UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF TOXIC SUBSTANCES

MEMORANDUM MAR 2 1983

SUBJECT: Larvin (Thiodicarb): 3G2782. Revision of tolerance for corn. Caswell 900 AA.

TO: Jay Ellengerber, PM-12
Registration Division (TS-767C)

THRU: Christine Chaisson, Section Head
Toxicology Branch (TS-769C)

Clood B Sandusky for CFC 2/24/83

Union Carbide Company in an October 28, 1982 letter requested an EUP and temperary tolerances for field and sweet corn, corn forage and fodder and sweet corn cannery wastes. This request was a approved in my memo of 2/17/83 to you (Larvin 3.2 and UCLF-2 Experimental use application on field and sweet corn for 1983. 264-EUP-AG, 264-EUP-AU, 3G2782, 3H5375. Caswell #900AA).

The Company revised the corn tolerance requests (12/16/82) to include:

Commodity	Tolerances
Corn, grain	0.05 ppm
Corn, fresh (including kernals and cobs with husks removed)	1.5 ppm
Corn, forage	60 ppm
Corn, fodder	60 ppm

dropping the tolerance for sweet corn cannery wastes.

The requested change does not alter the TMRC=0.352 mg/day and the % of the ADI= 1.96% (see attached computer printout) already approved as indicated by my 2/17/83 memo. Therefore Toxicology Branch has no objections to the proposed change in tolerances.

Stan Gross 2/24/83 for CFC 2/25/83

Stanley B. Gross, Toxicologist
Toxicology Branch (TS-769C)

10 AU - KAJI S ; ONCHI M ; MICHINOMAE M
TI - EFFECT OF ACETAMIDE ON THE MITOTIC RATE IN EHRLICH ASCITES TUMOR
SI - EMIC/76/023021
SO - JPN J GENET(IDENGAKU ZASSHI); 51:53-58,1976
AB - EMIC/ORNL SEE: CA 85-154051 The effect of acetamide and certain antibiotics on the multiplication of the Ehrlich ascites tumor cells in mice was examd. Acetamide had a marked effect on increasing the mitotic rate of the tumor cells. However, mitomycin-C or nitromin had a strong inhibitory effect on the multiplication of the cells. Acetamide appered to counteract the mitomycin-C and nitromin effects on the metabolic process of the multiplication of tumor cells. The mode of action on tumor cells by these 2 groups of chems. was similar to that on the facet formation in Drosophila. The acid amides not only are specific to the eye development in Drosophila, but also considerably increase the mitotic rate of tumor cells in the mouse.

26 AU - Merkle J ; Zeller H
AD - Abt. Gewerbehyg. Toxikol., BASF A.-G., Ludwigshafen/Rhein
TI - Studies on acetamides and formamides for embryotoxic and teratogenic activities in the rabbit
SI - CA/093/180514X
SO - Arzneim.-Forsch.; VOL 30, ISS 9, 1980,1557-62
LA - GER
AB - CBAC COPYRIGHT: CHEM ABS When aq. solns. of acetamides and formamides were administered by stomach tube to pregnant rabbits from the 6th to the 18th day past insemination, monomethylformamide had the greatest teratogenic activity. (123-39-7 Monomethylformamide) In contrast, embryotoxic effects from acetamide and dimethylacetamide occurred only with maternally toxic doses. (60-35-5 Acetamide)(127-19-5 Dimethylacetamide) Monomethylacetamide was also teratogenic, and formamide showed embryotoxic and weakly teratogenic effects at concns. that were not toxic to the mother (79-16-3 Monomethylacetamide)(75-12-7 Formamide) The rabbit was more sensitive to DMF than has been reported for other species, with fetal anomalies being induced by doses that were maternally acceptable. (68-12-2 DMF (amide))

32 AU - BOEHM KD ; DENARINIS F
TI - UPTAKE OF ACETAMIDE-1-C14 BY THE 70-HOUR STAGE IMAGINAL EYE DISCS OF THE BAR SERIES
SI - EMIC/77/004228
SO - DROS INFO SERV; 52:130-131,1977
AB - EMIC/ORNL

33 AU - KAJI S
TI - INCORPORATION OF THE TRITIATED ACETAMIDE INTO DNA IN DROSOPHILA MELANOGASTER
SI - EMIC/73/004165
SO - DROS INFO SERV; 50:35,1973
AB - EMIC/ORNL

37 AU - THIERSCH JB
TI - EFFECTS OF ACETAMIDES AND FORNAMIDES ON THE RAT LITTER IN UTERO
SI - ETIC/62/011278
SO - J REPROD FERT; 4:219-220,1962
AB - ETIC/ORNL

57 AU - Clark A ; Smucker L ; Hamilton D
AD - University of Delaware; School of Arts & Sciences; Dept. of Biology; Newark, Delaware 19711
TI - MUTAGENICITY OF ACETAMIDE IN WASPS
SI - SSIE/DP 547
SO - Toxicology Research Projects Directory, Vol.C4 iss.07 1979
AB - RPROJ Groups of 15 male parasitic wasps (Habrobracon) are being fed acetamide in a diet of 10% sucrose solution, then mated with 15 virgin females for 12 hours in a dominant lethal study. The numbers of eggs hatched, the stage of embryonic development at death, and the male/female ratio of hatched eggs will be studied as indicators of mutagenicity. Groups of wasps will receive a 25 millimolar solution of ethylmethanesulfonate, a known mutagen, as positive controls. Negative controls will receive a 10% sucrose solution.

63 AU - Hynes MJ
AD - Department of Genetics, La Trobe University, Bundoora, Victoria, Australia.
TI - Fine-structure mapping of the acetamidase structural gene and its controlling region in Aspergillus nidulans.
SI - TOXBIB/79/214438
SO - Genetics; VOL 91, ISS 3, 1979, P381-92
LA - Eng
AB - A large number of amdS mutants altered in acetamide utilization have been used to construct a fine-structure map of the amdS locus. The mutagen diepoxyoctane generated most of the deletion strains used for mapping. A minimum of 14 sites within the amdS gene were found. Biochemical analysis of amdS mutants defined the extent of the probable coding region. A new mutant, amd-205, which did not produce detectable inactive gene product, was found to be inseparable by recombination from the "up-promoter" mutation amdI18 and was located outside of the apparent amdS coding region. The cis-dominant mutation, amdI9, was also located at this end of the gene. This work, therefore, provides evidence for the separation of a eukaryotic gene into controlling and structural regions.

65 AU - Porter WR ; Gudzinowicz MJ ; Neal RA
AD - Sch. Med., Vanderbilt Univ., Nashville
TI - Thioacetamide-induced hepatic necrosis. II. Pharmacokinetics of thioacetamide and thioacetamide-S-oxide in the rat
SI - CA/091/152165Z
SO - J. Pharmacol. Exp. Ther.; VOL 208, ISS 3, 1979,386-91
LA - ENG
AB - CBAC COPYRIGHT: CHEM ABS ADDENDUM The distribution of radioactivity from 3H-, 14C-, or 35S-labeled thioacetamide and thioacetamide S-oxide was studied as a function of time in liver, kidneys, plasma, and muscle. (62-55-5 Thioacetamide)(2669-09-2 Thioacetamide-S-oxide) Liver and plasma concns. of thioacetamide, thioacetamide S-oxide, acetamide, sulfate, polar products, and products bound to tissue macromols. were also detd. (60-35-5 Acetamide) The development of centrilobular hepatic necrosis was first obsd. 6 h after peak plasma levels of thioacetamide S-oxide were obtained (6 h after administration of the s-oxide or 9 h after administration of thioacetamide). Max. hepatic necrosis occurred at 24 h and was correlated with the peak concns. of polar products in the liver and with radioactivity bound to hepatic macromols. Max. concns. of polar products in the liver and radioactivity bound to hepatic macromols. were obtained 3-6 h after peak plasma levels of thioacetamide S-oxide were reached. Equimolar doses of thioacetamide S-oxide produced a more rapid onset and a greater severity of centrilobular hepatic necrosis than did corresponding doses of thioacetamide. Thioacetamide-induced necrosis can be explained by a scheme which requires the metabolic conversion of thioacetamide to its S-oxide, followed by the further metab. of thioacetamide S-oxide to a reactive intermediate which can either bind to liver macromols. or be further degraded to acetamide and polar products. The Me group and thiocarbonyl C atom, but not the S atom, of thioacetamide or its S-oxide appear to be bound to tissue macromols. after reaction with the reactive intermediate. Under the conditions of these expts. acetamide, formed metabolically from thioacetamide or thioacetamide S-oxide, does not appear to be further degraded. Also, the administration of acetamide-14C did not lead to incorporation of a measurable amt. of radioactivity into the macromols. of liver.

81 AU - PORTER WR ; GUDZINOWICZ MJ ; NEAL RA
AD - Dep. Biochem., Cent. Environ. Toxicol., Vanderbilt Univ. Med. Sch., Nashville, Tenn. 37232, USA.
TI - Thioacetamide-induced hepatic necrosis; II., Pharmacokinetics of thioacetamide and thioacetamide-S-oxide in the rat.
SI - HEEP/79/13133
SO - J PHARMACOL EXP THER; 208 (3). 1979. 304-391.
AB - HEEP COPYRIGHT: BIOL ABS. The distribution of radioactivity from 3H-, 14C- or 35S-labeled thioacetamide and thioacetamide-S-oxide was studied as a function of time in liver, kidney, plasma and muscle. Liver and plasma concentrations of

81-CONT'D

thioacetamide, thioacetamide-S-oxide, acetamide, sulfate, polar products and products bound to tissue macromolecules were also determined. The development of centrilobular hepatic necrosis was first observed 6 h after peak plasma levels of thioacetamide-S-oxide were obtained (6 h after administration of the S-oxide or 9 h after administration of thioacetamide). Maximum hepatic necrosis occurred at 24 h and was correlated with the peak concentrations of polar products in the liver and with radioactivity bound to hepatic macromolecules. Maximum concentrations of polar products in the liver and radioactivity bound to hepatic macromolecules were obtained 3-6 h after peak plasma levels of thioacetamide-S-oxide were reached. Equimolar doses of thioacetamide-S-oxide produced a more rapid onset and a greater severity of centrilobular hepatic necrosis than did corresponding doses of thioacetamide. Thioacetamide-induced necrosis can be explained by a scheme which requires the metabolic conversion of thioacetamide to its S-oxide followed by the further metabolism of thioacetamide-S-oxide to a reactive intermediate which can either bind to liver macromolecules or be degraded to acetamide and polar products. The methyl group and thiocarbonyl carbon atom, but not the S atom, of thioacetamide or its S-oxide appear bound to tissue macromolecules after reaction with the reactive intermediate. Under the conditions of these experiments acetamide, formed metabolically from thioacetamide or thioacetamide-S-oxide, does not appear further degraded. The administration of (14C)acetamide does not lead to incorporation of a measurable amount of radioactivity into the macromolecules of liver.

87 AU - POIRIER LA ; WEISBURGER EK
AD - Lab. Carcinog. Metabol., Div. Cancer Cause Prevent., Natl. Cancer Inst., Bethesda, Md. 20014, USA.
TI - Selection of carcinogens and related compounds tested for mutagenic activity.
SI - HEEP/79/12917
SO - J NATL CANCER INST; 62 (4). 1979. 833-840.
AB - HEEP COPYRIGHT: BIOL ABS. A list of 102 chemicals was prepared for subsequent mutagenesis assays in a National Cancer Institute program to determine the extent of correlation between carcinogenesis and mutagenesis in standardized assays. The chemicals were divided into 5 major categories: 37 aromatic amines, 11 polycyclic aromatic hydrocarbons, 8 nitrosamines and nitrosamides, 16 alkylating agents and a miscellaneous category consisting of 11 heterocyclic compounds, 7 amides, ureas and acylating agents, 5 antimetabolites, 4 inorganic chemicals and 3 promoters. The chemicals were further described as procarcinogens (requiring metabolic activation to exert their biologic activities), ultimate carcinogens (direct-acting chemicals not requiring metabolic activation), and noncarcinogens (compounds shown to be inactive in 1 or more adequate carcinogenicity tests). An extensive bibliography documents the selection and categorization of the compounds.

88 AU - ROSENKRANZ HS ; POIRIER LA
AD - Dep. Microbiol., N.Y. Med. Coll., Valhalla, N.Y. 10595, USA.
TI - Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and noncarcinogens in microbial systems.
SI - HEEP/79/12912
SO - J NATL CANCER INST; 62 (4). 1979. 873-892.
AB - HEEP COPYRIGHT: BIOL ABS. The mutagenicity of 99 chemicals was determined in a standard Salmonella typhimurium assay with the use of strains TA1535 and TA1538; the DNA-modifying capacity was determined with normal and DNA polymerase-deficient Escherichia coli strains. The following categories of chemicals were studied: alkylating agents (15); nitrosamines, hyddrazines, and related substances (8); heterocyclics (10); aromatic amines (36); polycyclic aromatic hydrocarbons (11); amides, ureas, and acylating agents (7); antimetabolites (5); inorganics (4); and promoters (3). Of the substances studied, 21 were known noncarcinogens, 21 were ultimate carcinogens, and 45 were procarcinogens. Of the noncarcinogens, 35, 30, and 25% were positive in the Salmonella, E. coli, and both systems, respectively. All of the ultimate carcinogens were detectable as mutagens or DNA-modifying agents; 79, 100, and 79% gave positive tests in the Salmonella, E. coli, and both systems, respectively. Of the procarcinogens 72% were identifiable by these procedures: 52, 67, and 48% in the Salmonella, E. coli, and both assays, respectively. A tabulation of the combined data for ultimate carcinogens and procarcinogens indicates that 77% of the carcinogens gave positive results: 61, 74, and 59% in the Salmonella, E. coli, and both assays, respectively. For prescreening procedures with microbial assays, S. typhimurium strains TA98 and TA100 should be included and the standard E. coli DNA polymerase-deficient assay be run in tandem with the Salmonella mutagenicity assay. When the standard E. coli DNA polymerase-deficient assay does not give interpretable results because of the lack of zones of growth inhibition, a modified assay with the use of liquid suspension should be performed.

110 AU - Pak AD ; Esyrev OV
AD - Lab. Membrane Physiol., Inst. Physiol., Alma-Ata
TI - Effect of low-molecular-weight nonelectrolytes and hypotonia on contractile responses of frog sartorius muscles
SI - CA/092/035045V
SO - Tsitologiya; VOL 21, ISS 10, 1979,1209-13
LA - RUS
AB - CBAC COPYRIGHT: CHEM ABS The contractile responses of frog sartorius muscle to elec. stimulation or caffeine treatment were decreased within 15 min after incubation with 400 mM urea, acetamide, or ethylene glycol. (58-08-2 Caffeine)(57-13-6 Urea)(60-35-5 Acetamide)(107-21-1 Ethylene glycol) However, after prolonged incubation these nonelectrolytes potentiated the contractile responses to caffeine or elec. stimulation. When the muscles were incubated in a hypotonic soln., the caffeine-induced contraction almost completely disappeared whereas the elec. stimulated contraction was potentiated. The addn. of 400 mM glycerol to the hypotonic soln. increased the amplitude of contractions under both types of stimulation (caffeine and elec.).

116 AU - Porter WR ; Gudzinowicz MJ ; Neal RA
AD - Sch. Med., Vanderbilt Univ., Nashville
TI - Thioacetamide-induced hepatic necrosis. II. Pharmacokinetics of thioacetamide and thioacetamide-S-oxide in the rat
SI - CA/091/152165Z
SO - J. Pharmacol. Exp. Ther.; VOL 208, ISS 3, 1979,386-91
LA - ENG
AB - CBAC COPYRIGHT: CHEM ABS The distribution of radioactivity from 3H-, 14C-, or 35S-labeled thioacetamide and thioacetamide S-oxide was studied as a function of time in liver, kidneys, plasma, and muscle. (62-55-5 Thioacetamide)(2649-09-2 Thioacetamide-S-oxide) Liver and plasma concns. of thioacetamide, thioacetamide S-oxide, acetamide, sulfate, polar products, and products bound to tissue macromols. were also detd. (60-35-5 Acetamide) The development of centrilobular hepatic necrosis was first obsd. 6 h

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after peak plasma levels of thioacetamide S-oxide were obtained (6 h after administration of the s-oxide or 9 h after administration of thioacetamide). Max. hepatic necrosis occurred at 24 h and was correlated with the peak concns. of polar products in the liver and with radioactivity bound to hepatic macromols. Max. concns. of polar products in the liver and radioactivity bound to hepatic macromols. were obtained 3-6 h after peak plasma levels of thioacetamide S-oxide were reached. Equimolar doses of thioacetamide S-oxide produced a more rapid onset and a greater severity of centrilobular hepatic necrosis than did corresponding doses of thioacetamide. Thioacetamide-induced necrosis can be explained by a scheme which requires the metabolic conversion of thioacetamide to its S-oxide, followed by the further metab. of thioacetamide S-oxide to a reactive intermediate which can either bind to liver macromols. or be further degraded to acetamide and polar products. The Me group and thiocarbonyl C atom, but not the S atom, of thioacetamide or its S-oxide appear to be bound to tissue macromols. after reaction with the reactive intermediate. Under the conditions of these expts. acetamide, formed metabolically from thioacetamide or thioacetamide S-oxide, does not appear to be further degraded. Also, the administration of acetamide-14C did not lead to incorporation of a measurable amt. of radioactivity into the macromols. of liver.

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123 AU - Miura Y ; Sawatani S ; Terasawa T ; Masuda R
AD - Inst. Hematol., Jichi Med. Sch., Jichi
TI - Enhancement of heme synthesis in quail embryo yolk sac cells by highly polar compounds
SI - CA/091/102870E
SO - Blood; VOL 54, ISS 2, 1979,421-8
LA - ENG
AB - CBAC COPYRIGHT: CHEM ABS Dissccd. yolk sac cells from quail embryos at the definitive primitive streak stage were cultured in a gyratory shaker in a medium contg. DMSO or other polar compds. (67-68-5 DMSO) The single aggregates thus formed were further cultured in an egg agar medium contg. 59Fe. An increase in heme synthesis was obsd. in the explants incubated in DMSO, N,N-dimethylacetamide, 1-methyl-2-piperidone, N-methylacetamide, or triethylene glycol, but not in those incubated in acetamide, propionamide, or N,N-dimethylformamide. (14875-96-8 Heme)(127-19-5 N,N-Dimethylacetamide)(931-20-4 1-Methyl-2-piperidone)(79-16-3 N-Methylacetamide)(112-27-6 Triethylene glycol)(60-35-5 Acetamide)(79-05-0 Propionamide)(68-12-2 N,N-Dimethylformamide) The Hb and DNA contents were chem. detd. in the pooled explants treated with N,N-dimethylacetamide as an example of the effects of a polar compd. There was an obvious increase in Hb content in the treated explants. The DNA content of the treated explants was also higher than in the control. The cellular permeability for 59Fe was not affected by N,N-dimethylacetamide.

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215 AU - Vinogradova NA ; Nikol'skii NN ; Troshin AS
AD - Lab. Cell Physiol., Inst. Cytol., Leningrad, USSR
TI - Inhibition by amines and amides of the stimulation of sugar transport in frog sartorius muscles
SI - CA/088/183838P
SO - Tsitologiya; VOL 20, ISS 3, 1978,315-20
LA - RUS
AB - CBAC COPYRIGHT: CHEM ABS Studies on isolated frog sartorius muscles showed that amines and amides inhibited the stimulation of D-xylose transport induced by insulin, 2,4-dinitrophenol, or K+. (58-86-6 D-Xylose)(9004-10-8 Insulin)(51-28-5 2,4-Dinitrophenol) Inhibition was obsd. at 100 mM with urea, acetamide, guanidine, some diamines, and NH4Cl and its Me and Et derivs. (57-13-6 Urea)(60-35-5 Acetamide)(113-00-8 Guanidine) Cystamine (20 mM), tryptamine and mexamine (2 mM), and adenine, adenosine, and guanosine (1-10 mM) also inhibited xylose transport. (51-85-4 Cystamine)(61-54-1 Tryptamine)(66-83-1 Mexamine)(73-24-5 Adenine)(58-61-7 Adenosine)(118-00-3 Guanosine) In comparable concns., acetone, glycerol, tetramethylammonium, propylamine, butylamine, amino acids, spermine, spermidine, ATP, AMP, and cAMP were ineffective. The inhibitors may form H bonds from their -NH groups with neutral or negatively charged groups on the external surface of the muscle membrane. As a result, the closure of linkages required for the activation of sugar transport could not occur.

223 AU - Egyed MN ; Shlosberg A
TI - The efficiency of acetamide in the prevention and treatment of fluoroacetamide poisoning in chickens.
SI - PESTAB/77/0839
SO - Fluoride 10(1): 34-37; 1977.(11 references)
AB - PESTAB. The antidotal effect of acetamide (AA) was studied in chickens. For this purpose the acute LD50 of orally administered fluoroacetamide (FAA) was determined in 2 to 3 month old Leghorn chickens and was found to be 4.25 mg/kg. AA was administered orally at dose rates of 0.5 g and 2.5 g/kg. Only at the higher dosage rate did AA prevent the lethal action of FAA (10 mg/kg) when given one hour before, at the same time or 10 or 20 minutes after the administration of FAA. The same dose of AA failed to prevent the death of chickens when given 30 to 60 minutes after the administration of FAA.

237 AU - EGYED MN ; SHLOSBERG A
AD - Kimron Vet. Inst., Bet Dagan, Isr.
TI - The efficacy of acetamide in the prevention and treatment of fluoroacetamide poisoning in chickens.
SI - HEEP/77/09171
SO - FLUORIDE; 10 (1). 1977 34-37
AB - HEEP COPYRIGHT: BIOL ABS. The antidotal effect of acetamide (AA) was studied in chickens. The acute LD50 of orally administered fluoroacetamide (FAA, an effective rodenticide) was determined in 2-3 mo. old Leghorn chickens and was 4.25 mg/kg. AA was administered orally at dose rates of 0.5 g and 2.5 g/kg. Only at the higher dosage rate, did AA prevent the lethal action of FAA (10 mg/kg) when given 1 h before, at the same time or 10 or 20 min after the administration of FAA. The same dose of AA failed to prevent the death of chickens when given 30-60 min after the administration of FAA.

249 AU - Gorlinskaya EP
AD - USSR
TI - Metabolism of RNA from the liver and skeletal muscle of white rats treated with certain chemical compounds
SI - CA/090/001299Z
SO - Nekotor. Vopr. Eksperim. Prom. Toksikol; 1977,64-9
LA - RUS
AB - CBAC COPYRIGHT: CHEM ABS Title only translated. Acetamide liver muscle RNA Diethylamine liver muscle RNA Glutamate liver muscle RNA RNA liver muscle chem

253 AU - Gorlinskaya EP
AD - Leningr. Inst. Gig. Tr. Profaabolevanii, Leningrad, USSR
TI - Effect of nitrogen-containing substances on RNA metabolism in experimental animals
SI - CA/089/101153V
SO - Gig. Aspekty Okhr. Zdorov'ya Naseleniya; 1977,189-90
LA - RUS
AB - CBAC COPYRIGHT: CHEM ABS Chronic administration of acetamide, Et2NH, and Na glutamate (1/10 LD50 for 30 days) to rats caused significant changes in RNA metab. in skeletal muscle but had little effect on RNA metab. in the liver. (60-35-5 Acetamide)(109-89-7 Diethylamine)(142-47-2 Sodium glutamate)

TOXICOLOGY AND APPLIED PHARMACOLOGY 14, 163–175 (1969)

Prevention by Arginine Glutamate of the Carcinogenicity of Acetamide in Rats[1]

J. H. WEISBURGER, R. S. YAMAMOTO, R. M. GLASS, AND H. H. FRANKEL

Biology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20014

Received July 1, 1968

Prevention by Arginine Glutamate of the Carcinogenicity of Acetamide in Rats. WEISBURGER, J. H., YAMAMOTO, R. S., GLASS, R. M., and FRANKEL, H. H. (1969). *Toxicol. Appl. Pharmacol.* **14**, 163–175. In confirmation of an earlier report, it was found that administration of 2.5% acetamide in the diet of rats for 12 months led to malignant liver tumors after 12–15 months of observation in approximately 50% of the animals at risk. Additional animals exhibited hyperplastic nodules and similar precancerous lesions. The combined feeding of an equimolar amount of arginine glutamate (5.6%) with 2.5% acetamide, led to virtually complete inhibition of the carcinogenic process. Untreated controls or rats fed 5.6% arginine glutamate showed no lesions in the liver. The findings are consistent with, but not necessarily related to, the hypothesis that acetamide is carcinogenic to the liver because of chronic intracellular liberation of ammonia. However, an effort to demonstrate the possible carcinogenic effect of chronic treatment with ammonium ions was equivocal inasmuch as the feeding of 4.8% ammonium citrate alone (equimolar with 2.5% acetamide) did not lead to lesions in the liver.

of Chemicals to Man. Vol. 7. Some aromatic amines and related nitro substances, nitrofurans and azo dyes. International Agency for Research on Cancer, 1974.

ACETAMIDE*

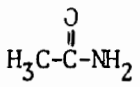
1. Chemical and Physical Data

1.1 Synonyms and trade names

Chem. Abstr. No.: 60-35-5

Acetic acid amide; ethanamide; methane carboxamide

1.2 Chemical formula and molecular weight



C_2H_5NO Mol. wt: 59.1

1.3 Chemical and physical properties of the pure substance

(a) Description: Deliquescent crystals

(b) Boiling-point: 222°C

(c) Melting-point: 81°C

(d) Density: d_4^{20} 1.159

(e) Refractive index: n_D^{78} 1.4274

(f) Solubility: At 25°C, 1 g is soluble in 0.5 ml water, 2 ml ethanol or 6 ml pyridine; soluble in chloroform, glycerol and hot benzene

(g) Chemical reactivity: Neutral reaction, K_b at 25°C = 3.1×10^{-15}

1.4 Technical products and impurities

In 1963 acetamide was reported to be available in the US as a technical grade (99% minimum acetamide and 0.3% maximum free acid) and as a chemically

* Considered by the Working Group in Lyon, June 1974

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pure, odourless grade (99.5-99.9% acetamide and a trace of free acid) (Lurie, 1963).

2. Production, Use, Occurrence and Analysis

A review article on acetamide has been published (Lurie, 1963).

2.1 Production and use[1]

A method for the synthesis of acetamide by fractional distillation of ammonium acetate was reported in 1923 (Coleman & Alvarado, 1923), and although many other synthesis routes are available, commercial production is believed to be based on this same distillation, the ammonium acetate being made by the reaction of ammonia with acetic acid at elevated temperature (Lurie, 1963). Acetamide has been produced commercially in the US for over 50 years: 5 producers reported a total production of 200 kg in 1921 (US Tariff Commission, 1922). In 1972, 2 US companies were believed to be making acetamide; but only 1 manufacturer was reporting commercial production to the US Tariff Commission, and separate production data were not given (US Tariff Commission, 1974).

Acetamide is produced in the following European countries (number of producing companies is shown in parentheses): the Federal Republic of Germany (3); France (1); Italy (2); and the United Kingdom (7) (Ben Brothers, Ltd., 1974; Chemical Information Services, Ltd., 1973; Econ Verlag GmbH, 1973-1975). The total annual European production is estimated to be less than 1 million kg.

It has been reported that acetamide has been used in cryoscopy, as a soldering flux ingredient, as a solvent, wetting agent and penetration accelerator for dyes, as a component of urea molding compounds, as an anti-acid in the lacquer, explosives and cosmetics industries, as a plasticizer in leather, cloth and coatings, as a humectant for paper, as an activator in bleach liquors, as a special food for molds, and as a chemical inter-

[1] Data from Chemical Information Services, Stanford Research Institute, USA

mediate in the synthesis of methylamine, thioacetamide, hypnotics, insecticides, medicinals and various plastics (Lurie, 1963). It was also reported that acetamide had found use as a stabilizer, in the manufacture of denatured alcohol and as an antidote in experimental fluoracetate poisoning (Merck & Co., 1968).

Whether acetamide still finds commercial use in any of the applications listed above could not be established.

2.2 Occurrence

Over-oxidized wine can contain acetamide (Datunashvili, 1963).

2.3 Analysis

Thin-layer chromatographic analysis of acid amides, including acetamide, has been described by Seeboth et al. (1966). Amounts down to 10 µg were detectable.

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Man

3.1 Carcinogenicity and related studies in animals

(a) Oral administration

Rat: Dessau & Jackson (1955) first suspected a tumourigenic effect with acetamide when 1/5 Rockland albino rats developed a liver tumour described by the authors as a hepatocellular adenoma after receiving oral doses of 4 g/kg bw/day in distilled water on 5 days per week for 205 days.

In a later study, four groups of 25 1-month old male Wistar rats were fed a diet containing 0, 1.25, 2.5 or 5% acetamide for 1 year. One rat/group was killed at monthly intervals, and the remaining rats were killed after 1 year. Liver tumours (most of them described as trabecular carcinomas and some as adenocarcinomas with lung metastases) were seen in 4/24, 6/22 and 1/18 rats autopsied from the low, medium and high dose level groups, respectively. The first liver tumour was seen after 16 weeks. No liver tumours occurred in 25 controls. In a further group of 50 male Wistar rats fed 5% acetamide continuously in the diet, 1 rat was killed

weekly from 0-26 weeks, after which 1 rat was killed every other week. Liver tumours (described as being trabecular carcinomas and some as adenocarcinomas with lung metastases) were observed in 4/48 rats treated for 38-52 weeks, compared with 0/43 in controls. When acetamide was administered at a concentration of 5% in the diet to 99 male Wistar rats, with 2 rats returned to a control diet each week, liver tumours were found after treatment for 14-40 weeks in 22/81 rats autopsied (Jackson & Dessau, 1961).

Two groups of 40 male Wistar rats were fed diets containing 2.5% acetamide or 2.5% acetamide + 5.6% L-arginine L-glutamate, and 2 groups of 15 males were fed a diet containing 5.6% arginine glutamate or a control diet for 1 year. In 2/8 rats fed acetamide and killed after 1 year, hepatomas ranging "from highly differentiated to undifferentiated anaplastic growths" were observed; 7/16 rats fed acetamide for 1 year and maintained on a control diet for a further 3 months developed liver tumours. In contrast, 1/11 rats that received acetamide + arginine glutamate for 1 year developed a hepatoma, and 1/19 rats receiving such a diet for 1 year and the control diet for 3 months had hyperplastic liver nodules. No liver tumours occurred in the control group nor in rats fed 5.6% arginine glutamate alone (Weisburger et al., 1969).

3.2 Other relevant biological data

Maximum tolerated single doses for male rats and male mice are 7.5 and 8 g/kg bw, and the corresponding LD_{50} values are 10.3 and 10.1 g/kg bw (observed after 24 hours). Animals administered 1/20 the lethal single dose, 400 mg/kg bw, daily for 36 days showed decreased growth; but no other signs of toxicity or pathological lesions were observed (Caujolle et al., 1970).

3.3 Observations in man

No data were available to the Working Group.

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4. Comments on Data Reported and Evaluation[1]

4.1 Animal data

Acetamide is carcinogenic in rats following oral administration, the only species and route tested, producing benign and malignant liver tumours.

4.2 Human data

No case reports or epidemiological studies were available to the Working Group.

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[1] See also the section, "Animal Data in Relation to the Evaluation of Risk to Man" in the introduction to this volume (p. 15).