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Some Naturally Occurring and Synthetic Food Components, Furocoumarins and Ultraviolet Radiation

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Last updated: 22 April 1998

BRACKEN FERN (*PTERIDIUM AQUILINUM*) AND SOME OF ITS CONSTITUENTS

VOL.: 40 (1986) (p. 47)

5. Summary of Data Reported and Evaluation

5.1 Exposure

Human exposure to bracken fern and its constituents occurs by direct ingestion of the fronds in some regions of the world, or by ingestion of dairy products from cattle grazing on the fern. In the past, bracken has found other end uses such as in bread flour and medicinals.

5.2 Experimental data

Bracken fern was tested for carcinogenicity by oral administration to mice, rats, guinea pigs, cows and toads. In all species except cows, bracken fern induced malignant or benign and malignant intestinal tumours, particularly in the small intestine. It also induced bladder carcinomas in rats, guinea-pigs and cows, liver tumours in toads, lymphocytic leukaemias in mice and mammary cancers in rats.

Administration in the diet to rats of bracken fern that had been processed as for human consumption produced intestinal tumours, but at a lower incidence than unprocessed bracken fern.

In one study in rats, starch made from bracken fern rhizomes did not produce tumours.

Oral administration of boiling-water extracts of bracken fern to rats induced intestinal and bladder tumours; administration of ethanol extracts to quails produced intestinal tumours.

In studies on the carcinogenicity of substances isolated from bracken fern, oral administration of ptaquiloside to rats produced mammary and intestinal tumours. Shikimic acid has not been adequately studied. Kaempferol, quercetin and tannins, which also occur in bracken fern, were evaluated in previous volumes of *IARC Monographs*.

Administration of bracken fern in the diet in one study in mice at one dose induced maternal toxicity, some embryotoxicity and some minor abnormalities in offspring.

An acetone extract of bracken fern was mutagenic to *Salmonella typhimurium* in the presence of anogenous metabolic system; light petroleum and methanol extracts of bracken fern activated by alkaline treatment were mutagenic to *S. typhimurium* in the absence of an exogenous metabolic system.

Ptaquiloside induced unscheduled DNA synthesis in primary rat liver hepatocytes.

Shikimic acid was not mutagenic in *Salmonella typhimurium*. It did not induce chromosomal aberrations in cultured Chinese hamster cells. Conflicting results were reported in the dominant lethal test and negative results in the heritable translocation test in mice.

5.3 Human data

One case-control study from Japan has suggested an association between intake of bracken fern and cancer of the oesophagus.

5.4 Evaluation

There is *sufficient evidence* for the carcinogenicity of bracken fern in experimental animals.

There is *limited evidence* for the carcinogenicity of ptaquiloside derived from bracken fern in experimental animals.

There is *inadequate evidence* for the carcinogenicity of shikimic acid derived from bracken fern in experimental animals.

There is *inadequate evidence* for the carcinogenicity of bracken fern to humans.

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

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

Last updated: [22 April 1998](#)

CITRININ

VOL.: 40 (1986) (p. 67)

CAS No.: 518-75-2

Chem. Abstr. Name: (3*R*-*trans*)-4,6-Dihydro-8-hydroxy-3,4,5-trimethyl-6-oxo-3*H*-2-benzopyran-7-carboxylic acid

5. Summary of Data Reported and Evaluation

5.1 Exposure

Citrinin is produced by various *Penicillium* and *Aspergillus* species that can contaminate foodstuffs, and has been found in some cereals and fruits and peanuts. Thus, human exposure can occur by ingestion of such contaminated products.

5.2 Experimental data

Citrinin was adequately tested for carcinogenicity in one experiment in one strain of male rats by oral administration in the diet; it produced renal tumours. In another experiment in rats, citrinin was administered in the diet after *N*-nitrosodimethylamine or *N*-(3,5-dichlorophenyl)succinimide; an increased incidence of renal tumours was observed as compared to that in animals receiving *N*-nitrosodimethylamine or *N*-(3,5-dichlorophenyl)succinimide alone.

In rodents, embryotoxicity occurred after injection of maternally toxic doses of citrinin.

Both positive and negative results have been reported with citrinin in the *Bacillus subtilis* rec assay; the compound was not mutagenic in *Salmonella typhimurium* in the presence or absence of an exogenous metabolic system. It did not induce recombination in *Saccharomyces cerevisiae* nor unscheduled DNA synthesis in mammalian cells *in vitro*. Chromosomal aberrations but no sister chromatid exchanges were induced by citrinin in Chinese hamster V79 cells in the presence of an exogenous metabolic system.

5.3 Human data

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

5.4 Evaluation

There is *limited evidence* for the carcinogenicity of citrinin to experimental animals.

No evaluation could be made of the carcinogenicity of citrinin to humans.

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

Subsequent evaluation: Suppl. 7 (1987) (p. 60: **Group 3**)

Synonym

- (3*R*,4*S*)4,6-Dihydro-8-hydroxy-3,4,5-trimethyl-6-oxo-3*H*-2-benzopyran-7-carboxylic acid

Last updated: 22 April 1998

PATULIN

VOL.: 40 (1986) (p. 83)

CAS No.: 149-29-1

Chem. Abstr. Name: 4-Hydroxy-4*H*-furo[3,2-*c*]pyran-2(6*H*)-one

5. Summary of Data Reported and Evaluation

5.1 Exposure

Patulin is produced by various *Penicillium*, *Aspergillus* and *Byssochlamys* fungi that can contaminate many common fruits and some vegetables. Human exposure may occur if these contaminated foods are consumed.

5.2 Experimental data

Patulin was tested for carcinogenicity in one experiment in mice and in two experiments in two strains of rats by oral administration. The study in mice and one of the studies in rats involved treatment of pregnant dams and the continued treatment of offspring of the F₁ generation. In one study, subcutaneous injection of patulin produced local sarcomas in rats. The studies were considered to be inadequate for evaluation.

No adequate data were available to evaluate the reproductive effects or prenatal toxicity of patulin to experimental animals.

Patulin induced DNA damage in *Bacillus subtilis*, but not in *Escherichia coli*. It was not mutagenic to *Salmonella typhimurium*. Patulin induced petite mutants but not mitotic recombination in *Saccharomyces cerevisiae*. The compound induced DNA strand breaks in HeLa cells, but not unscheduled DNA synthesis in cultured mammalian cells. It induced sister chromatid exchanges in cultured mammalian cells. Patulin induced chromosomal aberrations but not sister chromatid exchanges in the bone-marrow cells of Chinese hamsters treated *in vivo*. It did not induce dominant lethal mutations in rats or mice.

5.3 Human data

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

5.4 Evaluation

There is *inadequate evidence* for the carcinogenicity of patulin in experimental animals.

No evaluation could be made of the carcinogenicity of patulin to humans.

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

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

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

Synonyms

- Clairformin

- Clavacin
- Clavatin
- Claviformin
- (2,4-Dihydroxy-2*H*-pyran-3-(6*H*)ylidene)acetic acid, 3,4-lactone
- Expansin
- Expansine
- Mycoin
- Mycoin C
- Mycoin C3
- Patuline
- Penicidin
- Terinin

Last updated: 22 April 1998

RUGULOSIN

VOL.: 40 (1986) (p. 99)

CAS No.: 23537-16-8

5. Summary of Data Reported and Evaluation

5.1 Exposure

Rugulosin is a mycotoxin produced by certain fungal species that can contaminate cereal grains. Human exposure may occur by the ingestion of contaminated grain products.

5.2 Experimental data

Rugulosin was tested for carcinogenicity in two experiments in male mice by oral administration in the diet. Both experiments were considered to be inadequate for evaluation.

No data were available to evaluate the reproductive effects or prenatal toxicity of rugulosin.

Rugulosin induced DNA damage in *Bacillus subtilis*. It did not induce reverse mutations in *Salmonella typhimurium* but was reported to induce forward mutations. It did not induce mutations in *Escherichia coli*. It induced cytoplasmic petite mutations in yeast. Rugulosin did not induce unscheduled DNA synthesis in mammalian cells *in vitro*.

5.3 Human data

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

5.4 Evaluation

There is *inadequate evidence* for the carcinogenicity of rugulosin in experimental animals.

No evaluation could be made of the carcinogenicity of rugulosin to humans.

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

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

Synonyms

- 1,7,9,15,17,20-Hexahydroxy-3,11-dimethyl-5*H*,6*H*-6,13a,5a,14- [1,2,3,4]-butanetetraylcycloocta[1,2-*b*:5,6-*b'*]dinaphthalene-5,8,13,16(14*H*)-tetrone
- (5a*S*-(5a*R**,6*S**,13a*R**,14*S**,17*R**,18*S**,19*S**,20*R**)))-1,7,9,15,-17,20-Hexahydroxy-3,11-dimethyl-5*H*,6*H*-6,13a,5a,14-(1,2,3,4)butanetetraylcycloocta(1,2-*b*:5,6-*b'*)dinaphthalene-5,8,13,16(14*H*)-tetrone

BENZYL ACETATE

VOL.: 40 (1986) (p. 109)

CAS No.: 140-11-4

Chem. Abstr. Name: Acetic acid, phenylmethyl ester

5. Summary of Data Reported and Evaluation

5.1 Exposure

Benzyl acetate has been identified in several fruits, such as bael fruit (from the *Aegle marmelos* tree) and quince (*Cydonia vulgaris*), and in a mushroom (*Agaricus* species). It is a major volatile constituent of the flowers of a number of plants, including jasmine (*Jasminium grandiflorum* L.), hyacinth (*Hyacinthus orientalis*), gardenia (*Gardenia jasminoides*), ylang-ylang (*Cananga odorata*), alfalfa (*Medicago sativa* L.) and others. It has been used as a food additive in fruit flavours and as a component of perfumes since the early 1900s and is widely used as a fragrance in soaps, detergents and incense. There is widespread human exposure to benzyl acetate by ingestion, skin application and inhalation.

5.2 Experimental data

Benzyl acetate was tested for carcinogenicity by oral intubation in one experiment in mice of both sexes and in one experiment in rats of both sexes. In the study in mice, increased incidences of liver adenomas and of combined liver adenomas and carcinomas were observed in animals of each sex; the incidence of carcinomas of the liver alone was not statistically significantly increased in animals of either sex. An increased incidence of forestomach tumours was observed in mice of each sex. An increased incidence of acinar-cell adenomas of the pancreas was observed in male rats.

No data were available to evaluate the reproductive effects or prenatal toxicity of benzyl acetate to experimental animals.

Benzyl acetate was reported to give negative results in the *Bacillus subtilis* rec assay. It was not mutagenic to *Salmonella typhimurium* in the presence or absence of an exogenous metabolic system and did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells in the presence or absence of a metabolic system. Benzyl acetate was reported to be mutagenic in mouse lymphoma L5178Y cells in the presence of a metabolic system.

5.3 Human data

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

5.4 Evaluation

There is *limited evidence* for the carcinogenicity of benzyl acetate to experimental animals.

No evaluation could be made of the carcinogenicity of benzyl acetate to humans.

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

Subsequent evaluation: [Vol. 71 \(1999\)](#)

Synonyms

- Acetic acid, benzyl ester
- (Acetoxymethyl)benzene
- α -Acetoxytoluene
- Benzyl ethanoate
- Phenylmethyl acetate

Last updated: 13 April 1999

BUTYLATED HYDROXYANISOLE (BHA)

VOL.: 40 (1986) (p. 123)

CAS No.: 25013-16-5

Chem. Abstr. Name: (1,1-Dimethylethyl)-4-methoxyphenol

5. Summary of Data Reported and Evaluation

5.1 Exposure

Butylated hydroxyanisole (BHA) has been used since 1947 as an antioxidant in many foods, including edible fats and oils, meats, cereals, potato products, baked goods, nuts, snack foods, chewing-gum and beverages. It has also been used extensively in cosmetics, especially lipsticks and eye shadow. There is widespread human exposure to this compound by ingestion and skin application.

5.2 Experimental data

Butylated hydroxyanisole was tested for carcinogenicity in two experiments in rats and in two experiments in hamsters by administration in the diet, inducing benign and malignant tumours of the forestomach.

Butylated hydroxyanisole was studied in mice and rats for its ability to modify the carcinogenicity of selected chemical agents. When administered with known carcinogens, butylated hydroxyanisole either enhanced, inhibited or had no effect on carcinogenicity.

Butylated hydroxyanisole administered to rats at maternally toxic and occasionally lethal doses during, or before, during and after, gestation induced slight embryotoxicity but no definite indication of teratogenicity. No effect was seen in rabbits, pigs or rhesus monkeys.

In rats, feeding of butylated hydroxyanisole in the diet caused superficial necrosis, ulceration and hyperplasia of the squamous epithelium of the forestomach. Induction of forestomach hyperplasia also occurs in hamsters. Administration of butylated hydroxyanisole by gavage to monkeys was associated with an elevated mitotic index in the squamous epithelium of the distal oesophagus.

Butylated hydroxyanisole was not mutagenic to *Salmonella typhimurium*, *Drosophila melanogaster* or to Chinese hamster cells *in vitro*. It did not cause chromosomal effects in *D. melanogaster* or in cultured Chinese hamster cells.

When tested in combination with other chemicals (usually known mutagens or carcinogens), butylated hydroxyanisole often modified their DNA damaging, mutagenic and clastogenic activities. In most studies, butylated hydroxyanisole reduced the activity of indirectly-acting mutagens/carcinogens.

5.3 Human data

No data were available to evaluate the carcinogenicity of butylated hydroxyanisole to humans.

5.4 Evaluation

There is *sufficient evidence* for the carcinogenicity of butylated hydroxyanisole to experimental animals.

No data were available on the carcinogenicity of butylated hydroxyanisole to humans.

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

Subsequent evaluation: Suppl. 7 (1987) (p. 59: **Group 2B**)

Synonyms

- Antioxyne B
- Antrancine 12
- Butylhydroxyanisole
- *tert*-Butylhydroxyanisole
- *tert*-Butyl-*para*-hydroxyanisole
- *tert*-Butyl-4-hydroxyanisole
- 2(3)-*tert*-Butyl-4-hydroxyanisole
- Embanox
- Protex
- Sustan 1F
- Sustane 1F
- Tenox BHA

Last updated: 22 April 1998

BUTYLATED HYDROXYTOLUENE (BHT)

VOL.: 40 (1986) (p. 161)

CAS No.: 128-37-0

Chem. Abstr. Name: 2,6-Bis(1,1-dimethylethyl)-4-methylphenol

5. Summary of Data Reported and Evaluation

5.1 Exposure

Butylated hydroxytoluene (BHT) has been used since 1947 as a common antioxidant in rubber and petroleum products and, more recently, in plastics. It has been used since 1949 as an antioxidant in many fat-containing foods, in edible fats and oils and in cosmetics. There is thus widespread human exposure to this compound.

5.2 Experimental data

Butylated hydroxytoluene was tested for carcinogenicity in mice and rats by oral administration in the diet. In one study in mice, there was no difference in tumour incidence among treated and control groups. Another study in mice showed an increased incidence of pulmonary tumors in females at the lower but not at the higher dose level. In another study in mice using one dose level and a small number of animals, the number of mice with lung tumours was increased by feeding of butylated hydroxytoluene; this finding was not confirmed in a further study by the same investigator using a larger number of animals. In one study in rats, no increase in tumour incidence was seen. An increased incidence of pituitary adenomas was observed in female rats at the lower but not at the higher dose level in another study. In one further experiment in rats, liver tumours were observed; however, this study could not be evaluated because of differential survival among control and treated groups.

Butylated hydroxytoluene was studied in mice and rats for its ability to modify the carcinogenicity of selected chemical agents. When administered with known carcinogens, butylated hydroxytoluene either enhanced, inhibited or had no effect on carcinogenicity.

No adequate data were available to evaluate the reproductive effects or prenatal toxicity of butylated hydroxytoluene to experimental animals.

In mice, a single intraperitoneal dose or feeding of butylated hydroxytoluene can cause pulmonary alveolar cell necrosis and proliferation. Butylated hydroxytoluene also induces proliferation of smooth endoplasmic reticulum in rat-liver cells, leading to hepatomegaly.

Butylated hydroxytoluene did not induce DNA damage in *Bacillus subtilis* or mutation in *Salmonella typhimurium*. It did not induce chromosomal aberrations in plants or mutation or chromosomal aberrations in *Drosophila melanogaster*. In one study, it was reported to be mutagenic to cultured Chinese hamster cells in the presence of an exogenous metabolic system. Binding of butylated hydroxytoluene to the DNA of liver of rats treated *in vivo* has been reported. It did not induce micronuclei in bone marrow or dominant lethal mutations in mice. It induced sperm abnormalities in mice.

When tested in combination with other chemicals (usually, known mutagens or carcinogens), butylated hydroxytoluene often modified the DNA-damaging, mutagenic and clastogenic activities. In most studies, butylated hydroxytoluene reduced the activity of indirectly-acting mutagens or carcinogens.

5.3 Human data

No data were available to evaluate the carcinogenicity of butylated hydroxytoluene to humans.

5.4 Evaluation

There is *limited evidence* for the carcinogenicity of butylated hydroxytoluene in experimental animals.

No evaluation could be made of the carcinogenicity of butylated hydroxytoluene to humans.

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

Subsequent evaluation: Suppl. 7 (1987) (p. 59: **Group 3**)

Synonyms

- Advastab 401
- Agidol
- Alkofen BP
- Antioxidant 4
- Antioxidant 29
- Antioxidant 30
- Antioxidant DBPC
- Antioxidant 4K
- Antioxidant KB
- Buks
- Butylhydroxytoluene
- CA0-1
- CA0-3
- Catalin CA0-3
- Chemanox 11
- Dalpac
- DBPC
- Deenax
- Dibunol
- Dibutylated hydroxytoluene
- Di-*tert*-butyl-*para*-cresol
- *ortho,ortho'*-Di-*tert*-butyl-*para*-cresol
- 1,3-Di-*tert*-butyl-2-hydroxy-5-methylbenzene
- 3,5-Di-*tert*-butyl-4-hydroxytoluene
- 3,5-Di-*tert*-butyl-4-methylphenol
- E 321
- Impruvol
- Ionol
- Ionole
- Kerabit
- 4-Methyl-2,6-di-*tert*-butylphenol
- NCI-CO3598
- Nocrac 200
- Nonox TBC
- Parabar 441
- Paranox 441
- Stavox
- Sumilizer BHT
- Sustane BHT
- Swanox BHT
- Tenamene 3
- Tenox BHT

- Topanol
- Toxolan P
- Vanlube PC
- Vanlube PCX
- Vianol
- Vulkanox KB

Last updated: 22 April 1998

POTASSIUM BROMATE

VOL.: 40 (1986) (p. 207)

CAS No.: 7758-01-2

Chem. Abstr. Name: Bromic acid, potassium salt

5. Summary of Data Reported and Evaluation

5.1 Exposure

Potassium bromate is used in bread-making and in the production of fish paste and fermented beverages; however, manufacturing and baking practices are available that reportedly leave little or no residual bromate in the end product. Occupational exposure to potassium bromate occurs mainly in production plants. Consumers may be exposed through the use some permanent-wave kits with potassium bromate neutralizer solutions.

5.2 Experimental data

Potassium bromate was tested for carcinogenicity in one experiment in rats by oral administration in the drinking-water, producing renal-cell adenomas and adenocarcinomas in animals of each sex, peritoneal mesotheliomas in males and thyroid tumours in females. Experiments in mice and rats fed diets containing bread baked from flour containing potassium bromate were considered to be inadequate to evaluate the carcinogenicity of potassium bromate itself.

The incidence of renal-cell tumours in rats induced by administration of *N*-nitrosoethyl-*N*-hydroxyethylamine was increased by subsequent administration of potassium bromate.

In rats, administration of potassium bromate in the drinking-water caused tubular lesions of the kidney which were classified as dysplastic foci.

No data were available to evaluate the reproductive effects or prenatal toxicity of potassium bromate to experimental animals.

Potassium bromate was mutagenic in *Salmonella typhimurium* in the presence of an exogenous metabolic system. The compound induced chromosomal aberrations in cultured Chinese hamster cells and micronuclei in mice treated *in vivo*.

5.3 Human data

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

5.4 Evaluation

There is *sufficient evidence* for the carcinogenicity of potassium bromate in experimental animals.

No data were available on the carcinogenicity of potassium bromate to humans.

N.B. - After the meeting, the Secretariat became aware of a study in which 9% of male hamsters administered potassium bromate in the drinking-water developed kidney tumours (Takamura *et al.*, 1986).

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

Subsequent evaluations: Suppl. 7 (1987) (p. 70); [Vol. 73 \(1999\)](#)

Synonym

- E 924

Last updated: 30 September 1999

GLU-P-1 (2-AMINO-6-METHYLDIPYRIDO[1,2-*a*:3',2'-*d*]IMIDAZOLE)

VOL.: 40 (1986) (p. 222)

CAS No.: 67730-11-4

Chem. Abstr. Name: 6-Methyldipyrido[1,2-*a*:3',2'-*d*]imidazol-2-amine

5. Summary of Data Reported and Evaluation

5.1 Exposure

Glu-P-1 (2-amino-6-methyldipyrido[1,2-*a*:3',2'-*d*]imidazole) is found at low levels among the pyrolysis products of L-glutamic acid and casein, and human exposure may occur by ingestion of cooked foods containing these substances.

5.2 Experimental data

Glu-P-1 was tested for carcinogenicity in one experiment in mice and one experiment in rats by oral administration in the diet. It produced haemangioendotheliomas and haemangioendothelial sarcomas at various sites and hepatocellular adenomas in mice of each sex and liver carcinomas in female mice. In rats, it produced benign and malignant tumours of the liver, intestines and Zymbal gland in animals of each sex and tumours of the clitoral gland in females.

No data were available to evaluate the reproductive effects or prenatal toxicity of this compound to experimental animals.

Glu-P-1 induced prophage in bacteria. It was mutagenic in *Salmonella typhimurium* in the presence of an exogenous metabolic system, and gave positive results in the wing spot test in *Drosophila melanogaster*. Glu-P-1 induced mutations, chromosomal aberrations, sister chromatid exchanges and morphological transformation in cultured mammalian cells. It induced DNA damage in rats treated *in vivo* and positive results in the mouse spot test.

5.3 Human data

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

5.4 Evaluation

There is *sufficient evidence* for the carcinogenicity of Glu-P-1 to experimental animals.

No data were available on the carcinogenicity of Glu-P-1 to humans.

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

Subsequent evaluation: Suppl. 7 (1987) (p. 64: **Group 2B**)

Synonym

- 2-Amino-6-methyldipyrido[1,2-*a*:3',2'-*d*]imidazole

Last updated: 23 April 1998

GLU-P-2 (2-AMINODIPYRIDO[1,2-a:3',2'-d]IMIDAZOLE)

VOL.: 40 (1986) (p. 235)

CAS No.: 67730-10-3

Chem. Abstr. Name: Dipyrdo[1,2-a:3',2'-d]imidazo1-2-amine

5. Summary of Data Reported and Evaluation

5.1 Exposure

Glu-P-2 (2-aminodipyrdo[1,2-a:3',2'-d]imidazole) has been found in grilled fish and in L-glutamic acid and casein pyrolysates; therefore, consumption of grilled foods may result in human exposure.

5.2 Experimental data

Glu-P-2 was tested for carcinogenicity in one experiment in mice and one experiment in rats by oral administration in the diet. In mice, it produced haemangioendotheliomas and haemangioendothelial sarcomas at various sites and hepatocellular adenomas and carcinomas in animals of each sex. In rats, it produced benign and malignant tumours of the liver, intestines and zymbal gland in animals of each sex and tumours of the clitoral gland in females.

No data were available to evaluate the reproductive effects or prenatal toxicity of this compound to experimental animals.

Glu-P-2 induced prophage in bacteria. It was mutagenic in *Salmonella typhimurium* in the presence of an exogenous metabolic system and in cultured mammalian cells, and gave positive results in the wing spot test in *Drosophila melanogaster*. Experiments for the induction of sister chromatid exchanges and chromosomal aberrations in cultured mammalian cells were inadequate.

5.3 Human data

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

5.4 Evaluation

There is *sufficient evidence* for the carcinogenicity of Glu-P-2 to experimental animals.

No data were available on the carcinogenicity of Glu-P-2 to humans.

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

Subsequent evaluation: Suppl. 7 (1987) (p. 64: **Group 2B**)

Synonym

- 2-Aminodipyrdo[1,2-a:3',2'-d]imidazole

A- α -C (2-AMINO-9H-PYRIDO[2,3-*b*]INDOLE)

VOL.: 40 (1986) (p. 245)

CAS No.: 26148-68-5

Chem. Abstr. Name: 1*H*-Pyrido[2,3-*b*]indo1-2-amine

5. Summary of Data Reported and Evaluation

5.1 Exposure

A- α -C (2-amino-9*H*-pyrido[2,3-*b*]indole) has been found in a variety in grilled foods, in the pyrolysis products of proteins and in cigarette smoke. There is thus likely to be widespread human exposure to this compound.

5.2 Experimental data

A- α -C was tested for carcinogenicity in one experiment in mice by oral administration in the diet. It produced haemangioendothelial sarcomas and hepatocellular adenomas and carcinomas in animals of each sex.

No data were available to evaluate the reproductive effects or prenatal toxicity of this compound to experimental animals.

A- α -C induced prophage in bacteria. It induced DNA damage in *Bacillus subtilis* and mutations in *Salmonella typhimurium* in the presence of an exogenous metabolic system. It gave positive results in the wing spot test in *Drosophila melanogaster*. In cultured Chinese hamster lung cells, A- α -C induced mutations and chromosomal aberrations in the presence and polyploidy in the absence, of an exogenous metabolic system. It induced sister chromatid exchanges in human lymphoblastoid cells.

5.3 Human data

No case report or epidemiological study of the carcinogenicity of A- α -C was available to the Working Group.

5.4 Evaluation

There is *sufficient evidence* for the carcinogenicity of A- α -C to experimental animals.

No data were available on the carcinogenicity of A- α -C to humans.

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

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

Synonyms

- AC
 - Amino- α -carboline
 - 2-Amino- α -carboline
 - Glob-P-2
-

Last updated: 22 April 1998

MEA- α -C (2-AMINO-3-METHYL-9H-PYRIDO[2,3-*b*]INDOLE)

VOL.: 40 (1986) (p. 253)

CAS No.: 68006-83-7

Chem. Abstr. Name: 3-Methyl-1*H*-pyrido[2,3-*b*]indol-2-amine

5. Summary of Data Reported and Evaluation

5.1 Exposure

MeA- α -C (2-amino-3-methyl)-9*H*-pyrido[2,3-*b*]indole has been found in grilled foods, in the pyrolysis products of proteins and in cigarette smoke. There is thus likely to be widespread human exposure to this compound.

5.2 Experimental data

MeA- α -C was tested for carcinogenicity in one experiment in mice by oral administration in the diet. It produced haemangioendothelial sarcomas at various sites and hepatocellular adenomas and carcinomas in animals of each sex.

No data were available to evaluate the reproductive effects or prenatal toxicity of this compound to experimental animals.

MeA- α -C induced prophage in bacteria. It induced DNA damage in *Bacillus subtilis* and was mutagenic in *Salmonella typhimurium* in the presence of an exogenous metabolic system. It gave positive results in the wing spot test in *Drosophila melanogaster*. In cultured Chinese hamster lung cells, MeA- α -C induced polyploidy in the absence, and chromosomal aberrations in the presence, of an exogenous metabolic system.

5.3 Human data

No case report or epidemiological study of the carcinogenicity of MeA- α -C was available to the Working Group.

5.4 Evaluation

There is *sufficient evidence* for the carcinogenicity of MeA- α -C to experimental animals.

No data were available on the carcinogenicity of MeA- α -C to humans.

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

Subsequent evaluation: Suppl. 7 (1987) (p. 65: **Group 2B**)

Synonyms

- Glob-P-1
 - Me-amino- α -carboline
 - MEAC
 - Methyl-amino- α -carboline
-

Last updated: 22 April 1998

ANGELICIN AND SOME SYNTHETIC DERIVATIVES

VOL.: 40 (1986) (p. 291)

CAS No.: 523-50-2

Chem. Abstr. Name: 2*H*-Furo[2,3-*h*][1]benzopyran-2-one

5. Summary of Data Reported and Evaluation

5.1 Exposure

Angelicin and its methoxy derivatives occur in a number of plants belonging to the *Umbelliferae* family. These compounds have been tested clinically in combination with ultraviolet A radiation for use in the treatment of psoriasis. Human exposure occurs through contact with or ingestion of the plants in which these compounds occur.

5.2 Experimental data

Angelicin, 5-methylangelicin and 4,5'-dimethylangelicin, with and without ultraviolet A radiation, were tested for skin carcinogenicity in mice by skin application. All compounds produced skin cancers when administered with ultraviolet A radiation but not when given alone. The presence of some linear psoralen impurities in the methylangelicins cannot be excluded and may have influenced the results obtained. The studies were inadequate to evaluate the systemic carcinogenicity of these compounds. No data were available to evaluate the carcinogenicity to experimental animals of 4,4'-dimethylangelicin or 4,4',6-trimethylangelicin.

No data were available to evaluate the reproductive effects or prenatal toxicity of angelicin or its methyl derivatives.

Angelicin, in the presence of ultraviolet A radiation, bound covalently to isolated DNA and to DNA in bacteria, yeast and cultured mammalian cells. In the dark, both positive and negative findings were observed for mutagenicity in bacteria, but angelicin was not mutagenic to yeast. In the presence of ultraviolet A radiation, it was mutagenic to phage, bacteria and yeast. In the presence of ultraviolet A radiation, but not in the dark, it induced sister chromatid exchanges, chromosomal aberrations and micronuclei in mammalian cells *in vitro*.

5-Methylangelicin bound covalently to isolated DNA in the presence of ultraviolet A radiation. It was mutagenic to bacteria both in the dark and in the presence of ultraviolet A radiation. In combination with ultraviolet A radiation, it induced mutations and sister chromatid exchanges in mammalian cells *in vitro*.

4,4'-Dimethylangelicin, in the presence of ultraviolet A radiation, bound covalently to isolated DNA and to DNA in bacteria. In the dark, it was not mutagenic to *Salmonella typhimurium*. In the presence of ultraviolet A radiation, it was mutagenic to *Escherichia coli* and induced cytoplasmic petite mutations in *Saccharomyces cerevisiae*.

4,5'-Dimethylangelicin, in the presence of ultraviolet A radiation, bound covalently to isolated DNA and to DNA in cultured mouse tumour cells and was mutagenic to bacteria, yeast and cultured Chinese hamster cells.

4,4',6-Trimethylangelicin, in the presence of ultraviolet A radiation, bound covalently to isolated DNA. In the dark, it was not mutagenic to *Salmonella typhimurium*. In the presence of ultraviolet A radiation, it was mutagenic to *Escherichia coli*.

4.3 Human data

No case report or epidemiological study of the carcinogenicity of angelicin or its synthetic methyl derivatives was available to the Working Group.

5.4 Evaluation

There is *limited evidence* for the carcinogenicity to experimental animals of angelicin, 5-methylangelicin and 4,5'-dimethylangelicin in combination with ultraviolet A radiation. There is *inadequate evidence* for the carcinogenicity of these compounds to experimental animals in the absence of ultraviolet A radiation.

No data were available to evaluate the carcinogenicity to experimental animals of 4,4'-dimethylangelicin or 4,4',6-trimethylangelicin.

No evaluation could be made of the carcinogenicity of angelicin or its methyl derivatives to humans.

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

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

Synonyms

- Angecin
- Furo[2,3-*h*]coumarin
- Furo[5',4':7,8]coumarin
- 3-(4-Hydroxy-5-benzofuranyl)-2-propenoic acid, δ -lactone
- Isopsoralen

3-CARBETHOXYPSORALEN

VOL.: 40 (1986) (p. 317)

CAS No.: 20073-24-9

Chem. Abstr. Name: 7-Oxo-7H-furo[3,2-g][1]benzopyran-6-carboxylic acid, ethyl ester

5. Summary of Data Reported and Evaluation

5.1 Exposure

There is no known human exposure to 3-carbethoxypsoralen, other than in limited clinical trials for the treatment of psoriasis.

5.2 Experimental data

3-Carbethoxypsoralen was tested for skin carcinogenicity in two experiments in two strains of mice by skin application with and without ultraviolet A radiation and in one study in mice by intraperitoneal administration with subsequent ultraviolet A radiation. No skin tumour was observed in 3-carbethoxypsoralen-treated mice in any of the three studies, with ultraviolet A radiation. The studies were inadequate to evaluate the systemic carcinogenicity of 3-carbethoxypsoralen.

No data were available to evaluate the reproductive effects or prenatal toxicity of 3-carbethoxypsoralen to experimental animals.

In the presence of ultraviolet A radiation, 3-carbethoxypsoralen bound covalently to isolated DNA and induced DNA damage in *Salmonella typhimurium*, *Escherichia coli* and *Saccharomyces cerevisiae*. It was not mutagenic to *Salmonella typhimurium* in the dark in the absence of an exogenous metabolic system. In combination with ultraviolet A radiation, 3-carbethoxypsoralen induced mutations and mitotic recombination in yeast and mutations and sister chromatid exchanges in cultured mammalian cells *in vitro*.

5.3 Human data

No case report or epidemiological study of the carcinogenicity of 3-carbethoxypsoralen was available to the Working Group.

5.4 Evaluation

On the basis of experiments designed to test only the carcinogenicity to mouse skin of 3-carbethoxypsoralen in combination with ultraviolet A radiation, there is *no evidence* of carcinogenicity to experimental animals.

There is *inadequate evidence* for the carcinogenicity to experimental animals of 3-carbethoxypsoralen in the absence of ultraviolet A radiation.

No evaluation could be made of the carcinogenicity of 3-carbethoxypsoralen to humans.

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

Subsequent evaluation: Suppl. 7 (1987) (p. 59: **Group 3**)

Synonyms

- 3-CPs
- 3-Ethoxycarbonylpsoralen
- Ethyl 7-oxo-7*H*-furo[3,2-*g*][1]benzopyran-6-carboxylate
- Ethyl 3-psoralencarboxylate
- 6-Hydroxy-5-benzofuranyl)methylene]malonic acid, δ -lactone, ethyl ester

Last updated: 22 April 1998

5-METHOXYPSORALEN

VOL.: 40 (1986) (p. 327)

5. Summary of Data Reported and Evaluation

5.1 Exposure

5-Methoxypsoralen is found in a variety of plant species, including parsnips and celery, in bergamot and lime oils, and in derivative products. Use of foods, beverages, perfumes and sunscreen preparations containing these products results in human exposure. Exposure also occurs when 5-methoxypsoralen is used as a drug, in conjunction with ultraviolet A radiation, for the treatment of skin disorders. Occupational exposure occurs during the extraction of this compound from bergamot oil and its preparation into foods and consumer goods.

5.2 Experimental data

5-Methoxypsoralen was tested in combination with ultraviolet A or solar-simulated radiation for skin carcinogenicity in two experiments in two strains of mice by skin application. It produced papillomas and squamous-cell carcinomas of the skin.

The studies were inadequate to evaluate the systemic carcinogenicity of 5-methoxypsoralen.

Maternally toxic doses of 5-methoxypsoralen did not increase the number of anomalies in surviving fetuses of treated rats.

5-Methoxypsoralen in the presence of ultraviolet A radiation bound covalently to isolated DNA and to DNA in yeast and cultured mammalian cells, and induced prophage expression in bacteria. In the presence of ultraviolet A radiation, it was mutagenic to bacteria, green algae and yeast and induced mutations, sister chromatid exchanges and chromosomal aberrations in mammalian cells *in vitro*. Studies of 5-methoxypsoralen in the absence of ultraviolet A radiation were inadequate for evaluation.

5.3 Human data

One small survey showed no excess prevalence of skin tumours in workers in the bergamot oil production industry, but this study had methodological weaknesses.

5.4 Evaluation

On the basis of experiments designed to test only the carcinogenicity to mouse skin of 5-methoxypsoralen in combination with ultraviolet A radiation or solar-simulated radiation, there is *sufficient evidence* of carcinogenicity to experimental animals.

There is *inadequate evidence* for the carcinogenicity of 5-methoxypsoralen to experimental animals in the absence of ultraviolet A radiation.

There is *inadequate evidence* for the carcinogenicity of 5-methoxypsoralen to humans.

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

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

Last updated: 22 April 1998

PYRIDO[3,4-*c*]PSORALEN AND 7-METHYLPYRIDO[3,4-*c*]PSORALEN

VOL.: 40 (1986) (p. 349)

Pyrido[3,4-*c*]psoralen

CAS No.: 85878-62-2

Chem. Abstr. Name: 5*H*-Furo[3',2':6,7][1]benzopyrano[3,4-*c*]pyridin-5-one

7-Methylpyrido[3,4-*c*]psoralen

CAS No.: 85878-63-3

Chem. Abstr. Name: 7-Methyl-5*H*-furo[3',2':6,7][1]benzopyrano[3,4-*c*]pyridin-5-one

5. Summary of Data Reported and Evaluation

5.1 Exposure

There is no known human exposure to pyrido[3,4-*c*]psoralen or 7-methylpyrido[3,4-*c*]psoralen, other than in limited clinical trials for the treatment of psoriasis.

5.2 Experimental data

In one incompletely reported study of pyrido[3,4-*c*]psoralen and 7-methylpyrido[3,4-*c*]psoralen in combination with ultraviolet A radiation in mice, skin tumours were observed. No data were available to evaluate the carcinogenicity to experimental animals of pyrido[3,4-*c*]psoralen or 7-methylpyrido[3,4-*c*]psoralen in the absence of ultraviolet A radiation.

No data were available to evaluate the reproductive effects or prenatal toxicity of pyrido[3,4-*c*]psoralen or 7-methylpyrido[3,4-*c*]psoralen to experimental animals.

In the presence of ultraviolet A radiation, pyrido[3,4-*c*]psoralen and 7-methylpyrido[3,4-*c*]psoralen bound covalently to isolated DNA. In combination with ultraviolet A radiation, 7-methylpyrido[3,4-*c*]psoralen induced DNA damage in yeast and human fibroblasts *in vitro*. Both compounds were mutagenic to *Salmonella typhimurium* in the dark. In the presence of ultraviolet A radiation, pyrido[3,4-*c*]psoralen and 7-methylpyrido[3,4-*c*]psoralen induced mutations and mitotic recombination in yeast. In the dark, 7-methylpyrido[3,4-*c*]psoralen, but not pyrido[3,4-*c*]psoralen, induced sister chromatid exchanges in mammalian cells *in vitro*; and, in combination with ultraviolet A irradiation, both compounds induced sister chromatid exchanges in cultured mammalian cells.

5.3 Human data

No case report or epidemiological study of the carcinogenicity of pyrido[3,4-*c*]psoralen or 7-methylpyrido[3,4-*c*]psoralen was available to the Working Group.

5.4 Evaluation

There is *inadequate evidence* that pyrido[3,4-*c*]psoralen or 7-methylpyrido[3,4-*c*]psoralen in combination with ultraviolet A radiation is carcinogenic to experimental animals. No data were available to evaluate the carcinogenicity of pyrido[3,4-*c*]psoralen or 7-methylpyrido[3,4-*c*]psoralen to experimental animals in the absence of ultraviolet A radiation.

No evaluation could be made of the carcinogenicity of pyrido[3,4-*c*]psoralen or 7-methylpyrido[3,4-*c*]psoralen to humans.

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

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

Synonym for *Pyrido[3,4-c]psoralen*

- 4-(6-Hydroxy-5-benzofuranyl)nicotinic acid, δ -lactone

Synonym for *7-Methylpyrido[3,4-c]psoralen*

- 4-(6-Hydroxy-7-methyl-5-benzofuranyl)nicotinic acid, delta-lactone;

Last updated: 21 April 1998

4,5',8-TRIMETHYLPSORALEN

VOL.: 40 (1986) (p. 357)

5. Summary of Data Reported and Evaluation

5.1 Exposure

4,5',8-Trimethylpsoralen (trioxsalen) has been used in conjunction with ultraviolet A radiation in the treatment of vitiligo, psoriasis and other skin disorders. Human exposure occurs through the oral administration or skin application of these products.

5.2 Experimental data

In one incompletely reported study of the skin carcinogenicity of 4,5',8-trimethylpsoralen in combination with ultraviolet A radiation in mice, no skin tumour was described. No data were available to evaluate the carcinogenicity to experimental animals of 4,5',8-trimethylpsoralen in the absence of ultraviolet A radiation.

No data were available to evaluate the reproductive effects or prenatal toxicity of 4,5',8-trimethylpsoralen to experimental animals.

In the presence of ultraviolet A radiation, 4,5',8-trimethylpsoralen bound covalently to isolated DNA and to DNA in bacteria, yeast and mammalian cells in culture, and in guinea-pig skin *in vivo*. It induced DNA damage in bacteria in the dark. In combination with ultraviolet A radiation, it induced mutation in bacteriophage. The compound was mutagenic to bacteria in the dark and with ultraviolet A radiation, and to yeast in the presence of ultraviolet A radiation. 4,5',8-Trimethylpsoralen induced chromosomal aberrations in *Hordeum vulgare* grown under normal daylight and in the presence of ultraviolet A radiation induced sister chromatid exchanges and chromosomal aberrations in cultured mammalian cells.

5.3 Human data

One case of melanoma was reported in a patient treated orally with 4,5',8-trimethylpsoralen. In a small series of patients treated topically with 4,5',8-trimethylpsoralen and ultraviolet radiation, no skin malignancy was seen after short-term follow-up.

5.4 Evaluation

There is *inadequate evidence* for the carcinogenicity of 4,5',8-trimethylpsoralen in combination with ultraviolet A radiation to experimental animals. No data were available to evaluate the carcinogenicity of 4,5',8-trimethylpsoralen to experimental animals in the absence of ultraviolet A radiation.

There is *inadequate evidence* for the carcinogenicity of 4,5',8-trimethylpsoralen to humans.

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

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