or 1 000 ppm were significantly increased. The weight of the cauda epididymidis and the spermatid count were significantly decreased in 1000-ppm males.

With regard to assessment of a NOAEC or LOAEC, the lowest tested concentration in the 3-month study by NTP was 62.5 ppm. This caused a reported elevation of relative liver and kidney weights in male rats and an increased incidence of chronic focal inflammation in the livers of female mice. However, the relative liver weight in male rats exposed under these conditions increased only marginally, by about 5–6 %; absolute organ weights were not affected. In female rats, relative kidney weight was increased at 250 ppm and higher, but histopathological changes were not observed. In female mice, the incidences of chronic focal hepatic inflammation showed the following pattern: 10, 10 and 9 (of 10) animals at 62.5, 125 and 250 ppm, respectively. At 500 ppm, 7 (of 10) showed chronic focal inflammation, while this was seen in 2 (of 2) at 1 000 ppm. Liver necrosis was seen in 2 (of 10) animals at 500 ppm and in 1 (of 10) of the controls. The chronic inflammation reported in the liver of female mice in the 90-day cumene study was of minimal grade and is a normal finding in the liver of mice and rats. Therefore, this liver lesion is seen by SCOEL to represent a normal background variation that does not carry much scientific weight. In consequence, SCOEL considers a NOAEC of 62.5 ppm based on this subchronic study. The evaluation is in general accordance with conclusions reached at the 3rd International ESTP (European Society of Toxicologic Pathology) Expert workshop (Hall *et al* 2012).

Oral

Oral application of 8.47 mmol/kg per day of 2-phenylpropane (gavage) on 5 days/week for 2 weeks did not produce ototoxicity in SD rats (Gagnaire and Langlais 2005). Groups of 10 rats per dose were given 0, 154, 462 and 769 mg/kg per day 2-phenylpropane by gavage over a period of 6 months (5 days/week) (Wolf *et al* 1956). The only effect detected was a significant increase of average kidney weights at 462 mg/kg per day. From these data, a NOAEL of 154 mg/kg per day and a LOAEL of 462 mg/kg per day can be estimated for oral application of 2-phenylpropane.

Dermal

A 10 % solution of a mixture containing 30 % 2-phenylpropane, 58 % glycol ether and 12 % "Busan 72" was topically applied to the shaved dorsal skin (approximately 10 % of the body surface) of New Zealand white rabbits on 5 days/week for 28 days (2 ml/kg per day of the 10 % mixture, corresponding to approximately 57 mg/kg per day of 2-phenylpropane; unpublished results, Procter & Gamble Comp. 1985). Skin oedema, fissuring and moderate to severe erythema as well as dermatitis, acanthosis and hyperkeratosis occurred. However, dermal application of 2-phenylpropane did not cause systemic toxicity in these animals.

3.6. Genotoxicity

3.6.1. In vitro

In earlier studies, 2-phenylpropane was not mutagenic in several bacterial tests performed with *Salmonella typhimurium* (TA97, TA98, TA100, TA1535, TA1537) with and without metabolic activation (summarised in ECB 2000). It gave negative results in a chromosome aberration assay with Chinese hamster ovary (CHO) cells (Putman 1987a), in two HGPRT mutation assays with CHO cells (Yang 1987, Gulf Oil Corp. 1985b) and in an unscheduled DNA synthesis (UDS) test using rat hepatocytes (Curren 1987). 2-Phenylpropane was weakly positive regarding DNA repair activity in primary rat hepatocytes (Gulf Oil Corp. 1984). This test prompted a repeat with clearly negative result (WHO 1999). A morphological cell transformation assay with BALB/3T3 mouse embryo cells was negative after application of 50, 100, 150 and 200 µg/ml of 2-phenylpropane (Putman 1987b).

Because of concern regarding the volatility of 2-phenylpropane, the compound was again subjected to a battery of genotoxicity tests within the frame of the US National Toxicology Program (NTP 2009, 2012a,b). It was tested in the bacterial reverse mutation assay using *Salmonella typhimurium* strains TA98 and TA100 and *Escherichia coli* strain WP2 *uvrA* (pKM101) in the pre-incubation method with and without metabolic activation (10 % phenobarbital/benzoflavone induced rat liver S9). This was addressed as the standard protocol employed by NTP for bacterial mutagenicity assessment, and these three strains of bacteria permit detection of the vast majority of bacterial mutagens, including chemicals that induce base substitutions, frame-shifts, and oxidative damage. Pre-incubation was conducted in sealed tubes to maximise exposure of the bacteria. In dose range finding tests, toxicity was observed at 250 or 500 µg/plate; therefore, the highest dose tested was 250 or 500 µg/plate. The observation of toxicity at 250 or 500 µg/plate confirmed that exposure to 2-phenylpropane had occurred. Under these test conditions, 2-phenylpropane did not induce increases in revertant counts up to dose levels that induced toxicity.

3.6.2. In vivo – Human data

No data were available.

3.6.3. In vivo – Animal data

A micronucleus test with CDR-1 BR Swiss mice (10 per sex and group) indicated no clastogenic potential after oral application of 250, 500 and 1 000 mg/kg per day of 2-phenylpropane on 2 consecutive days (Gulf Oil Corp. 1985c).

In recent studies conducted by NTP (2012a,b), male Fisher 344 rats and male and female B6C3F1 mice (6 animals/dose group) were administered vehicle (corn oil), 2-phenylpropane or (as positive control) ethyl methanesulphonate by gavage, once daily

for 4 consecutive days. The top doses of 2-phenylpropane used in these studies (800 mg/kg/day for male rats; 1 250 and 1 000 mg/kg/day for male and female mice, respectively) were selected on the basis of a range finding study. The final (4th) dose was administered 21 hours following the previous dose; 3 hours later, peripheral blood and liver, lung and kidney tissues were collected from each animal. Blood samples were prepared for micronuclei analysis, while blood and tissue samples were processed for the comet assay. Frequencies of micronucleated polychromatic erythrocytes were measured using flow cytometry. Cells from the kidney, liver and lung, as well as blood leukocytes, were analysed for extent of DNA migration (DNA damage) using the alkaline (pH > 13) comet assay. Micronuclei and comet assay data were evaluated. Results of the micronucleus tests for 2-phenylpropane in both rats and mice were negative. Results of the comet assay for all tissues in all species/sexes were negative with two exceptions: results in female mouse lung and male rat liver were judged to be positive based on the presence of a significant trend and a significant increase in DNA damage at the highest dose tested in both tissues, compared with the concurrent vehicle control group.

It was concluded by NTP (2012b) that 2-phenylpropane did not show evidence of bacterial mutagenicity or evidence of chromosomal breakage in pro-erythrocytes of male and female mice, and male rats. Significant, dose-related increases in DNA damage were observed in male rat liver cells and female mouse lung cells; none of the other tissues sampled in mice and rats showed evidence of DNA damage.

3.7. Carcinogenicity

3.7.1. Human data

There were no published data on carcinogenicity in humans.

3.7.2. Animal data

In a recent study (NTP 2009), male and female F344/N rats and B6C3F1 mice were exposed to 2-phenylpropane (> 99.9 % pure) by inhalation for 2 years. In the following, a summary of the results is given. The range-finding studies of shorter duration are reported in Section 3.5.2.

Groups of 50 male and 50 female rats were exposed to 2-phenylpropane vapour at concentrations of 0, 250, 500 or 1 000 ppm, 6 hours per day, 5 days per week for 105 weeks. Survival of all exposed groups of rats was similar to that of the chamber controls. Mean body weights of 1 000-ppm females were slightly less than those of the chamber controls during the second year of the study but were similar to the chamber controls at the end of the study.

Incidences of adenoma of the respiratory epithelium in the nose occurred with a positive trend in males and were significantly increased in all exposed groups of males and in 250-ppm females. Incidences of hyperplasia of basal cells in the olfactory epithelium in the nose of all exposed groups and hyperplasia of the respiratory epithelium in the nose of all exposed groups of males and 1 000-ppm females were significantly increased.

The incidences of renal tubule adenoma in all exposed groups of males, renal tubule carcinoma in 500- and 1 000-ppm males, and renal tubule adenoma or carcinoma (combined) in all exposed groups of males were increased; the difference from chamber controls for the combined incidence was significant at 500 ppm. The incidences of hyperplasia of the renal tubule and transitional epithelium of the renal pelvis in 500- and 1 000-ppm males and mineralisation of the renal papilla in all

exposed groups of males were significantly greater than those of the chamber controls.

Groups of 50 male and 50 female mice were exposed to 2-phenylpropane vapour at concentrations of 0, 125 (female mice only), 250, 500 or 1 000 (male mice only) ppm, 6 hours per day, 5 days per week for 105 weeks. An exposure concentration-related decrease in survival occurred in male mice, and the survival of 1 000-ppm males was significantly less than that of the chamber controls. Mean body weights of 1 000-ppm males were generally less than those of the chamber controls after week 8 of the study, and those of 500-ppm females were less from week 28 until week 76 of the study.

The incidences of alveolar/bronchiolar adenoma, alveolar/bronchiolar carcinoma, and alveolar/bronchiolar adenoma or carcinoma (combined) in all exposed groups of mice occurred with positive trends and were significantly greater than those in the chamber controls. The incidences of alveolar epithelial bronchiole metaplasia and bronchiole hyperplasia were significantly increased in all exposed groups of mice. *p53* and *K-ras* mutations were found in 52 % and 87 % of lung neoplasms in exposed mice compared to 0 % and 14 % in the chamber controls, respectively.

In female mice, the incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) occurred with positive trends and were significantly increased in the 500-ppm group. In male mice, there were significant increases in the incidences of eosinophilic foci of the liver.

In the nose, the incidences of olfactory epithelium atrophy, basal cell hyperplasia of the olfactory epithelium, atypical hyperplasia of the olfactory epithelium, hyperplasia of olfactory epithelium glands, and suppurative inflammation were generally significantly increased in 500- and 1 000-ppm males and 500-ppm females. The incidence of squamous metaplasia of the respiratory epithelium was significantly increased in 500-ppm females. The incidence of basal cell hyperplasia was also significantly increased in 250-ppm females.

The incidences of epithelial hyperplasia of the forestomach in the 500- and 1 000-ppm groups of males and the incidences of ulceration and inflammation of the forestomach in 1 000-ppm males were significantly increased.

All groups of animals exposed to 2-phenylpropane exhibited hyperplasia of the epithelial tissues of the nose, and exposed male and female mice experienced metaplasia and hyperplasia of the lung.

3.7.3. Interpretation of the carcinogenicity data

The NTP panel (NTP 2009) concluded that under the conditions of the 2-year inhalation studies there was clear evidence of carcinogenic activity of 2-phenylpropane in male F344/N rats based on increased incidences of respiratory epithelial adenoma in the nose and renal tubule adenoma or carcinoma (combined). Some evidence of carcinogenic activity of 2-phenylpropane was seen in female F344/N rats based on the incidences of respiratory epithelium adenoma in the nose. Clear evidence of carcinogenic activity of 2-phenylpropane was seen in male B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms. Clear evidence of carcinogenic activity of 2-phenylpropane was seen in female B6C3F1 mice based on increased incidences of alveolar/bronchiolar neoplasms. Increased incidences of hepatocellullar adenoma or carcinoma (combined) in female mice were also considered to be related to exposure to 2-phenylpropane. Exposure to 2-phenylpropane resulted in non-neoplastic lesions in the nose and kidney of male rats; the nose of female rats; the

lung, nose, liver and forestomach of male mice; and the lung and nose of female mice. The incidences of alveolar/bronchiolar adenomas and carcinomas in 2-phenylpropane-treated B6C3F1 mice were significantly greater than those of the control animals (Hong *et al* 2008). Lung neoplasms were evaluated for point mutations in the *K-ras* and *p53* genes that are often mutated in humans. *K-ras* mutations were detected in 87 % of 2-phenylpropane-induced lung neoplasms. *p53* protein expression was detected by immunohistochemistry in 56 % of 2-phenylpropane-induced neoplasms, and mutations were detected in 52 % of neoplasms. No *p53* mutations and 1 of 7 (14 %) *K-ras* mutations were detected in spontaneous neoplasms. 2-Phenylpropane-induced lung carcinomas showed loss of heterozygosity (LOH) on chromosome 4 near the *p16* gene (13 %) and on chromosome 6 near the *K-ras* gene (12 %). No LOH was observed in spontaneous carcinomas or normal lung tissues examined. The pattern of mutations identified in the lung tumours suggests that DNA damage and genomic instability may be contributing factors to the mutation profile and development of lung cancer in mice exposed to 2-phenylpropane (NTP 2009).

In another study (Wakamatsu *et al* 2008), the authors performed global gene expression analysis to distinguish patterns of gene regulation between 2-phenylpropane-induced tumours and normal lung tissue and to look for patterns based on the presence or absence of *K-ras* and *p53* mutations in the tumours. Principal component analysis segregated the carcinomas into groups with and without *K-ras* mutations, but failed to separate the tumours based on *p53* mutation status. Gene expression analysis also suggested that 2-phenylpropane-induced carcinomas with *K-ras* mutations have greater malignant potential than those without mutations. The gene expression analysis suggested that the formation of alveolar/bronchiolar carcinomas in 2-phenylpropane-exposed mice typically involves mutation of *K-ras*, which results in increased Erk MAP kinase signalling and modification of histones.

Hoenerhoff *et al* (2009) evaluated spontaneous and 2-phenylpropane-induced lung neoplasms for mutations in *K-ras* and *Tp53* genes, as well as chemical-specific mutations that could function as biomarkers of chemical exposure with potential human health importance. The results suggest that in 2-phenylpropane-induced pulmonary tumours in mice, DNA damage and genomic instability leading to *K-ras* and *Tp53* dysregulation leads to up-regulation of pathways associated with the development of lung cancer in 2-phenylpropane-exposed mice and that tumours resulting from mutations in *K-ras* possess a gene expression associated with a greater degree of malignancy.

3.7.4. Carcinogenic activity of metabolites

Male and female F344/N rats and B6C3F1 mice were exposed to α-methylstyrene (99.5 % pure), which is one of the metabolites of 2-phenylpropane, by inhalation for 2 years (NTP 2007). Groups of 50 male and 50 female rats and groups of 50 male and 50 female mice were exposed by whole body inhalation to α-methylstyrene at concentrations of 0, 100, 300 or 600 (mice) alternatively 1 000 (rats) ppm for 6 hours per day, 5 days per week, except holidays, for 105 weeks. It was concluded that, under the conditions of this inhalation study, there was some evidence of carcinogenic activity of α-methylstyrene in male F344/N rats based on increased incidences of renal tubule adenomas and carcinomas (combined). The increased incidence of mononuclear cell leukaemia in 1 000-ppm male F344/N rats may have been related to α-methylstyrene exposure. There was no evidence of carcinogenic activity of α-methylstyrene in female F344/N rats exposed to 100, 300 or 1 000 ppm. There was equivocal evidence of carcinogenic activity of α-methylstyrene in male B6C3F1 mice based on marginally increased incidences of hepatocellular adenoma or carcinoma (combined). There was clear evidence of carcinogenic activity of α-methylstyrene in

female B6C3F1 mice based on increased incidences of hepatocellular adenomas and carcinomas. Exposure of rats to α-methylstyrene resulted in kidney toxicity, which in males exhibited some features of $\alpha_{2\mu}$-globulin nephropathy. Exposure to α-methylstyrene resulted in non-neoplastic lesions of the nose in male and female rats and mice and of the liver and kidney in female mice.

3.8. Reproductive toxicity

3.8.1. Human data

No data were available.

3.8.2. Animal data

Fertility

No compound-related differences in the counts of testicular sperm heads or epididymal spermatozoa occurred in rats after inhalation exposure to 50, 100, 500 and 1 200 ppm (250, 500, 2 500 and 6 000 mg/m^3) 2-phenylpropane for 13 weeks (6 hours/day, 5 days/week) (Cushman *et al* 1995). Also, the morphology and stages of spermatogenesis were normal in all groups.

Developmental toxicity

Pregnant Sprague-Dawley rats (gestational day 6–15, n = 25 per group) and New Zealand white rabbits (gestational day 6–18, n = 15 per group) were exposed for 6 hours/day by inhalation to 2-phenylpropane at concentrations of 0, 100, 500 and 1 200 ppm (rats; 0, 500, 2 500 and 6 000 mg/m^3) and 0, 500, 1 200 and 2 300 ppm (rabbits; 0, 2 500, 6 000 and 11 500 mg/m^3) (Darmer *et al* 1997). At 1 200 ppm, the body weight gain of the rats was decreased and the relative liver weights were increased. Feed consumption of both rats and rabbits was decreased at 500 ppm. The liver weights of rabbits exposed to 2 300 ppm were significantly increased and 2 rabbits of this exposure group died. According to the authors, the NOAEC for maternal toxicity in rats was 100 ppm and no NOAEC for maternal toxicity in rabbits could be derived from this study. Despite of maternal toxicity in animals of both species there were no statistically significant alterations in gestational parameters, including the number of corpora lutea, the number of resorptions and stillborns, the number of live pups, the sex ratio and the foetal body weight, at any concentration tested (the analysis by EPA (1997) of the original report identified "non-significant increases in nonviable implants, and early resorption and a non-significant decrease in the percent of live foetuses" at the highest concentration). In rats, no significant changes in the incidences of any malformations or variations occurred, indicating a NOAEC for developmental toxicity of 1 200 ppm.

In rabbits, there were also no significant differences in the incidences of malformations, but one variation (ecchymosis on the head, i.e. haemorrhagic areas of the skin) was significantly increased in the 500-ppm group (not concentration related). However, since the incidence of this variation was in the range of historical control values, the authors did not consider it to be a treatment-related effect. In conclusion, the authors derived a NOAEC of 2 300 ppm for the developmental toxicity of 2-phenylpropane in rabbits. However, though the alterations in gestational parameters were not statistically significant (see above), EPA (1997) regarded these findings as potential developmental effects. Thus, these authors considered 1 200 ppm to be the NOAEC for both developmental and maternal effects.

4. Recommendation

The acute toxicity of 2-phenylpropane is low and mostly related to pre-narcotic solvent effects. For neurobehavioural effects, a NOAEC of 100 ppm has been reported (see Section 3.2.2).

For the question of recommending an OEL, the critical effect of 2-phenylpropane, carcinogenicity, as experimentally demonstrated in animals, must be considered. Under conditions of a recent 2-year inhalation inhalation bioassay (NTP 2009, see Section 3.7.2), increased incidences in male F344/N rats of (benign) respiratory epithelial adenoma in the nose and renal tubule adenoma or carcinoma (combined) were observed. In female F344/N rats, there were adenomas of the nose respiratory epithelium. In male B6C3F1 mice, evidence of carcinogenic activity was based on increased incidences of alveolar/bronchiolar neoplasms. In female B6C3F1 mice, there was evidence of carcinogenic activity based on increased incidences of alveolar/bronchiolar neoplasms. Also, increased incidences of hepatocelullar adenoma or carcinoma (combined) in female mice were related to the exposure.

In mutagenicity/genotoxicity assays, both *in vitro* and *in vivo*, 2-phenylpropane was overwhelmingly negative (for details, see Section 3.6); dose-related increases in DNA damage were observed in male rat liver cells and female mouse lung cells, but not in other tissues. Although ring-hydroxylated metabolites of potential genotoxicity may be formed, the mode of action of 2-phenylpropane appears to be primarily non-genotoxic. The observed difference between rats and mice in lung carcinogenicity may be explained by differences in the local metabolism, as there are more Clara cells in mice than in rats, which contain the ring-oxidising cytochromes P-450 CYP2F and CYP2E1 (Section 3.1.2). As in humans there are even less Clara cells than in rats, a very low susceptibility of humans may be reasonably anticipated. By analogy to other solvents, e.g. phenylethane (ethyl benzene), the renal effects of 2-phenylpropane in male rats (tubular adenomas/carcinomas) may reasonably be related to the specific $\alpha_{2\mu}$-globulin-nephropathy, which is not relevant to humans. In the case of 2-phenylpropane, this is supported by measurements of $\alpha_{2\mu}$-globulin in kidneys of rats exposed subchronically (NTP 2009, NTP 2012a; see Section 3.5.2). Damage to rat nasal tissue was not observed in subchronic studies at any concentration tested, up to 500 ppm 2-phenylpropane (Section 3.5.2). In the 2-year study by NTP (2009), there were signs of chronic inflammation in the nasal epithelium of rats in conjunction with the occurrence of adenomas of the respiratory epithelium (Section 3.7.2). Based on these arguments, the existence of a threshold for the experimentally observed carcinogenic effects of 2-phenylpropane is very likely. In total, the data suggest that 2-phenylpropene is an overwhelmingly non-genotoxic carcinogen. In consequence, the compound is grouped into *SCOEL carcinogenicity group D, for which a health-based OEL may be derived*.

The derivation of a recommended OEL requires a well-founded experimental NOAEC/LOAEC. Within the NTP (2009) bioassay, the lowest tested inhalation concentrations in the chronic study of 250 ppm (rats) or 125 ppm (female mice) were not negative. The lowest tested concentration in the 3-month study was 62.5 ppm. As discussed in Section 3.5.2, this level was regarded by SCOEL as a NOAEC. For the transition from rodents to humans a small uncertainty factor of appears sufficient, in view of the only low adversity of the reported effects. Therefore, a health-based *OEL of 10 ppm is recommended*, which is also in accordance with the preferred value approach of SCOEL. This recommended OEL provides a sufficient margin of safety to reported adverse effects. *A STEL of 50 ppm can be recommended* to protect against possible short-term behavioural effects; and is also protective against local irritation.

The database for human biological monitoring has been described in Section 3.1.3. Because of non-invasiveness, the excretion of the metabolite 2-phenyl-2-propanol in the urine appears as an appropriate parameter, with a sampling time not later than 2 hours after a shift. With the reasoning given in Section 3.1.3, *a BLV is recommended of a urinary excretion 7 mg 2-phenyl-2-propanol per g creatinine*. This BLV is equivalent to the recommended OEL.

Other assignments

No consistent information is given on the dermal absorption of this compound through the intact skin. 2-Phenylpropane did not clearly show skin absorption in two older studies (Valette *et al* 1954, Wolf *et al* 1956), but it caused severe systemic effects in another investigation (Monsanto Co. 1978). Because of its high lipophilicity and its analogy to benzene and xylene, a relevant skin penetration can be assumed. Fiserova-Bergerova *et al* (1990) calculated a human skin penetration rate of about 0.34 mg/cm^2/hour for a saturated aqueous solution of 2-phenylpropane. Therefore, a *"skin notation" is recommended*, which is also in line with current assessments of the European Union Risk Assessment Report (ECB 2001), the UK Health and Safety Executive (Gardner and Delic 1994) and the German MAK Commission (Greim 1996).

As there were no experimental signs of ototoxicity of 2-phenylpropane (Cushman *et al* 1995, Section 3.5.2), there is no need for a "noise notation".

At the recommended OEL, no measurement difficulties are foreseen. Standard methods for determination of solvents can be applied.

The present Recommendation was adopted by SCOEL on Date Month Year.

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