



WORLD HEALTH ORGANIZATION  
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

# Volume 31

## Some Food Additives, Feed Additives and Naturally Occurring Substances

### Summary of Data Reported and Evaluation

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AF-2 [2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide]  
Agaritine (*L*-glutamic acid-5-[2-(4-hydroxymethyl)phenylhydrazide])  
2-Amino-5-nitrothiazole  
Carrageenan  
Cholesterol  
Cinnamyl anthranilate  
Furazolidone  
Gyromitrin (acetaldehyde formylmethylhydrazone)  
Kaempferol  
Nithiazide  
Nitrovin  
Petasitenine  
Quercetin  
Senkirkine  
Symphytine  
Trp-P-1 (3-Amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole) and its acetate  
Trp-P-2 (3-Amino-1-methyl-5*H*-pyrido[4,3-*b*]indole) and its acetate

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Last updated: 16 April 1998

# AF-2 [2-(2-FURYL)-3-(5-NITRO-2-FURYL)ACRYLAMIDE]

**VOL.:** 31 (1983) (p. 47)

**CAS No.:** 3688-53-7

**Chem. Abstr. Name:** 2-Furanacetamide,  $\alpha$ -[(5-nitro-2-furyl)methylene]-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

AF-2 was tested for carcinogenicity in three experiments in mice, in two experiments in rats and in two experiments in hamsters by administration in the diet. It produced benign and malignant forestomach tumours in mice of both sexes, benign and malignant mammary tumours and forestomach papillomas in rats of both sexes and benign and malignant forestomach tumours in hamsters of both sexes and oesophageal tumours in male hamsters. In one experiment in weanling mice by subcutaneous injection, it produced lung tumours. It produced multiple lung tumours in the offspring of mice treated subcutaneously during pregnancy.

AF-2 induced DNA damage in bacteria and in human cells and mutations in bacteria, fungi, insects and mammalian cells *in vivo* and *in vitro*. It caused chromosomal anomalies in mammalian cells, including human cells. AF-2 caused neoplastic transformation in hamster cells. There is *sufficient evidence* that AF-2 is active in short-term tests.

AF-2 induced foetal deaths in mice and was teratogenic to survivors of dams pretreated with phenobarbital.

### 5.2 Human data

AF-2 has been used in Japan since at least 1965, but it is not used presently. Its use as a food preservative was a source of exposure for the general population.

No data were available to assess the teratogenicity or chromosomal effects of this compound in humans.

The one available epidemiological study in which a regional correlation between AF-2 consumption and breast cancer mortality was analysed was considered inadequate to evaluate the carcinogenicity of AF-2.

### 5.3 Evaluation

The epidemiological data were *inadequate* to evaluate the carcinogenicity of AF-2 to humans.

There is *sufficient evidence* for the carcinogenicity of AF-2 in experimental animals.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Subsequent evaluation:** Suppl. 7 (1987) (p. 56: **Group 2B**)

### Synonyms

- AF2
- FF
- Furylfuramide

- 2-(2-Furyl)-3-(5-nitro-2-furyl)acrylic acid amide
- $\alpha$ -(Furyl)- $\beta$ -(5-nitro-2-furyl)acrylic amide
- *trans*-2-(2-Furyl)-3-(5-nitro-2-furyl)acrylamide
- Tofuron

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Last updated: 16 April 1998

# AGARITINE

**VOL.:** 31 (1983) (p. 63)

**CAS No.:** 2757-90-6

**Chem. Abstr. Name:** L-Glutamic acid,5-[2-[4-(hydroxymethyl)phenyl]hydrazide]

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Agaritine was tested for carcinogenicity in mice by administration in the drinking-water; no increase in the incidence of tumours was observed. *N'*-Acetyl-4-(hydroxymethyl)phenylhydrazine (a stable derivative of the hydrolysis product of agaritine) was tested in one experiment in mice by administration in the drinking-water, producing increased incidences of lung tumours and of blood-vessel tumours. 4-(Hydroxymethyl)benzenediazonium ion tetrafluoroborate (another stabilized hydrolysis product of agaritine) was tested in mice by subcutaneous injection, increasing the incidence of fibrosarcomas and of skin papillomas and carcinomas at the injection site.

Agaritine was weakly mutagenic in *Salmonella typhimurium*. The data were *inadequate* to evaluate the activity of agaritine in short-term tests.

No data were available to evaluate the teratogenicity of agaritine to experimental animals.

N.B. - Subsequent to the meeting, the Secretariat became aware of a study in which 4-(hydroxymethyl)benzenediazonium tetrafluoroborate was administered to Swiss mice as a single intragastric instillation of 400 mg/kg bw, producing glandular stomach tumours (Toth *et al.*, 1982).

### 5.2 Human data

Agaritine is a natural substance found in several mushrooms of the *Agaricus* species, which are eaten both raw and cooked in many parts of the world.

No data were available to evaluate the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of agaritine was available to the Working Group.

### 5.3 Evaluation

The results of one experiment in mice do not provide evidence of carcinogenicity of agaritine to experimental animals. There is *limited evidence* of the carcinogenicity of derivatives of two fungal metabolites of agaritine in experimental animals. In the absence of epidemiological data, no evaluation of the carcinogenicity of agaritine to humans could be made.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Subsequent evaluation:** Suppl. 7 (1987) (p. 56: **Group 3**)

### Synonyms

- $\beta$ -N-[ $\gamma$ -L(+)-glutamyl]4-hydroxymethylphenylhydrazine

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Last updated: 16 April 1998

# 2-AMINO-5-NITROTHIAZOLE

**VOL.:** 31 (1983) (p. 71)

**CAS No.:** 121-66-4

**Chem. Abstr. Name:** 2-Thiazolamine, 5-nitro-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

2-Amino-5-nitrothiazole was tested for carcinogenicity in one experiment in mice and in two experiments in two strains of rats by administration in the diet. In one experiment in female rats, 2-amino-5-nitrothiazole increased the incidence of benign mammary tumours. In the other experiment in rats it increased the incidences of malignant lymphomas, lymphocytic and undifferentiated leukaemias, and granulocytic leukaemias in male rats. The results of studies in mice were not indicative of a carcinogenic effect.

2-Amino-4-nitrothiazole was mutagenic in bacteria. The data were inadequate to evaluate the activity of this compound in short-term tests.

No data were available to evaluate the teratogenicity of this compound to experimental animals.

### 5.2 Human data

2-Amino-5-nitrothiazole, a synthetic veterinary antiprotozoal agent, has been produced and used since 1950. It is also used as an intermediate in the manufacture of disperse azo dyes. Manufacturers of the compound itself, handlers of feed and people involved in the synthesis of the dyes concerned are exposed to 2-amino-5-nitrothiazole.

No data were available to assess the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of 2-amino-5-nitrothiazole was available to the Working Group.

### 5.3 Evaluation

There is *limited evidence* for the carcinogenicity of 2-amino-5-nitrothiazole in experimental animals. In the absence of epidemiological data, no evaluation of the carcinogenicity of 2-amino-5-nitrothiazole to humans could be made.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Subsequent evaluation:** Suppl. 7 (1987) (p. 57: **Group 3**)

### Synonyms

- Aminonitrothiazole
- Aminonitrothiazolum
- Amnizol soluble
- Enheptin
- Enheptin Premix

- Enheptin T
- Entramin
- NCI CO3065
- Nitramin
- Nitramine
- Nitramin Ido
- 5-Nitro-2-aminothiazole
- 5-Nitro-2-thiazolylamine

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Last updated: 16 April 1998

# CARRAGEENAN

**VOL.:** 31 (1983) (p. 79)

**CAS No.:** 9000-07-1

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Native (undegraded) carrageenan was tested for carcinogenicity in rats and hamsters by administration in the diet; no evidence of carcinogenicity was found. In female rats treated with azoxymethane or *N*-nitrosomethylurea together with native carrageenan in the diet, a greater incidence of colorectal cancers was observed than with treatment by azoxymethane or *N*-nitrosomethylurea alone. Degraded carrageenan was tested in rats by administration in the diet, in the drinking-water and by oral intubation, in four experiments; colorectal cancers were induced in each study.

Native carrageenan has not been tested in short-term assays. Degraded carrageenan was not mutagenic in bacteria or in mammalian cells *in vitro*. The data were *inadequate* to evaluate the activity of degraded carrageenan in short-term tests.

Native or degraded carrageenan had no reproductive or teratogenic effect in rats or hamsters.

### 5.2 Human data

Carrageenan-containing seaweeds have been used since at least two hundred years, and isolated carrageenan has been used as a food additive since 1937. Carrageenan is used in the manufacture of food, drug and cosmetic products and in multiple industrial applications, resulting in wide human exposure.

No data were available to assess the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study on the carcinogenicity of native or degraded carrageenan was available to the Working Group.

### 5.3 Evaluation

The available data do not provide evidence that native (undegraded) carrageenan is carcinogenic to experimental animals. In the absence of epidemiological data, no evaluation of the carcinogenicity of native carrageenan to humans could be made.

Experiments in rats with doses of degraded carrageenan comparable to those used to test native carrageenan provide *sufficient evidence* for the carcinogenicity of degraded carrageenan in rats. No data on humans were available.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Previous evaluation:** [Vol. 10 \(1976\)](#)

**Subsequent evaluation:** Suppl. 7 (1987) (p. 59: Carrageenan, native - **Group 3**; Carrageenan, degraded - **Group 2B**)

## Synonyms

- Aubygel GS, LGA, MR50, TRS, X52, X100 & X120
- Aubygum DM
- Burtonite V-40-E
- Carastay
- Carastay C, E, K, M, S, & X; Colloid 775
- Carrageen
- $\kappa$ ,  $\lambda$  and  $\iota$ -Carrageenan
- Carrageenan gum
- Carrageenin
- Carragheanin
- Carragheen
- Carragheenan
- Chondrus extract
- Coreine
- Eucheuma spinosum gum
- Flanogen ELA, RS1; RS2, 531 & 553
- Galozone
- Gelcarin
- Gelcarin HMR, LA, SI
- Gelogen 2, 4, 8, P10, 28, 406 & 440
- Gelozone
- Genu
- Genugel
- Genugel CJ, CMJ-2, CMJ-343, CWG, CWG-122, KWG, LC-1, LC-4, MGW, PWG, UE & WG
- Genugol RLV
- Genulacta
- Genulacta CL-126, CP-100, K-100, L-100, MDS, P-100 & PL-93
- Genuvisco J
- Gum carrageenan
- Gum chon 2
- Gum chond
- Irish gum
- Irish moss extract
- Lygomme CDS, DP, GB3, LA60, 34, 35 & 267/3
- Pellugel
- Pellugel ID
- Pencogel
- Satiagel GS350, HV, HVX, K40 & K80
- Satiagum 3
- Satiagum standard
- Seakem Carrageenin
- Seakem 3 & LCM
- Seaspen PF
- Sulphate ester of a polysaccharide of galactose
- Viscarin
- Viscarin 402 & TP-4

# CHOLESTEROL

VOL.: 31 (1983) (p. 95)

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Cholesterol was tested for carcinogenicity in mice by administration in the diet, by subcutaneous administration and by bladder implantation. These studies were all inadequate for evaluation. Cholesterol was also tested in combination with various carcinogens, but the results are insufficient to assess the co-carcinogenic potential of this compound.

Cholesterol, when free of oxidation products, was not mutagenic in bacteria and did not cause cell transformation. The data were *inadequate* to evaluate the activity of cholesterol in short-term tests.

Cholesterol induced cleft palate in rats.

### 5.2 Human data

Cholesterol and cholesterol derivatives are widely distributed in human tissues and in the human diet. Cholesterol is used in a multitude of pharmaceutical and cosmetic preparations.

As in the preceding presentation of epidemiological data, the evidence is summarized according to the three contexts in which cholesterol has been measured, i.e., in the diet, the blood and the faeces.

Few epidemiological studies of cancer have examined dietary cholesterol specifically, although many have examined total saturated fat intake. At the population level, cancers of the colon and female breast (and, to a lesser extent, the prostate, endometrium, ovary, pancreas and rectum) are strongly positively correlated with estimated per-caput intake of dietary saturated fat and, where studied, cholesterol. In the few case-control studies that have estimated individual dietary cholesterol intake, cancers of the breast and colon-rectum have tended to be positively associated with dietary total fat, saturated fat and cholesterol. Although there is moderately consistent, albeit limited, evidence of an association between high dietary intake of cholesterol and cancers of the colon, breast and, less convincingly, some other cancers, a causal relationship cannot be inferred from these epidemiological data. In particular, there is a difficulty in distinguishing between any effect of cholesterol and the effects of other dietary factors with which cholesterol is positively or negatively correlated.

With respect to serum cholesterol, the findings from seven cholesterol-lowering intervention trials (five by diet, two by drugs) indicate no alteration in cancer risk consequent upon a reduction in individual serum cholesterol. However, long-term observational follow-up studies have shown either an inverse relationship between individual serum cholesterol (measured at entry into the study) and subsequent total cancer risk (mortality or incidence) or no such relationship. The lack of consistency of these studies, and the partial attributability of the observed inverse relationships to a presumed cholesterol-lowering effect of subclinical cancer (the 'undetected cancer effect'), preclude any conclusion that there is an increased general cancer risk consequent upon low serum cholesterol.

It seems clear that serum cholesterol does not have a strong or direct relationship with human carcinogenesis in general, of the kind it apparently has with coronary heart disease. The inverse relationship with total cancer risk, when present, is not strong, is not graded (but, instead, tends to occur in stepwise fashion below concentrations of 180-190 mg/dl), and applies predominantly to men. For cancer of the colon, specifically, the prospective observational studies show a moderately consistent inverse association with serum cholesterol.

No data were available to assess the teratogenicity or chromosomal effects of this compound in humans.

### 5.3 Evaluation

No evaluation of the carcinogenicity of cholesterol to experimental animals could be made.

There is *inadequate evidence* from epidemiological studies that cholesterol as such is carcinogenic to humans.

There is *limited evidence* to indicate that raised dietary intake of cholesterol by individuals is associated with an increased risk of breast and colo-rectal cancer.

There is strong evidence that a low serum cholesterol level attained by dietary or pharmacological means is not per se associated with an increased risk of cancer.

There is *limited evidence* that, within the populations studied, those male individuals with relatively low serum concentrations have an increased risk of colon cancer; the data pertaining to women were inadequate for evaluation. There is *inadequate evidence* that a low serum cholesterol level increases the risk of cancer at sites other than the colon.

The available epidemiological and experimental studies do not permit an evaluation of the carcinogenicity to humans of cholesterol *per se*.

N.B. - The pattern of associations between cholesterol and human cancer risk contains some apparent contradictions. Depending on whether cholesterol is measured in the diet, blood or faeces, its association with cancer risk may tend to be either positive or negative. Because the biological significance, in relation to carcinogenesis, of cholesterol in each of these basically different contexts is not sufficiently understood, it is not yet possible to reconcile these apparently divergent findings.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Previous evaluation:** [Vol. 10 \(1976\)](#)

**Subsequent evaluation:** [Suppl. 7 \(1987\)](#)

# CINNAMYL ANTHRANILATE

**VOL.:** 31 (1983) (p. 133)

**CAS No.:** 87-29-6

**Chem. Abstr. Name:** Benzoic acid, 2-amino-, 3-phenyl-2-propenyl ester

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Cinnamyl anthranilate was tested for carcinogenicity in mice and rats by administration in the diet and in mice by intraperitoneal injection. In mice, a dose-related increase in the incidence of hepatocellular tumours was found following its oral administration and an increased incidence of lung tumours following its intraperitoneal injection. The study in rats could not be evaluated.

Cinnamyl anthranilate was not mutagenic to *Salmonella typhimurium*. The data were *inadequate* to evaluate the activity of this compound in short-term tests.

No data were available to evaluate the teratogenicity of this compound to experimental animals.

### 5.2 Human data

Cinnamyl anthranilate has been used since at least 1939, but its use during the last few years has diminished. Its consumption as a flavouring agent and to a lesser extent as a fragrance in cosmetics are sources of exposure for the general population.

No data were available to evaluate the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of cinnamyl anthranilate was available to the Working Group.

### 5.3 Evaluation

There is *limited evidence* for the carcinogenicity of cinnamyl anthranilate in experimental animals. In the absence of epidemiological data, no evaluation of the carcinogenicity of cinnamyl anthranilate to humans could be made.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Previous evaluation:** [Vol. 16 \(1978\)](#)

**Subsequent evaluation:** Suppl. 7 (1987) (p. 60: **Group 3**); [Vol. 77 \(2000\)](#)

### Synonyms

- Anthranilic acid, cinnamyl ester
- Cinnamyl alcohol anthranilate
- Cinnamyl 2-aminobenzoate
- Cinnamyl *ortho*-aminobenzoate

- 3-Phenyl-2-propen-1-yl anthranilate
- 3-Phenyl-2-propenyl anthranilate

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Last updated: 16 April 1998

# FURAZOLIDONE

**VOL.:** 31 (1983) (p. 141)

**CAS No.:** 67-45-8

**Chem. Abstr. Name:** 2-Oxazolidinone, 3-([(5-nitro-2-furanyl)methylene]amino)-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Data on the carcinogenicity of furazolidone were reported only in secondary sources and therefore could not be evaluated. (See 'General Remarks on the Substances Considered', in this volume.)

Furazolidone has been shown to induce DNA damage and mutations in bacteria and mutations in fungi and insects. It caused unscheduled DNA synthesis in mammalian cells *in vitro* and yielded conflicting results when tested for chromosomal anomalies in human cells *in vitro*. There is *sufficient evidence* that furazolidone is active in short-term tests.

Furazolidone induced abortion in mice. The data were inadequate to evaluate other prenatal effects.

### 5.2 Human data

Furazolidone has been produced commercially since 1955. It is used in human and veterinary medicine as an antibacterial and antiprotozoal agent.

No data were available to assess the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of furazolidone was available to the Working Group.

### 5.3 Evaluation

No evaluation of the carcinogenicity of furazolidone to experimental animals could be made. In the absence of epidemiological data, no evaluation of the carcinogenicity of furazolidone to humans could be made.

**Subsequent evaluation:** Suppl. 7 (1987) (p. 63: **Group 3**)

### Synonyms

- Bifuron
- Corizium
- Diafuron
- Enterotoxon
- Furaphen
- Furaxon
- Furaxone
- Furazol
- Furazolidon
- Furazon
- Furidon
- Furovag

- Furox
- Furoxal
- Furoxane
- Furoxon
- Furoxone
- Furoxone Swine Mix
- Furozolidine
- Giardil
- Giarlam
- Medaron
- Neftin
- NF 180
- NF 180 Custom Mix Ten
- Nicolen
- Nifulidone
- Nifuran
- *N*-(5-Nitro-2-furfurylidene)-3-amino-2-oxazolidone
- Nitrofurazolidone
- Nitrofurazolidonum
- Nitrofuroxon
- 5-Nitro-*N*-(2-oxo-3-oxazolidinyl)-2-furanmethanimine
- Optazol
- Ortazol
- Puradin
- Roptazol
- Sclaventerol
- Tikofuran
- Topazone
- Trichofuron
- Tricofuron
- Trifurox
- Viofuragyn

# GYROMITRIN (ACETALDEHYDE FORMYLMETHYLHYDRAZONE)

VOL.: 31 (1983) (p. 163)

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Gyromitrin was tested for carcinogenicity in one experiment in mice by gavage, producing increased incidences of lung, forestomach and clitoral gland tumours in females and of preputial tumours in males. *N*-Methyl-*N*-formylhydrazine, a metabolite, was tested in mice by administration in the drinking-water, increasing the incidence of tumours of the liver, lung, gall bladder and bile duct. *N*-Methylhydrazine, another metabolite, was tested in mice and hamsters by administration in the drinking-water; it produced increased incidences of histiocytomas and caecal tumours in hamsters.

Gyromitrin was not mutagenic in bacteria, but the metabolite *N*-methylhydrazine gave positive results. The data were *inadequate* to evaluate the activity of gyromitrin in short-term tests.

No data were available to evaluate the teratogenicity of this compound to experimental animals.

### 5.2 Human data

Gyromitrin is a natural substance found in the false morel. Although most of the compound is destroyed by proper preparation before eating, there is still a possibility for human exposure.

No data were available to assess the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of gyromitrin was available to the Working Group.

### 5.3 Evaluation

Results of studies on gyromitrin itself, supported by studies on two of its metabolites, provide *sufficient evidence* for the carcinogenicity of gyromitrin in experimental animals. No data on humans were available.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Subsequent evaluation:** [Suppl. 7 \(1987\)](#)

# KAEMPFEROL

**VOL.:** 31 (1983) (p. 171)

**CAS No.:** 520-18-3

**Chem. Abstr. Name:** 4*H*-1-Benzopyran-4-one, 3,5,7-trihydroxy-2-(4-hydroxyphenyl)-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Kaempferol was tested for carcinogenicity in one experiment in rats by administration in the diet. The data are inadequate to make an evaluation.

Kaempferol was mutagenic in bacteria and insects and in mammalian cells *in vitro*; it induced micronuclei in mice. There is *limited evidence* that kaempferol is active in short-term tests.

No data were available to evaluate the teratogenicity of kaempferol to experimental animals.

### 5.2 Human data

The natural occurrence of kaempferol, an aglycone widely distributed in fruit and other edible plants, results in wide human exposure to this compound.

No data were available to evaluate the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of kaempferol was available to the Working Group.

### 5.3 Evaluation

The available data were *inadequate* to evaluate the carcinogenicity of kaempferol to experimental animals. In the absence of epidemiological data, no evaluation of the carcinogenicity of kaempferol to humans could be made.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Subsequent evaluation:** Suppl. 7 (1987) (p. 65: **Group 3**)

### Synonyms

- Campherol
- C.I. 75640
- Indigo yellow
- Kaempherol
- Kampherol
- Kempferol
- Nimbecetin
- Pelargidenolon 1497
- Populnetin
- Rhamnolutein

- Rhamnolutin
- Robigenin
- Swartziol
- Trifolitin
- 5,7,4'-Trihydroxyflavonol

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Last updated: 16 April 1998

# NITHIAZIDE

**VOL.:** 31 (1983) (p. 179)

**CAS No.:** 139-94-6

**Chem. Abstr. Name:** Urea, *N*-ethyl-*N'*-(5-nitro-2-thiazolyl)-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Nithiazide was tested for carcinogenicity in one experiment in mice and in one experiment in rats by administration in the diet. It increased the incidence of hepatocellular carcinomas and adenomas in male mice. In female rats, it increased the incidences of fibroadenomas and cystadenomas of the skin, subcutaneous tissue and mammary gland (significant only if individual incidences for each site were combined) and the incidence of endometrial stromal polyps of the uterus.

No data were available to assess the mutagenic or teratogenic effects of nithiazide in experimental systems.

### 5.2 Human data

Nithiazide, a synthetic antiprotozoal agent, was first produced in 1961. Humans may be exposed as a result of its manufacture and use in veterinary medicine.

No data were available to assess the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of nithiazide was available to the Working Group.

### 5.3 Evaluation

There is *limited evidence* for the carcinogenicity of nithiazide in experimental animals. In the absence of epidemiological data no evaluation of the carcinogenicity of nithiazide to humans could be made.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Subsequent evaluation:** Suppl. 7 (1987) (p. 67: **Group 3**)

### Synonyms

- Hepzide
- Hepzide 30
- Nithiazid

# NITROVIN

**VOL.:** 31 (1983) (p. 185)

**CAS No.:** 804-36-4

**Chem. Abstr. Name:** Hydrazinecarboximidamide, 2-[3-(5-nitro-2-furanyl)-1-[2-(5-nitro-2-furanyl)ethenyl]-2-propenylidene]-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Nitrovin was tested for carcinogenicity in one experiment in female rats by administration in the diet. The experiment was inadequate for evaluation.

Nitrovin induces DNA damage and mutations in bacteria and mutations in insects. There is *limited evidence* that nitrovin is active in short-term tests.

No data were available to evaluate the teratogenicity of this compound to experimental animals.

### 5.2 Human data

Nitrovin, a veterinary bacteriostatic and bactericidal compound, has been used since 1952 as a growth promotor in chickens. Humans may be exposed as a result of its manufacture and use in veterinary medicine.

No data were available to assess the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of nitrovin was available to the Working Group.

### 5.3 Evaluation

No evaluation of the carcinogenicity of nitrovin to experimental animals could be made. In the absence of epidemiological data, no evaluation of the carcinogenicity of nitrovin to humans could be made.

**Subsequent evaluation:** Suppl. 7 (1987) (p. 68: **Group 3**)

### Synonyms

- 1,5-Bis(5-nitro-2-furanyl)-1,4-pentadien-3-one, (aminoiminomethyl)hydrazone
- *sym*-Bis(5-nitro-2-furfurylidene) acetone guanylhydrazone
- 1,5-Bis(5-nitro-2-furyl)-3-pentadienone guanylhydrazone
- 1,5-Bis(5-nitro-2-furyl)-3-pentadienone amidinohydrazone
- Bis(5-nitrofurfurylidene)acetone guanylhydrazone
- Difuran
- Difurazone
- Panazon
- Payzone

# PETASITENINE

**VOL.:** 31 (1983) (p. 207)

**CAS No.:** 60102-37-6

**Chem. Abstr. Name:** 4,8-Secosenecionan-8,11,16-trione, 15,20-epoxy-15,20-dihydro-12-hydroxy-4-methyl-,(15 $\beta$ ,20R)-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Petasitenine isolated from young flower stalks of wild *Petasites japonicus* Maxim. was tested for carcinogenicity in rats by administration in the drinking-water; haemangioendothelial sarcomas of the liver and liver-cell adenomas were observed. Flower stalks of *Petasites japonicus* Maxim. were tested in mice, rats and hamsters by administration in the diet. They increased the incidence of lung adenomas and adenocarcinomas in mice of one strain and of haemangioendothelial sarcomas of the liver and of hepatocellular adenomas and hepatocellular carcinomas in rats. No increase in tumour incidence was observed in hamsters.

Petasitenine is mutagenic in bacteria and in mammalian cells *in vitro*. It also induced chromosomal aberrations, unscheduled DNA synthesis and transformation in mammalian cells *in vitro*. There is *sufficient evidence* that petasitenine is active in short-term tests.

No data were available to evaluate the teratogenicity of this compound to experimental animals.

### 5.2 Human data

Petasitenine is found in a plant species to which limited human exposure occurs from its use as a herbal remedy and as a food.

No data were available to evaluate the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of petasitenine was available to the Working Group.

### 5.3 Evaluation

There is *limited evidence* for the carcinogenicity of both petasitenine and flower stalks of *Petasites japonicus* Maxim. in experimental animals. In the absence of epidemiological data, no evaluation of the carcinogenicity of petasitenine to humans could be made.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Subsequent evaluation:** Suppl. 7 (1987) (p. 69: **Group 3**)

### Synonym

- Fukinotoxin
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Last updated: 16 April 1998

# QUERCETIN

**VOL.:** 31 (1983) (p. 213)

**CAS No.:** 117-39-5

**Chem. Abstr. Name:** 4*H*-1-Benzopyran-4-one, 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Quercetin has been tested for carcinogenicity in mice, rats and hamsters in several experiments by administration in the diet and in mice by skin application and urinary bladder implantation. Increased incidences of ileal and urinary bladder carcinomas were observed in only one experiment in rats fed quercetin, whereas several other experiments, using the same or higher doses, do not provide evidence of a carcinogenic effect.

The 3-rhamnoglucoside of quercetin (rutin) was tested in rats and hamsters by administration in the diet. No evidence of carcinogenicity was found.

Quercetin is mutagenic in bacteria and insects and caused gene conversion in yeast. Equivocal results were obtained with respect to mutations in mammalian cells *in vitro*. It induced chromosomal anomalies in cultured cells, but equivocal results were obtained in the micronucleus test *in vivo*. Quercetin induced morphological transformation of hamster embryo cells *in vitro*. There is *sufficient evidence* that quercetin is active in short-term tests.

In one experiment with rats, no teratogenic effect was seen.

### 5.2 Human data

The natural occurrence of quercetin in fruit and other edible plants results in wide human exposure to this compound.

No data were available to evaluate the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of quercetin was available to the Working Group.

### 5.3 Evaluation

Results from one experiment in rats provide *limited evidence* for the carcinogenicity of quercetin in experimental animals. In the absence of epidemiological data, no evaluation of the carcinogenicity of quercetin to humans could be made.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Subsequent evaluations:** Suppl. 7 (1987) (p. 71: **Group 3**); see also [Vol. 40 \(1986\) \(Bracken fern\)](#); [Vol. 73 \(1999\)](#)

### Synonyms

- C.I. 75670
- C.I. Natural Red 1
- C.I. Natural Yellow 10 & 13
- Cyanidenolon 1522
- Meletin
- 3,5,7,3',4'-Pentahydroxyflavone
- Quercetine
- Quercetol
- Quercitin
- Quertine
- Sophoretin
- Xanthaurine

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Last updated: 30 September 1999

# SENKIRKINE

**VOL.:** 31 (1983) (p. 231)

**CAS No.:** 2318-18-5

**Chem. Abstr. Name:** 4,8-Secosenecionan-8,11,16-trione,12-hydroxy-4-methyl-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Senkirkine was tested for carcinogenicity in male rats by intraperitoneal administration; it significantly increased the incidence of liver-cell adenomas. In rats fed the herb *Tussilago farfara* L., which has been shown to contain senkirkine as the only pyrrolizidine alkaloid, an increased incidence of liver haemangioendothelial sarcomas was observed.

Senkirkine is mutagenic in bacteria and in mammalian cells in vitro. It also induced chromosomal aberrations and unscheduled DNA synthesis in mammalian cells in vitro. There is sufficient evidence that senkirkine is active in short-term tests.

No data were available to evaluate the teratogenicity of this compound to experimental animals.

### 5.2 Human data

Senkirkine is found in a number of plant species which are used as foods, herbal remedies and toiletries, resulting in limited human exposure.

No data were available to evaluate the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of senkirkine was available to the Working Group.

### 5.3 Evaluation

There is *limited evidence* for the carcinogenicity of both senkirkine and *Tussilago farfara* L. in experimental animals. In the absence of epidemiological data, no evaluation of the carcinogenicity of senkirkine to humans could be made.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Previous evaluation:** [Vol. 10 \(1976\)](#)

**Subsequent evaluation:** Suppl. 7 (1987) (p. 71: **Group 3**)

### Synonyms

- *trans*-15-Ethylidene-12 $\beta$ -hydroxy-4,12 $\alpha$ ,13 $\beta$ -trimethyl 8-oxo-4,8 secosenec-1-enine
- NSC-89945
- Renardin
- Renardine

- Senkirkin

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Last updated: 16 April 1998

# SYMPHYTINE

**VOL.:** 31 (1983) (p. 239)

**CAS No.:** 22571-95-5

**Chem. Abstr. Name:** 2-Butenoic acid, 2-methyl-, 7-[[2,3-dihydroxy- 2-(1-methylethyl)-1-oxobutoxy]methyl]-2,3,5,7a-tetrahydro-1*H*-pyrrolizin-1-yl ester,[1*R*-[1 $\alpha$ (*E*), 7(2*S*\*,3*S*\*),7 $\alpha$  $\beta$ ]]-

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Symphytine was tested for carcinogenicity in male rats by intraperitoneal administration; a non-significant increase in the incidence of liver tumours was observed. When leaves and roots of *Symphytum officinale* L. were tested in rats by administration in the diet, the incidence of liver tumours was increased.

Symphytine was mutagenic in *Salmonella typhimurium* and in mammalian cells *in vitro*. The data were inadequate to evaluate the activity of symphytine in short-term tests.

No data were available to evaluate the teratogenicity of this compound to experimental animals.

### 5.2 Human data

Symphytine is found in several plant species which are used as foods and as herbal remedies, resulting in wide human exposure.

No data were available to evaluate the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of symphytine was available to the Working Group.

### 5.3 Evaluation

No evaluation of the carcinogenicity of symphytine to experimental animals could be made. Results of experiments in rats provide *limited evidence* that the leaves and roots of *Symphytum officinale* L. are carcinogenic to experimental animals. In the absence of epidemiological data, no evaluation of the carcinogenicity of symphytine to humans could be made.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Subsequent evaluation:** Suppl. 7 (1987) (p. 72: **Group 3**)

### Synonyms

- 7-Tiglylretronecine viridiflorate
- 7-Tiglyl-9-viridiflorylretronecine

# TRP-P-1 (3-AMINO-1,4-DIMETHYL-5H-PYRIDO[4,3-*b*]INDOLE) AND ITS ACETATE

VOL.: 31 (1983) (p. 247)

## Trp-P-1

CAS No.: 62450-06-0

Chem. Abstr. Name: 5*H*-Pyrido[4,3-*b*]indol-3-amine, 1,4-dimethyl-

## Trp-P-1 acetate

CAS No.: 75104-43-7 (acetate); 68808-54-8 (monoacetate)

Chem. Abstr. Name: 5*H*-Pyrido[4,3-*b*]indol-3-amine, 1,4-dimethyl-, acetate; 5*H*-pyrido[4,3-*b*]indol-3-amine, 1,4-dimethyl-, monoacetate

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Trp-P-1 was tested for carcinogenicity in mice by administration in the diet, by skin application and by bladder implantation, and in rats and hamsters by subcutaneous administration. Hepatic tumours were induced by oral administration in both male and female mice, although the increased incidence was significant only in females. In female rats, there was a significant increase in the incidence of fibrosarcomas at the site of injection; in hamsters there was an increased incidence of subcutaneous sarcomas. Bladder carcinomas were observed in female mice after implantation of paraffin pellets containing Trp-P-1 at this site. The study in mice by skin painting was inadequate for evaluation.

Trp-P-1 is mutagenic to bacteria following metabolic activation. It induced chromosomal anomalies in mammalian cells, including human cells, in vitro. It also caused morphological transformation of hamster embryo cells. There is sufficient evidence that Trp-P-1 is active in short-term tests.

No data were available to evaluate the teratogenicity of this compound to experimental animals.

### 5.2 Human data

Trp-P-1 is found in the charred fraction of cooked fish and meat, and the consumption of these foods is a source of exposure for the general population.

No data were available to evaluate the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of Trp-P-1 was available to the Working Group.

### 5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of Trp-P-1 in experimental animals. No data on humans were available.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Subsequent evaluation:** Suppl. 7 (1987) (p. 73: **Group 2B**)

**Synonyms for Tr-P-1**

- 3-Amino-1,4-dimethyl- $\gamma$ -carboline
- TRP-PI
- Tryptophan P1

### **Synonyms for Tr-P-1 acetate**

- 3-Amino-1,4-dimethyl-5*H*-pyrido[4,3-*b*]indole acetate

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Last updated: 16 April 1998

# TRP-P-2 (3-AMINO-1-METHYL-5H-PYRIDO[4,3-*b*]INDOLE) AND ITS ACETATE

VOL.: 31 (1983) (p. 255)

## Trp-P-2

CAS No.: 62450-07-1

Chem. Abstr. Name: 5*H*-Pyrido[4,3-*b*]indol-3-amine, 1-methyl-

## Trp-P-2 acetate

CAS No.: 75104-43-7

Chem. Abstr. Name: 5*H*-Pyrido[4,3-*b*]indol-3-amine, 1-methyl-, monoacetate

## 5. Summary of Data Reported and Evaluation

### 5.1 Experimental data

Trp-P-2 was tested for carcinogenicity in mice and rats by administration in the diet, in mice by skin application and bladder implantation and in rats and hamsters by subcutaneous administration. An increased incidence of liver tumours was observed in female mice and female rats following its oral administration. Bladder carcinomas were observed in female mice after implantation of Trp-P-2 in paraffin pellets at this site. The results of the experiments by subcutaneous injection and by skin application were considered inadequate for evaluation.

Trp-P-2 is mutagenic to *Salmonella typhimurium* following metabolic activation. It induced chromosomal anomalies in mammalian cells, including human cells, *in vitro*. It caused neoplastic transformation *in vitro* in Syrian golden hamster cells. There is *sufficient evidence* that Trp-P-2 is active in short-term tests.

No data were available to evaluate the teratogenicity of this compound to experimental animals.

### 5.2 Human data

Trp-P-2 is found in the charred fraction of cooked fish, and the consumption of this food is a source of exposure for the general population.

No data were available to evaluate the teratogenicity or chromosomal effects of this compound in humans.

No case report or epidemiological study of the carcinogenicity of Trp-P-2 was available to the Working Group.

### 5.3 Evaluation

There is *sufficient evidence* for the carcinogenicity of Trp-P-2 in experimental animals. No data on humans were available.

For definition of the italicized terms, see [Preamble Evaluation](#).

**Subsequent evaluation:** Suppl. 7 (1987) (p. 73: **Group 2B**)

**Synonyms for Trp-P-2**

- 3-Amino-1-methyl-gamma-carboline
- 1-Methyl-3-amino-5*H*-pyrido[4,3-*b*]indole
- TRP-P2
- Tryptophan P2

### **Synonym for Trp-P-2 acetate**

- TRP-P-2 (acetate)

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Last updated: 16 April 1998