ALLYL ISOVALERATE

Data were last reviewed in IARC (1985) and the compound was classified in *IARC Monographs* Supplement 7 (1987).

1. Exposure Data

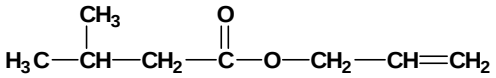
1.1 Chemical and physical data

1.1.1 *Nomenclature*

Chem. Abstr. Services Reg. No.: 2835-39-4

Systematic name: Butanoic acid, 3-methyl-, 2-propenyl ester

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_8H_{14}O_2$ Relative molecular mass: 142.2

1.1.3 *Physical properties* (for details, see IARC, 1985)

(*a*) *Boiling-point*: 89–90°C

(*b*) *Conversion factor*: mg/m^3 = 5.82 × ppm

1.2 Production and use

Allyl isovalerate has been used since the 1950s as a raw material for fragrances in cosmetics, lotions and perfumes and in certain food products, although it is not known whether it is currently used in this way (IARC, 1985).

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Allyl isovalerate was tested for carcinogenicity by gavage in mice and rats. In mice, it induced squamous-cell papillomas of the forestomach in males and increased the

incidence of lymphomas in females. In rats of both sexes, increases in the incidence of mononuclear-cell leukaemia were observed (IARC, 1985).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No data were available to the Working Group.

4.1.2 *Experimental systems*

Allyl isovalerate is metabolized to isovaleric acid, which can conjugate with glycine, and allyl alcohol, which could then be further metabolized via two pathways to form either acrolein or glycidol, from which a variety of metabolites could result (IARC, 1985).

4.2 Toxic effects

4.2.1 *Humans*

Allyl isovalerate has low irritancy potential. It is deduced that one of its metabolites, isovaleric acid, is toxic, based upon the effects of an inborn error of leucine metabolism caused by isovaleryl-coenzyme A dehydrogenase deficiency. This is a syndrome of neonatal vomiting and lethargy progressing to coma, pancytopenia and ketoacidosis that can be alleviated by glycine treatment, which enhances the synthesis and excretion of isovalerylglycine (Cohn *et al*., 1978; IARC, 1985).

4.2.2 *Experimental systems*

Allyl isovalerate can cause liver-cell necrosis in orally dosed rats (IARC, 1985). This was substantiated in a 13-week dose ranging study in which Fischer 344/N rats dosed by gavage at 250 mg/kg bw developed hepatic multifocal coagulative necrosis, cholangiofibrosis, nodular hyperplasia and bile-duct hyperplasia in both sexes and cytoplasmic vacuolization in males. As part of the same study, some $B6C3F_1$ mice of each sex also developed hepatic coagulative necrosis at the same dose level; other lesions observed in the mice included ulcerative inflammation of the stomach, thickening of the stomach mucosa and thickening of the urinary bladder wall (United States National Toxicology Program, 1983). Further studies in the same strains of rats and mice administered doses of 250 mg/kg bw to rats and 125 mg/kg bw to mice by gavage on five days a week for two weeks showed that allyl isovalerate had no effect upon haematology or bone marrow cellularity, but there were subtle myelotoxic effects in mice and hepatotoxicity in rats (Hong *et al*., 1988).

4.3 Reproductive and developmental effects

No data were available to the Working Group.

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

Allyl isovalerate was not mutagenic in bacteria, but did induce sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary CHO cells.

5. Evaluation

No epidemiological data relevant to the carcinogenicity of allyl isovalerate were available.

There is *limited evidence* in experimental animals for the carcinogenicity of allyl isovalerate.

Overall evaluation

Allyl isovalerate is *not classifiable as to its carcinogenicity to humans (Group 3).*

6. References

Cohn, R.M, Yudkoff, M., Rothman, R. & Segal, S. (1978) Isovaleric acidemia: use of glycine therapy in neonates. *New Engl. J. Med*., **299**, 996–999

Gulati, D.K., Witt, K., Anderson, B., Zeiger, E. & Shelby, M.D. (1989) Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells *in vitro*. III. Results with 27 chemicals. *Environ. mol. Mutag*., **13**, 133–193

Hong, H.L., Huff, J.E., Luster, M.I., Maronpot, R.R., Dieter, M.P., Hayes, H.T. & Boorman, G.A. (1988) The effects of allyl isovalerate on the hematopoietic and immunologic systems in rodents. *Fundam. appl. Toxicol*., **10**, 655–663

IARC (1985) *IARC Monographs on the Evaluation of the Carcinogenic Risks of Chemicals to Humans*, Vol. 36, *Allyl Compounds, Aldehydes, Epoxides and Peroxides*, Lyon, pp. 32–33, 69–74

IARC (1987) *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, Supplement 7, *Overall Evaluations of Carcinogenicity: An Updating of* IARC Monographs *Volumes 1 to 42*, Lyon, p. 56

United States National Toxicology Program (1983) *Carcinogenesis Studies of Allyl Isovalerate (CAS No. 2835-39-4) in F344/N Rats and B6C3F1 Mice (Gavage Studies)* (NTP TR No. 253), Washington DC, US Department of Health and Human Services

Table 1. Genetic and related effects of allyl isovalerate

Test system	Result[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	166	US National Toxicology Program (1983)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	166	US National Toxicology Program (1983)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	500	US National Toxicology Program (1983)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	500	US National Toxicology Program (1983)
SIC, Sister chromatid exchange, Chinese hamster ovary CHO cells *in vitro*	+	(+)	250	Gulati *et al.* (1989)
CIC, Chromosomal aberrations, Chinese hamster ovary CHO cells *in vitro*	–	+	300	Gulati *et al.* (1989)

[a] +, positive; (+), weak positive; –, negative
[b] LED, lowest effective dose; HID, highest ineffective dose; in-vitro tests, µg/mL