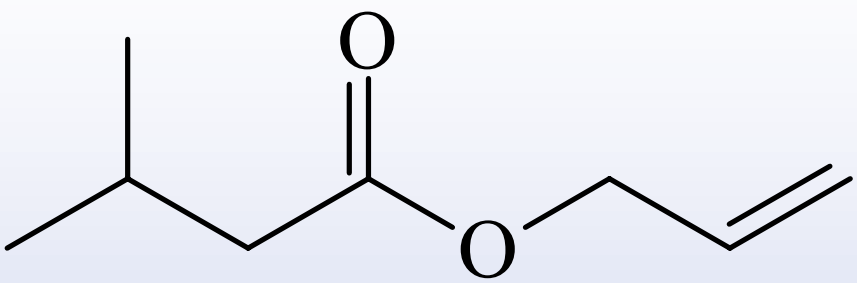
Allyl Isovalerate
(AIV)



Molecular Weight: 142.2 CAS Reg. No.: 2835-39-4

Office of Environmental Health Hazard Assessment

Allyl Isovalerate Use/Occurrence

- Synthetic flavoring agent
- Not naturally occurring
- FDA: “may be safely used in food”
- Use reported in numerous food and personal hygiene products above one ppm

Carcinogenicity of AIV

- **Carcinogenicity in humans:**
  - No data
- **Carcinogenicity in experimental animals:**
  - Long-term gavage studies in rats (NTP, 1983)
  - Long-term gavage studies in mice (NTP, 1983)

Tumors in F344 Rats (NTP, 1983)

Tumor Site and Type		Dose (mg/kg)			Trend Test
		0	31	62	
Males					
Hematopoietic	Mononuclear cell leukemia	1/50	4/50	7/50*	0.021
	Malignant lymphoma, histiocytic	0/50	0/50	2/50	n.s.
Preputial gland	Adenomas	0/50	4/50	1/50	n.s.
	Combined adenomas / carcinomas	0/50	5/50*	2/50	n.s.
Females					
Hematopoietic	Mononuclear cell leukemia	4/50	6/50	8/49	n.s.
	Leukemia, not otherwise specified	0/50	0/50	1/49	n.s.
	Leukemia, combined	4/50	6/50	9/49	0.082
	Malignant lymphoma, histiocytic	1/50	0/50	1/49	n.s.
	Thymoma	0/41	0/43	1/39	n.s.

* Significant increase over controls ($p<0.05$, by Fisher's exact test).

Tumors in $B6C3F_1$ Mice (NTP, 1983)

Tumor site and type		Dose (mg/kg)			Trend test
		0	31	62	
Males					
Gastric mucosa	Squamous cell papillomas	0/50	1/50	3/48	0.056
Hematopoietic	Malignant lymphoma, all	4/50	6/50	8/50	n.s.
Females					
Gastric mucosa	Squamous cell papillomas	1/50	0/50	2/50	n.s.
Hematopoietic	Malignant lymphoma, lymphocytic	5/50	5/50	4/50	n.s.
	Malignant lymphoma, histiocytic	0/50	1/50	4/50	0.026
	Malignant lymphoma, mixed type	6/50	5/50	10/50	n.s.
	Malignant lymphoma, all	11/50	11/50	18/50*	0.071**

* Significant increase over controls by Life Table test ($p<0.05$) (Fisher's exact test, $p=0.093$).
** Significant positive trend by Life Table ($p=0.26$) and Incidental Tumor tests ($p=0.037$).

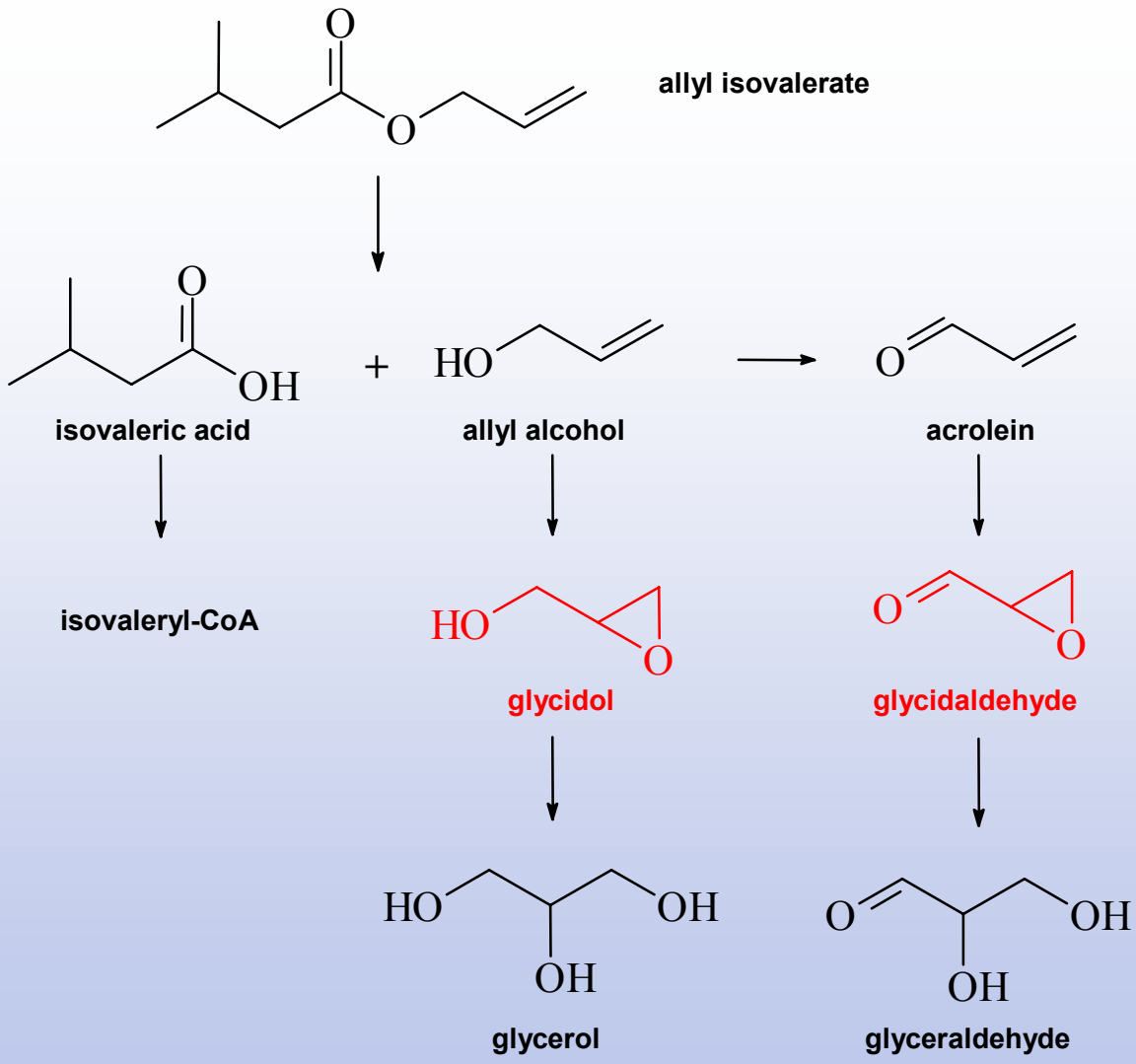
Summary of Animal Data

- **Male rats**
  - Leukemia – mononuclear cell
    - Increased incidence, positive trend
  - Preputial gland –
    - Increased incidence (low dose only)
- **Female rats**
  - Leukemias – primarily mononuclear cell
    - Positive trend
- **Male mice**
  - Gastric mucosa papillomas
    - Positive trend
- **Female mice**
  - Malignant lymphoma
    - Increased incidence, positive trend

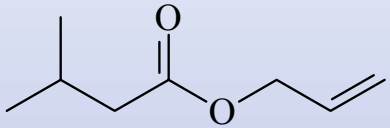
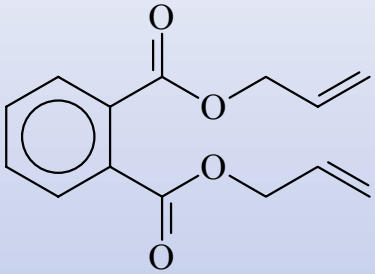
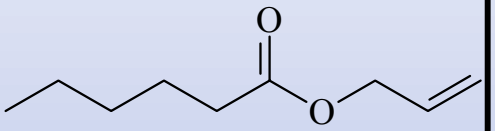
Genotoxicity of AIV

- **Bacterial assays**
  - Negative in *Salmonella*
- **Mammalian cell assays**
  - Positive in hamster (CHO) cells
    - Sister chromatid exchange
    - Chromosomal aberrations
  - [Positive in mouse lymphoma assay]
  - Negative in mouse 3T3 morphological transformation
- **Insect assay**
  - Negative for *Drosophila* sex-linked recessive lethal mutations

Proposed Metabolic Scheme for AIV



Structure-Activity Comparisons

Allyl Isovalerate	Diallyl Phthalate	Allyl Hexanoate
Lymphoma, leukemia; gastric papillomas	Lymphoma, leukemia; forestomach papillomas	Bile duct adenomas
Chromosomal aberrations SCE Neg. in Salmonella	Chromosomal aberrations SCE Neg. in Salmonella	---
		

Allyl Isovalerate: Summary

- **Animal evidence of carcinogenicity:**
  - Hematopoietic tumors in male rats and female mice in long-term gavage studies

- **Other relevant evidence:**
  - Genotoxicity
  - Proposed metabolites cause cancer
  - Structure-activity analogies

Authoritative Bodies

- **National Toxicology Program (1983)**
  - Carcinogenic in rats and mice under the conditions of the bioassay
- **International Agency for Research on Cancer**
  - Group 3 (1985, 1999) – “not classifiable”
    - No epidemiological data
    - “Limited evidence in experimental animals”