2-Phenylpropene

(CAS No: 98-83-9)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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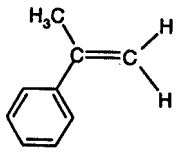
1 Introduction

The present document contains the assessment of the health hazard of 2-phenylpropene by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by JJC Paulussen, Ph.D., Ir M Busschers, and H Stouten, M.Sc. (TNO Nutrition and Food Research, Zeist, The Netherlands).

The evaluation of the toxicity of 2-phenylpropene has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG99). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in April 1999, literature was searched in the on-line databases Medline, Toxline, CA, and NIOSHTIC covering the period 1966 to May 1999, 1965 to February 1999, 1967 to May 1999, and 1973 to August 1998, respectively, and using the following key words: phenylpropylene, 2-phenyl-2-propene, 2-phenylpropene, isopropenylbenzene, 1-methyl-1-phenylbenzene, 1-methyl-1-phenylethylene, 1-methylethenylbenzene, 1-methylvinylbenzene, 1-phenyl-1-methylethylene, 2-phenyl-1-propene, methylstyrene, methylstyrol, and 98-83-9. HSDB and RTECS, databases available from CD-ROM, were consulted as well (NIO99, NLM99). The final search was carried out in Toxline and Medline in December 2002.

In April 2003, the President of the Health Council released a draft of the document for public review. The committee received no comments.

2 Identit

name	:	2-phenylpropene
synonyms	:	α-methylstyrene; isopropenylbenzene; 1-methyl-1-phenylethylene; β-phenylpropene; β-phenylpropylene; 1-methylethenylbenzene; 1-methylethylenebenzene; 1-phenyl-1-methylethylene; 2-phenyl-1-propene; 2-phenylpropylene
molecular formula	:	C_9H_{10}
structural formula	:	
CAS number	:	98-83-9

Data from ACG99, NLM99.

3 Physical and chemical properties

molecular weight	:	118.18
boiling point	:	165.4ºC
melting point	:	-23ºC
flash point	:	83.9ºC (closed cup); 57.8ºC (open cup)
vapour pressure	:	at 20ºC: 0.25 kPa
solubility in water	:	insoluble
log $P_{octanol/water}$	:	3.48
conversion factors	:	at 20ºC, 101.3 kPa: 1 ppm = 4.9 mg/m^3 1 mg/m^3 = 0.20 ppm

Data from ACG99, Lid94, NLM99.

2-Phenylpropene is a colourless liquid, with a sweet, aromatic, penetrating odour. The odour threshold is about 0.3 ppm (1.4 mg/m^3) (Amo83).

During storage, 2-phenylpropene will polymerise, and is, therefore, usually stabilised with *tert*-butyl catechol as an inhibitor (ACG99, HSE96).

4 Uses

2-Phenylpropene is used mainly as a monomer in plastic and resin manufacture (ACG99, Cav94, HSE96, NLM99).

5 Biotransformation and kinetics

Dermal absorption may be limited since application of (an unknown amount of) undiluted 2-phenylpropene to the rabbit skin (5 days/week, for 2-4 weeks) did not result in signs of systemic toxicity (Wol56). Referring to an abstract, it was stated that absorption rates of 9.5 and 0.048-0.256 mg/cm^2 were found for pure 2-phenylpropene and for various aqueous dilutions, respectively. These figures were calculated based on spectophotometrical analysis of the amount remaining and washed off with ethanol after 0.1 mL of the test material was put in contact with human skin for 10 minutes (no more details available) (EPA87, NLM99).

Urinary excretion data from inhalation experiments in human volunteers, rats, and guinea pigs and from oral experiments in rats and dogs indicate that 2-phenylpropene can be metabolised into 2-hydroxy-2-phenylpropionic acid (atrolactic acid or a-methylmandelic acid) while in human urine an additional metabolite, 2-hydroxy-2-phenylpropanol glucuronide, was identified (Bar70, EPA87). According to an abstract cited by EPA, the amount of 2-hydroxy-2-phenylpropionic acid excreted as percentage of inhaled 2-phenylpropene was 21, 15.7, and 26.2% in guinea pigs, rats, and in humans, respectively, after exposure to 20-4000 mg/m^3. In humans, the excretion kinetics of 2-phenylpropene metabolites were stated to be a first-order process being monophasic for 2-hydroxy-2-phenylpropanol glucuronide and biphasic for 2-hydroxy-2-phenylpropionic acid (no more data presented) (EPA87). In rats treated orally with 2000 mg/kg, 2-phenylpropene was detected in the blood, liver, and placenta (abstract cited in EPA87; no further details given).

In order to obtain a definitive characterisation of the metabolism of 2-phenylpropene, the ^{14}C-labelled compound was orally and intravenously administered to 1 and 4 male rats (F344), respectively, and tissue distribution, metabolism, and excretion (intravenous injection of 11 mg/kg bw) were investigated and metabolites characterised (oral dose of 1000 mg/kg bw). Following intravenous injection, ca. 34, 53, and 86% of the dose administered were excreted (cumulatively) in the urine within 6, 12, and 72 hours, respectively. About 2% each were excreted in the faeces and as breath volatiles within 72 hours while elimination as carbon dioxide was negligible. At sacrifice

(at 72 hours), only 0.3% of the radioactivity administered was found in the tissues sampled with the highest concentrations in the spleen (blood/tissue ratio: 17), kidney (blood/tissue ratio: 12), bladder (blood/tissue/ratio: 7), and lung (blood/tissue ratio: 6). After oral administration, the percentage radioactivity excreted in urine and the urinary metabolite profile were similar to those after intravenous injection. The following 5 metabolites were isolated from the urine: 2-phenyl-1,2-propanediol (3% of urinary radioactivity) and its glucuronide (50%), 2-hydroxy-2-phenylpropionic acid (atrolactic acid; 27%), *S*-(2-hydroxy-2-phenylpropyl)-*N*-acetylcysteine (13%), and 2-phenylpropionic acid (1%); the glucuronides and mercapturates were each conjugated on the methylene carbon *beta* to the ring. The presence of both of the diastereomeric forms of those conjugates suggested that the initial epoxidation of 2-phenylpropene was not selective and proceeded with addition of active oxygen to yield enantiomeric epoxide. Incubation of 2-phenylpropene with human liver slices for 5 hours, resulted in the formation of the same as found *in vivo* in rats, with 2-phenyl-1, 2-propanediol accounting for 25% of the radioactivity, 2-hydroxy-2-phenylpropionic acid (atrolactic acid) and 2-phenylpropionic acid each for about 1%, and the remainder for less than 0.3%. Based on these data, a metabolism scheme as presented in Figure 1 (see Annex I) has been proposed (Cos01).

An *in vitro* study in rat liver mitochondria revealed that 2-phenylpropene uncouples the oxidative phosphorylation, stimulates the Mg^{2+}-dependent ATPase activity, and thereby stimulates the passive entry of protons into mitochondria (Mic88).

6 Effects and mechanism of action

Human data

In letters sent to the Document Control Officer at US EPA, two cases of urticaria were reported, for which there was reasonable medical indication that these allergic reactions were probably related to occupational exposure to 2-phenylpropene. The first, more severe case, was described in more detail: since the allergy occurred, the symptoms like itching and hives with pressure or skin scratching (dermatographism) had progressed without known 2-phenylpropene exposure (Ano86, Ano88). In an attachment, abstracts of two papers (the results of a literature search on dermal sensitisation of 2-phenylpropene) were presented. In one of these, 2-phenylpropene was stated to be one of the chemicals used in the production of divinylstyrene rubber causing skin sensitisation. In the other paper, exposure was to ‘methylstyrene’ (not ‘α-methylstyrene’) and,

therefore, no definitive statement to the sensitisation potential of 2-phenylpropene was said to be possible (Ano88).

Human subjects quickly entering a room in which 2-phenylpropene was present in the atmosphere reported no detectable odour at concentrations less than 48 mg/m^3 (10 ppm) while 241 mg/m^3 (50 ppm) was detectable but not irritating. A level of 483 mg/m^3 (100 ppm) resulted in a strong odour but was tolerable without excessive discomfort and 970 mg/m^3 (200 ppm) caused an objectionable, strong odour and slight eye irritation. Concentrations of 2900 mg/m^3 (600 ppm) and higher had a very strong odour and induced strong eye and nasal irritation (Wol56).

EPA has summarised data - all from abstracts - on occupationally exposed workers. Findings included effects on the nervous system, the respiratory tract, and the haematopoietic system. However, mostly, exposure was to mixtures of chemicals and no information on exposure levels was available (EPA87).

Animal data

Irritation and sensitisation

Moderate to marked irritation and slight necrosis were observed when undiluted 2-phenylpropene was applied to the ear and onto the shaved abdomen of white rabbits, 10-20 times, over a period of 2-4 weeks (Wol56). Uncovered application of 0.01 mL of undiluted 2-phenylpropene to the belly of 5 rabbits resulted in marked capillary injection in all rabbits within 24 hours (Mye75). Irritation scores of 0.0 (maximum: 8.0) were found when 0.5 mL of undiluted ‘crude’ 2-phenylpropene (purity unknown) or 0.5 mL undiluted cumene-containing material (purity: 95%, amount of cumene unknown) were applied to the clipped skin of rabbits (1 female and 2 males per compound), under occlusion for 24 hours (observation period: 7 days). Testing 0.5 mL of another lot of undiluted ‘crude’ material (purity unknown), under occlusion for 4 hours, caused very slight to slight erythema and very slight to clear oedema at 4, 24, 48, and 72 hours while readings were zero at 1, 120, and 168 hours (Bir72). Referring to an abstract, it was stated that 20 daily applications of 30% 2-phenylpropene, caused inflammation, hyperaemia, oedema, hyperkeratosis, changes in the thickness of the epithelial layer, and desquamation of the skin of the treated rabbits (EPA87).

Two drops of 2-phenylpropene applied to the eyes of rabbits resulted in slight conjunctival irritation and no corneal injury (Wol56). No corneal injury was observed, 24 hours after instillation of 0.5 mL of undiluted 2-phenylpropene into

the eyes of 5 rabbits (Mye75). When 0.1 mL undiluted 'crude' 2-phenylpropene was instilled into the right eye of one male and 2 female rabbits, the average maximum score was 14.0 (maximum: 110) found at 1 hour declining to 2.0 at 72 hours. Readings were zero at 120 and 168 hours. During the observation period, slight to severe erythema, very slight to slight oedema, and slight to copious discharge were observed. Similar results were obtained with the aforementioned cumene-containing test substance (Bir72).

With respect to the respiratory tract, the sensory irritation in the upper part was studied by determining the concentration associated with a 50% decrease in the respiratory rate (RD_{50}). Using (probably 10 Swiss OF1) mice, the RD_{50} for 2-phenylpropene was approximately 1320 mg/m^3 (264 ppm) (Mul84; see also Bos92).

No data were available on the potential sensitising properties of 2-phenylpropene.

Acute toxicity

Three out of 6 male rats died within 48 hours following a 6-hour exposure to 22,850 mg/m^3 (4570 ppm) of 'crude' 2-phenylpropene of unknown purity. During exposure, shallow and rapid respiration and roughened fur were observed while all animals collapsed in the second part of the exposure period. At autopsy, slight lung congestion was seen in the survivors sacrificed at the end of the 10-day observation period while haemorrhagic lungs, slight liver discolouration, and gastrointestinal inflammation were observed in the treatment-related deaths. Following exposure to 10,000 mg/m^3 cumene-containing 2-phenylpropene (see section on irritation), no mortality was observed. No toxic signs were seen during exposure and the 10-day post-exposure observation period. There were no changes at macroscopic examinations (Bir72). In another report, an 8-hour exposure to 'substantially saturated vapour' caused mortality in 2/6 rats. Clinical signs included closed eyes, poor coordination, prostration, followed by complete anaesthesia within 5 hours and eventually death within 7 hours. There were no remarkable changes at post-mortem gross examinations (Mye75). Exposure to 14,500 mg/m^3 (3000 ppm) has been reported to cause mortality in rats and guinea pigs (no details) (Cav94, NLM99). Further, it was summarised that exposure to 2920 ppm (14 g/m^3), for 5 hours, caused respiratory irritation and central nervous system depression in rats, mice, and guinea pigs within 15 to 60 minutes, and mortality in mice after about 4 hours while rats and guinea pigs survived the 5-hour exposure (Her87). In a subacute experiment, mortality - of which the cause could not be established - was found in 1/18, 10/18, and 5/24 mice after the

first 6-hour exposure to mean actual concentrations of 596, 799, and 1056 ppm (2920, 3915, 5174 mg/m^3), respectively (Mor99).

Following dermal application of 'crude' compound (purity: unknown), no mortality was observed in rabbits (n=1/dose) at doses of 501 to 7940 mg/kg bw (observation time: 10 days). Toxic signs included reduced appetite, reduced activity, and weight loss in female animals. No changes were seen upon post-mortem examinations. When cumene-containing material (see section on irritation) was applied at doses of 2000 (1 male), 3160 (1 female), 5010 (1 male), and 7940 (1 male, 1 female) mg/kg bw, the high-dose male rabbit died, autopsy revealing haemorrhagic areas of the lungs and slight liver discolouration. In the surviving animals, reduced appetite and activity, lethargy, collapse, and some weight loss were seen. Viscera were normal at macroscopic examination (Bir72). Dermal application of 16 mL/kg (ca. 14,400 mg/kg), for 24 hours, killed 3 out of 7 rabbits. Erythema and leathery or scaly skin, and hiccup-like spasms were noted. Spleens and kidneys were congested in the animals that died during the study while no remarkable changes were seen in the animals sacrificed at the end of the observation period (Mye75).

Following the administration of single oral doses in male rats, an LD_{50} of 4900 mg/kg was reported. At autopsy, slight liver changes were observed (Wol56). Using both male and female rats, an LD_{50} of 2840 mg/kg bw has been estimated for 'crude' 2-phenylpropene (purity unknown). Most animals died within 3 days. Signs observed included reduced appetite and activity, increased weakness, ocular discharge, and collapse. At autopsy, hyperaemia of lungs and liver and gastrointestinal inflammation were seen in the treatment-related deaths while there were no changes in the other animals. For the aforementioned cumene-containing lot, an LD_{50} of 4470 mg/kg bw was estimated (Bir72). In a separate study performed in young (3-4 weeks) male rats, mortality rates of 0/5, 4/5, and 5/5 were found after single oral doses of 4.0, 8.0, and 16.0 mL/kg respectively, resulting in a LD_{50} of 6.50 mL/kg (ca. 5900 mg/kg). Clinical signs included rubbing mouth on bottom of cage immediately after dosing, sluggishness, prostration, and unsteady gait. Necropsy of the treatment-related deaths revealed slight petechial haemorrhages in the lungs, mottled livers and spleens, distended stomachs filled with liquid or gas, white pylorus, yellow, liquid- or gas-filled transparent intestines, slightly congested kidneys, and full bladders. In the animals sacrificed at the end of the observation period, mottled livers were observed (Mye75).

Repeated-dose toxicity

When rats (F344; n=5/sex/group) were exposed to target concentrations of 0, 600, or 1000 ppm (2940, 4900 mg/m^3), 6 hours/day, 5 days/week, for a total of 12 exposures, no mortality, sedation, or effects on body weight or clinical chemistry values were observed. Post-mortem examinations of lungs, liver, kidneys, spleen, nasal cavity, brain, stomach, heart, thymus, and adrenal glands showed significant increases in relative weights of the livers of the animals of both exposure groups, of the lungs of the male animals of the high-concentration group, and of the kidneys of the males of the low-concentration group. Microscopically, no significant lesions other than increased accumulation of hyaline droplets in the renal tubules of the male animals exposed to 600 and 1000 ppm were found. In order to better characterise this latter effect, male and female F344 rats and male NBR rats (an α2u-globulin-deficient strain) (n=4/strain/sex/group) were exposed to target concentrations of 0, 125, 250, and 500 ppm (0, 612, 1225, 2450 mg/m^3), 6 hours/day, 5 days/week. After a total of 9 exposures, animals were sacrificed and (only) the kidneys were collected for histological evaluation. There was no effect on body or kidney weight in any of the treated groups. The only renal lesion observed was hyaline droplet accumulation. This was seen only in male F344 rats exposed to 250 and 500 ppm and not in female F344 rats, male NBR rats, or male F344 rats exposed to 125 ppm (Mor99). When mice (B6C3F1; n=30 males, 18 females/group) were exposed to actual mean levels of 0, 133, 245, and 489 ppm (652, 1200, 2396 mg/m^3), 6 hours/day, 5 days/week, for 12 days, no compound-related effects were found on body or organ weights, haematology, clinical chemistry, or histology in any of the treated groups. In a follow-up study, mice (n=18/sex/group, plus an additional 6/sex in the high-concentration group) were exposed to mean actual concentrations of 596, 799, and 1056 ppm (2920, 3915, 5174 mg/m^3), 6 hours/day, 5 days/week, for 12 days (target concentrations: 600, 800, 1000 ppm). Interim sacrifices (n=6/sex/group) were performed after 1 (only for liver weighing and glutathione analysis) and 5 exposures. Treatment induced mortality in female animals only: after the first exposure, 5/24, 10/18, 1/18 animals were found dead in the high-, mid- and low-concentration group, respectively. The cause of death could not be established. Immediately after the first 6-hour exposure, all mice of all groups were sedated. During exposure and for about 1-hour post-exposure, the animals were hypoactive and did not respond to noise. By the second week, there was adaptation, and animals were no longer sedated during exposure. Significant decreases in body weights were found in the male animals of all exposure groups while those of female animals were comparable to those of controls throughout

the study. Significant relative organ weight changes found included decreases in spleen weights in all exposure groups and increases in liver weights in male animals exposed to 799 and 1056 ppm for 1, 5, or 12 days and to 596 ppm for 5 days and in female animals of all exposure groups at all these time points (except those exposed to the low concentration for 1 day). There were no changes in clinical chemistry. Liver glutathione levels measured after 1 and 5 exposures were decreased. No lesions were found at microscopic examinations of lungs, kidneys, nasal cavity, brain, stomach, heart, thymus, or adrenal glands (Mor99).

In a subchronic study, rats (F344; n=10/sex/group) were exposed by whole-body inhalation to 2-phenylpropene vapour concentrations of 0, 75, 150, 300, 600, or 1000 ppm (i.e., 0, 367.5, 735, 1470, 2940, 4900 mg/m^3), 6 hours/day, 5 days/week, for 13 weeks. No mortality or clinical signs of toxicity were seen in any of the groups. In the animals of the high-concentration group, there was a small - not statistically significant - decrease in mean final body weight (4.4 and 5.1% in females and males, respectively). Exposure did not induce remarkable changes in haematology parameters in any of the treated groups. The most notable changes in clinical chemistry and urinalysis parameters included increased total bile acid concentrations in both sexes on day 3 and 23 at concentrations $\geq$600 ppm (on day 23 also in males at concentrations of 150 and 300 ppm), increased blood urea nitrogen on day 3 in males and females and day 23 (in males) at concentrations $\geq$600 ppm, and elevated urinary protein and enzymes in males and females at concentrations $\geq$300 and $\geq$600 ppm, respectively. Post-mortem examinations showed increases in absolute kidney weights in males and females at 1000 ppm, in relative kidney weights in males at $\geq$150 ppm and in females at $\geq$600 ppm, in absolute liver weights in males and females at $\geq$600 ppm, and in relative liver weights in males at $\geq$150 ppm and in females at $\geq$600 ppm. No gross lesions were seen in any of the treated groups. Histological changes included increased incidences in hepatocellular necrosis in females animals exposed to 600 (4/10) and 1000 ppm (9/10) when compared with controls (2/10). In males, incidences in hyaline droplets and tubular regeneration in the renal cortex were increased at $\geq$150 ppm. In male rats, the amount of α2u-globuline in the kidneys was dose dependently increased at $\geq$75 ppm while renal cortical cell turnover rates using proliferating cell nuclear antigen immunohistochemistry were elevated at 300 and 1000 ppm. No effects on the respiratory tract were observed (data, i.e., abstract and summary tables only, submitted to, but not peer reviewed by NTP) (NTP01). The committee considers the kidney lesions found in the male rats as an α2u-globuline-induced, typical male rat event and, therefore, not for human risk assessment. Based on

the increased relative liver weights in male rats exposed to 150 ppm and higher, the committee sets the NOAEL in this study at 75 ppm (367.5 mg/m^3).

In a similar study, mice (B6C3F1; n=10/sex/group) were whole-body exposed to 0, 75, 150, 300, 600, or 1000 ppm (i.e., 0, 367.5, 735, 1470, 2940, 4900 mg/m^3), 6 hours/day, 5 days/week, for 13 weeks. Except for 2 females in the 1000-ppm group dying after 2 exposures following sedation and coma, no mortality was observed. Clinical signs of toxicity were limited to moderate to severe sedation and ataxia in almost all male and female animals after exposure to 1000 ppm on day 1 and 2 (ataxia only) and in female animals on day 9 after 3 days off exposure. Decreases in mean final body weights were observed in male animals exposed to 300 (-5.1%), 600 (-13.0%; $p \leq 0.01$), and 1000 ppm (-16.6%; $p \leq 0.01$) and in females exposed to 75 (-8.7%; $p \leq 0.01$), 300 (-8.8%; $p \leq 0.01$), 600 (-4.2%), and 1000 ppm (-10.8%; $p \leq 0.01$). Apart from a very mild, non-regenerative anaemia in females exposed to 1000 ppm, no haematological effects were found in any of the other treated groups. Post-mortem examinations did not reveal remarkable gross lesions. Organ weight changes included increases in absolute liver weights in females at $\geq$600 ppm, in relative liver weights in males and females at $\geq$300 ppm, and in increased relative lung weights in males at $\geq$300 ppm (and in both sexes at 75 ppm), and in decreases in absolute thymus weights in males at $\geq$600 ppm and in females at 75 and 1000 ppm. Histologically, there were centrilobular hypertrophy in the livers of male and female mice exposed to 600 and 1000 ppm and nasal lesions (olfactory epithelial necrosis, atrophy, and metaplasia; glandular atrophy and hyperplasia; respiratory epithelial hyaline degeneration) at concentrations of $\geq$75 ppm (data, i.e., abstract and summary tables only, submitted to but not peer reviewed by NTP) (NTP01). The committee could not establish a NOAEL in this study since nasal lesions were induced at 75 ppm (367.5 mg/m^3), the lowest level tested.

In a - limitedly reported - inhalation study, rats (10-25), guinea pigs (5-10), rabbits (1-2), and monkeys (1-2) were exposed 7-8 hours/day, 5 days/week, for up to 7 months. Male and female rats and guinea pigs were exposed to 970, 2900, 3860, and 14,490 mg/m^3 (200, 600, 800, 3000 ppm), for 197, 212, 38, and 3-4 days, respectively. Exposure to 14,490 mg/m^3 (3000 ppm) for 3-4 days resulted in severe mortality (not specified) in both species. At 3860 mg/m^3 (800 ppm), both in rats and guinea pigs, slight growth depression and slight liver and kidney weight changes (direction not indicated) were observed, while the 212-day exposure to 2900 mg/m^3 (600 ppm) resulted in liver weight changes in rats and guinea pigs and in kidney weight changes in rats. There were no effects on growth, mortality, behaviour, appearance, organ weights, and gross and microscopic examinations (of lungs, heart, liver, kidneys, spleen, testes,

adrenals, pancreas, femoral bone marrow) following exposure to 970 mg/m^3 (200 ppm) for 197 days. In male and female rabbits exposed to 2900 mg/m^3 (600 ppm) and 970 mg/m^3 (200 ppm) for 212 and 197 days, respectively, no effects were observed at the lower concentration level while a slight increase in mortality and slight growth depression were seen at 2900 mg/m^3 (600 ppm). Female monkeys exposed to 2900 mg/m^3 (600 ppm) and female and male monkeys exposed to 970 mg/m^3 (200 ppm) for 212 and 197 days, respectively, showed no effects at all (Wol56). The committee notices that the results of this study were only limitedly reported in a table in a qualitative way without presenting incidences.

Short-term exposure of male mice (Swiss; n=10/group) to 2-phenylpropene vapours increased the threshold for the onset of clonic convulsions induced by pentetrazole. For 2-phenylpropene, the concentration in air causing a 50% increase in this seizure threshold was 3589 mg/m^3 (743 ppm) (Cea81).

Citing abstracts, US EPA reported changes in neurotransmitter levels, amino acid content, and enzyme activities in various organs of rats exposed to concentrations of 2-phenylpropene of 3000-5000 mg/m^3, for 1-6 days, and biochemical changes in the brain of rats exposed to 40-70 mg/m^3, 4-6 hours/day or continuously, for 1-6 months (EPA87).

Mutagenicity and genotoxicity

In an Ames test with *S. typhimurium* strains TA97, TA98, TA100, and TA1535, 2-phenylpropene (maximum dose: 3333 µg/plate) was negative when tested with and without metabolic activation (S9 fraction derived from both induced rat and hamster liver) (Zei92). In a separate study, negative results were reported as well when tested with and without an S-9 mix from induced rat livers in strains TA98, TA100, TA1535, TA1537, and TA1538 (maximum dose: 1000 µg/plate) (San91).

In vitro SCE-tests in human whole blood lymphocytes showed a significant increase (but no doubling compared to control) in the number of SCEs. A similar slight increase was noted in isolated human lymphocytes. This indicated that the induction of SCEs by 2-phenylpropene is independent of erythrocytes, in contrast to styrene and several other styrene derivatives (Nor83a, Nor83b, Nor84).

Negative results were obtained in a chromosomal aberration test using Chinese hamster ovary (CHO) cells tested with and without metabolic activation (S9 activation system) at dose levels up to 0.15 µL/mL. Cytotoxicity was observed at the two highest concentration levels of 0.10 and 0.15 µL/mL (Put91).

Reproduction toxicity

In an abstract of a 4-month inhalation study, it was stated that exposure of female rats to maximum permissible concentrations (not further specified; possibly 5 mg/m^3: see EPA87) of 2-phenylpropene induced increases in embryolethality (from 7.5 to 33%) and teratogenic effects (not specified; from 3.0 to 21.0%) in their offspring (Ser78).

In a preliminary study, young pregnant rats received intraperitoneal injections of 250 mg/kg bw of methylstyrene (not further specified) in corn oil on days 1-15 of gestation. No teratogenic effects (i.e., grossly visible external or internal - visceral or skeletal - malformations) nor maternal toxicity (i.e., reduced body weight gain or altered weights - absolute or relative - of two or more organs) were observed, but fetal toxicity was indicated by a statistically significant increase in the incidence of resorptions and a statistically significant change in fetal sex ratio (decrease in female fetuses) (Har81).

The committee did not find studies on the carcinogenicity and reproduction toxicity of 2-phenylpropene, but noticed that the compound was selected by the National Toxicology Program* for 2-year toxicity/carcinogenicity inhalation studies in rats and mice (n=50/sex/group) at concentrations of 0, 100, 300, 1000 ppm, and 0, 100, 300, and 600 ppm, respectively, which were started in July 2001.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) for 2-phenylpropene in the Netherlands is 240 mg/m^3 (50 ppm), 8-hour TWA.

Existing occupational exposure limits for 2-phenylpropene in some European countries and in the USA are summarised in Annex II.

8 Assessment of health hazard

Limited information on the kinetics suggests that 2-phenylpropene is metabolised via an epoxide intermediate into 2-hydroxy-2-phenylpropanol glucuronide and 2-hydroxy-2-phenylpropionic acid.

Information on effects on humans is limited as well. The compound may cause allergic reactions and effects on the nervous system, the respiratory tract, and the haematopoietic system. Exposure to levels as high as 483 mg/m^3 (100 ppm) for an unknown, short period was found not irritating although odour was

* see: http://ntp-server.niehs.nih.gov/htdocs/Results_Status/Resstatm/98839.html.

strong. Levels of 970 mg/m^3 (200 ppm) produced a strong, objectionable odour and slight eye irritation.

Experimental animal testing did not show 2-phenylpropene to be a skin irritant following single applications but repeated applications caused moderate to marked irritation. Transient signs of irritation were found when the compound was instilled into the eyes of rabbits. The committee did not find experimental animal data on the sensitising properties of 2-phenylpropene.

From lethal toxicity data, the committee concluded that 2-phenylpropene is of low toxicity following single or acute inhalation, dermal, or oral exposure.

In a 2-week inhalation study with F344 rats (Mor99), increased relative liver weights (without accompanying histological lesions) in male and female animals and hyaline droplet formation in the kidneys of males were found after 12 exposures (6 hours/day, 5 days/week) to ca. 2900 mg/m^3 (600 ppm). No other organs including - among others - lungs, nasal cavity, and brain were affected. In a follow-up study addressing the kidney lesions only (Mor99), similar hyaline droplet formation was found in male F344 rats at concentrations of 1225 and 2450 mg/m^3 (250, 500 ppm), but not at 612 mg/m^3 (125 ppm), while none of these concentrations induced such effects in female F344 rats or in male rats of an α2u-globulin-deficient strain (NBR). In mice (Mor99), no compound-related effects were seen at similar exposures up to ca. 2400 mg/m^3 (489 ppm). At the next higher level of 2920 mg/m^3 (596 ppm), nervous system depression (during the first week only), decreased body weights, decreased relative spleen weights, and increased relative liver weights were noted; there were no clinical chemistry or histology changes. In a 13-week study in rats and mice with exposure levels ranging from 367.5 to 4900 mg/m^3 (75-1000 ppm) (NTP01), effects on the kidneys (increased relative weights, hyaline droplet formation and tubular regeneration in renal cortex) were seen in male rats exposed to levels of 735 mg/m^3 (150 ppm) and higher. However, since these effects were not seen in female rats and were accompanied by, amongst others, dose-dependent increases in the amount of α2u-globuline, the committee considers these effects as male-rat specific and not relevant for human risk assessment. Further, there were increased relative liver weights in male rats, not accompanied by histological lesions, at exposure levels ≥735 mg/m^3 (150 ppm) and in female rats, accompanied by hepatocellular necrosis at levels ≥2940 mg/m^3 (600 ppm). There were no effects on respiratory tract tissues. In mice, nasal lesions consisting of olfactory epithelial necrosis, atrophy, and metaplasia, glandular atrophy and hyperplasia, and respiratory epithelial hyaline degeneration were found at all concentration levels. Effects on organ weights were found at concentrations ≥1470 mg/m^3 (300 ppm). Based on the relative liver weight changes found at 735

mg/m^3 (150 ppm) in males, the committee considers the next lower dose of 367.5 mg/m^3 (75 ppm) as the NOAEL for rats. For mice, the committee could not establish a NOAEL since nasal lesions were found at 367.5 mg/m^3 (75 ppm), the lowest concentration tested.

In a condensedly reported, 6-7-month inhalation study (Wol56), a NOAEL of 970 mg/m^3 (200 ppm) was found in rats, guinea-pigs, and rabbits, based on slight liver (rat, guinea pig) and kidney (rat) weight changes, and slightly increased mortality and growth depression (both in rabbits), observed at the next higher dose level of 2900 mg/m^3 (600 ppm).

Negative results were obtained in several Ames tests and an *in vitro* chromosomal aberration test. In human lymphocytes, 2-phenylpropene induced a small (less than twice the control value), but significant increase in the number of SCEs.

The committee did not find data on the carcinogenicity of 2-phenylpropene but noticed that the compound was selected by the National Toxicology Program for 2-year toxicity/carcinogenicity inhalation studies in rats and mice, which were started in July 2001.

The committee takes the LOAEL of 367.5 mg/m^3 found in the 13-week inhalation study in mice in which nasal lesions were observed (NTP01) as a basis for deriving a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, an overall assessment factor of 16 is established. This factor covers the following aspects: the absence of a NOAEL, intra- and interspecies variation, differences between experimental conditions and the exposure pattern of the worker, and the type of critical effect. Thus, applying this factor of 16 and the fixed/preferred value approach, a health-based occupational exposure limit of 20 mg/m^3 is recommended for 2-phenylpropene.

The committee recommends a health-based occupational exposure limit for 2-phenylpropene of 20 mg/m^3, as an 8-hour time-weighted average (TWA).

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Annex I

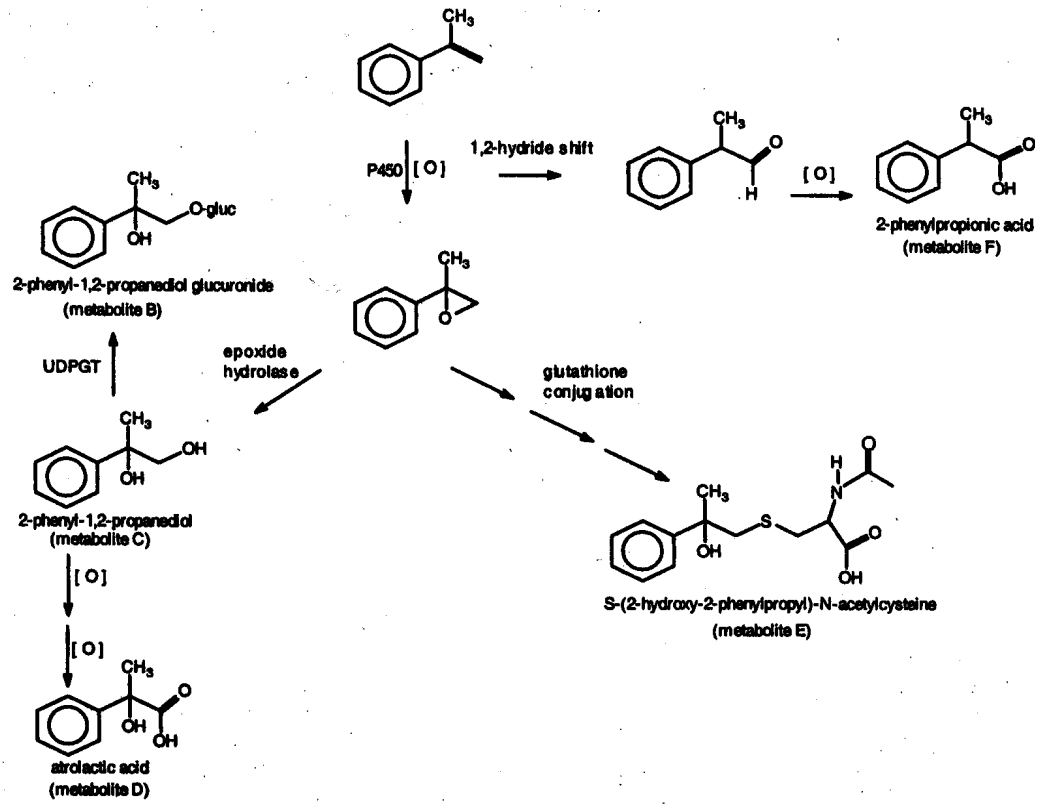

Figure 1 Metabolism scheme for 2-phenylpropene (Cos01).

Annex II

Occupational exposure limits for 2-phenylpropene in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands						
- Ministry of Social Affairs and Employment	50	240	8 h	administrative		SZW03
Germany						
- AGS	100	480	8 h			TRG00
	100	480	15 min			
- DFG MAK-Kommission	100	490	8 h			DFG02
	100	490	15 min[c]			
Great-Britain						
- HSE	50	246	8 h	OES		HSE02
	100	491	15 min			
Sweden	-	-				Swe00
Denmark	50	240	8 h			Arb02
USA						
- ACGIH	50	-	8 h	TLV		ACG03b
	100	-	15 min	STEL		
- OSHA	100	480	15 min, ceiling	PEL		ACG03a
- NIOSH	50	240	10 h	REL		ACG03a
	100	485	15 min	STEL		
European Union						
-SCOEL	50	246	8 h	ILV[d]		EC03
	100	492	15 min			

[a] S = skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b] Reference to the most recent official publication of occupational exposure limits.

[c] Maximum frequency per shift: 4, with a mininum time interval between peaks of 1 hour.

[d] Listed among compounds for which OELs are agreed to be included in next Commission Directive.