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Monsanto

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MARTIN GREIF
MAR 12 REC'D

March 9, 1981

Mr. Martin Greif
Executive Secretary
Toxic Substances Control Act
Interagency Testing Committee
401 M Street, SW
Washington, DC 20460

Dear Mr. Greif:

Thank you for the opportunity to comment on the Hazard Information Review of Ethoxyquin (6-ethoxy-1,2-dihydro-2,2 & trimethylquinoline) for use by the TSCA Interagency Testing Committee. In addition to my comments, I have included listings of available toxicity and environmental literature on ethoxyquin and a few reprints which I reference in my comments.

These references and papers should be of use to you in assessing ethoxyquin. In addition, they will fill in areas such as teratogenicity, embryotoxicity, fetotoxicity, special studies, subacute studies and chronic studies on which Enviro-Control's review said no data was available.

Based on the tremendous amount of data available on ethoxyquin, we recommend that ethoxyquin be removed from the list of chemicals under review by the ITC.

If you feel that a meeting with you, the member of the ITC committee heading the ethoxyquin review, the director of the Enviro-Control group authoring the report and Monsanto (the only domestic producer) would be beneficial, please contact me.

Also contact us if we can be of assistance in the review of other Monsanto products.

Sincerely,

Margaret E. Klaus

Margaret E. Klaus
Coordinator
Product Acceptability and
Environmental Affairs

mec

Attachments

Comments of Hazard Information Review on Ethoxyquin

I.A.3. Synonyms

Santoflex® AW - Monsanto Trade Name
Santoquin® - Monsanto Trade Name
ethoxyquin

I.D.1. Release Rate: None is released to the environment at production site.

I.D.3. Production

The quantity produced by this company annually is between 100,000 and 1,000,000 pounds. Total imports are estimated to be substantially lower than domestic production.

I.D.4. Use

- Scald inhibitor (post harvest perservation of apples and pears) in Europe.

  (Latest on ethoxyquin from European Economic Community regulations - See Attachment 1 from the Official Journal of the European Communities: Use of ethoxyquin on apples and fruits is not forbidden but is permitted under EEC regulations.)

- Herbicide - Ethoxyquin is not used as a herbicide. Reference given is to a Monsanto patent which never applied to use.

- Pesticide - Ethoxyquin is not an active ingredient in pesticides.

II.A. Metabolism

All conclusions from the Skarre and Nafstad (1979) paper are misleading because approximately 164 times the level of ethoxyquin was present in the animal stomach per unit time than would normally be there if the ethoxyquin had been ingested via the diet at normal rates. Federal regulations limit dietary levels to 150 ppm. In cases of radioactivity measurements, the paper referred to "ethoxyquin and metabilites" but no identification was given. These compounds could have been compressed largely of normal metabolic by-products.

I suggest any of a number of papers using permitted federal levels be used as references for this discussion (see references attached).

III.A. Carcinogenicity

Epstein et al (1970)

Feeding levels exceeded the acute toxicity of ethoxyquin. Testing ground rules always establish the feeding dose level below the acute toxicity level. Epstein, et al concluded "An increase in solitary pulmonary adenomas is an unreliable carcinogenic index" and "repeat testing" "particularly Santoquin" needs to be done before conclusion indicating carcinogenicity can be reached. As the authors state, as far as ethoxyquin is concerned, no conclusion of carcinogenicity can be reached. Therefore, results are not contradictory. This reference is best omitted.

Also, the conclusions of mutagenicity studies support ethoxyquin not being carcinogenic. Results thus far show all carcinogens are also mutagens, although not all mutagens are carcinogens. Since ethoxyquin is not a mutagen as shown in numerous screenings, it follows that it would not be a carcinogen.

III.C. Teratogenicity, Embryotoxicity, and Fetotoxicity

D. Special Studies

F. & Short-Term Studies (Subacute)

G. Long-Term Studies (Chronic)

Although the report states no information is available, many papers and studies (including Federal Government studies) are available as shown in the reference lists attached.

Some in particular you may be interested in include.

1. Wilson, R.H. and De Eds, F., "Toxicity Studies on the Antioxidate 6-ethoxy-1,2-dihydro-2,2,4-trimethylquinoline," J. Agr. Food Chem. 7:203-6, 1959 (attachment 2).

   This is a paper covering a 200-day rat feeding study of 0, 0.2, and 0.4 ethoxyquin levels.

2. Isenstein, R. S., "Ethoxyquin in Rabbit Feed Study of Relationship to Abortion and Early Neonatal Death," Am. J. Vet. Res., 31-907, 1970 (Attachment 3).

3. Gassner, F. X., et al., "Effect of Feeding 1,2-dihydro-6-ethoxy-2,2,4-trimethylquinoline to Chickens," Poultry Sci. 39:524-533, 1960 (Attachment 4).

This paper covers a 12-week chicken feeding study.

IV. Observation in Humans

It should be noted that no toxicity data on humans exists. The moderately toxic rating is an opinion of Gosselin. No human toxicity rating should be given.

V.A. 2. Environmental Concentrations

It should be noted that:

Ethoxyquin is rapidly and nearly completely excreted in urine and feces. There is little breakdown to CO_2 indicating stability of the ring system. The small quantities found in the several tissues are distributed in such a way as to suggest a modification of the molecule to make it more water soluble. (Residues are usually less than 1 ppm in all species and tissues and in milk and eggs.)

V.C.1. Effects of microorganisms

Reference to Ayres, et al, 1978 should note the following:

The ethoxyquin used was dissolved in acetone. Acetone has been shown in low concentration to stimulate secondary biosynthesis of aflatoxins in A parasiticus (Bennett et al.)

Bennett, J. W. et al., "Effect of Acetone on Production of Aflatoxins and Versicolorin Pigments by Resting Cell Cultures of Aspergillus Parasiticus," Mycopathologia 58: 9-12 (Attachment 5).

Based on this data, the overview should be changed. There are not conflicting carcinogenicity results on ethoxyquin, in fact, all long term studies to date have shown no carcinogenic signs. In addition, laboratory tests show ethoxyquin to be slightly toxic; not moderately toxic.

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Attachment #3

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EFFECT OF ACETONE ON PRODUCTION OF AFLATOXINS AND VERSICOLORIN PIGMENTS BY RESTING CELL CULTURES OF ASPERGILLUS PARASITICUS

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Abstract

Resting cell cultures of *Aspergillus parasiticus* were grown in medium containing four different concentrations of glucose, with and without acetone. In addition, the effect of different equimolar concentrations of acetone, acetic acid, ethanol, and sodium acetate was compared at two glucose levels. Aflatoxin and versicolorin pigment production increased in resting cell medium containing increasing concentrations of glucose. In the presence of glucose high concentrations of acetone (1.0 and 0.25 M) inhibited secondary biosynthesis and low concentrations of acetone (0.1, 0.025 and 0.01 M) stimulated secondary biosynthesis of aflatoxins and versicolorin pigments.

Introduction

Intensive research on aflatoxins began in 1960 as a result of diseases in poultry and fish related to mold contaminated feeds. Since then, aflatoxins have been shown to be extremely toxic and carcinogenic to a number of domestic and laboratory animals, including primates (5). Several biogenetic pathways for the synthesis of these economically important toxins have been proposed and these schemes for aflatoxin biosynthesis have been reviewed (5, 15, 7, 17).

In recent years, experimental evidence has been accumulating which supports certain of these biosynthetic schemes. Results of these experiments with radioactive compounds have shown that both [^{14}-C]averufin (12, 13) and sterigmatocystin (8) are efficiently converted to aflatoxin B_1. These experiments were conducted using a resting cell system developed by Hsieh & Matales (9) and then modified by Lin et al. (12), which utilizes acetone as a solvent for the delivery of the labeled precursor (averufin or sterigmatocystin). Similar experiments in our laboratory, testing the conversion of [^{14}-C]versicolorin A (11) utilized this acetone containing system. These studies indicated that the carrier solvent itself may have had an effect on the biosynthesis of aflatoxin B_1.

Experiments on the effect of acetone on aflatoxin and versicolorin pigment production in a resting cell system of *Aspergillus parasiticus* containing 4 different levels of glucose are described in this report. In addition, the effect of different equimolar concentrations of acetone, acetic acid, ethanol, and sodium acetate were compared at two levels of glucose.

Materials and methods

Strains and culture conditions

The aflatoxin producing strain of *Aspergillus parasiticus* Speare designated SU-1 (NRRL A-16,462) was used throughout the study. Isolation and subsequent history of this strain have been described by Mayne et al. (14). Stock cultures were maintained on potato dextrose agar (Difco)* plus 0.5% yeast extract. All cultures were incubated at 30 C and high humidity.

Mycelial pellets were prepared by inoculating 1 ml of a dense spore suspension (10^6 spores/ml) into 100 ml of the defined liquid medium devised by Adye & Matales (1). This growth medium (GM) was composed of the following, per l: $(NH_4)_2SO_4$, 3.0 g; KH_2PO_4, 10.0 g; $MgSO_4 \cdot 7H_2O$,

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2.0 g; sucrose, 50.0 g; $NaB_4O_7 \cdot 10\ H_2O$, 0.8 mg; $(NH_4)_6 Mo_7O_{24} \cdot 4H_2O$, 0.5 mg; $Fe_2(SO_4)_3 \cdot 6H_2O$, 10.0 mg; $CuSO_4 \cdot 5H_2O$, 0.3 mg; $MnSO_4 \cdot H_2O$, 0.11 mg; and $ZnSO_4 \cdot 7H_2O$, 17.6 mg. Cultures were incubated for 48 hr on a rotary shaker. Mycelial pellets were collected on cheesecloth, rinsed, and weighed on sterile, tared weighing paper. Flasks containing 10 ml medium were inoculated with 1.0 g (wet weight) of mycelial pellets and those containing 100 ml were inoculated with 10 g (wet weight).

In some experiments 0.2 ml of acetone was placed in 50 ml flasks, and 9.8 ml of a replacement cell medium (RC) containing different levels of glucose was added slowly with shaking. RC medium contained per l, KH_2PO_4, 5.0 g; $MgSO_4 \cdot 7\ H_2O$, 0.5 g; KCl, 0.5 g; and the same trace elements as GM. Glucose was added to RC at levels of 0, 1.62, 15.0, and 50.0 g/l. On a larger scale, 0.2 ml of acetone was placed in a 250 ml flask and 100.0 ml of RC medium (15 g/l glucose) was added.

In other experiments, 1.0, 0.1, and 0.01 M solutions of acetone, ethanol, acetic acid, or sodium acetate were prepared by dissolving appropriate quantities of the given compound in RC medium containing 0 or 15 g/l glucose in volumetric flasks. Then 10 ml of each appropriate molar solution was placed in a 50 ml flask. In all experiments weighed mycelial pellets were added to flasks already containing medium and then incubated on a reciprocal shaker at 30 C.

Assay for aflatoxins and versicolorin pigments

Cultures were removed from incubation after 48 hr growth. The mycelial pellets and the culture filtrate from each experiment were separated, and the culture filtrate was extracted by partitioning 2 times into chloroform in a separatory funnel. The mycelial pellets were soaked in acetone for 10 min, and pellets were removed by filtration. 2 vol of water was added to the acetone extract, and the acetone-water solution was extracted with chloroform in a separatory funnel. The respective chloroform extracts from the mycelial pellets and the culture filtrates were combined and evaporated to near dryness on a steam bath. The samples were then appropriately diluted in chloroform and subjected to thin layer chromatography (tlc) on silica gel coated plates.

Aflatoxin concentration was determined by comparing fluorescence intensities of known standards against those of the samples. Standard description for procedural details regarding tlc and densitometry of aflatoxin is given in Pons et al. (16). Versicolorin pigments were separated by tlc using benzene-ethyl acetate-formic acid (95/5/5, v/v/v) and fluorescence intensities under ultraviolet light visually compared to those of known amounts of purified standards of each pigment, chromatographed on the same plate.

Results

When resting cell cultures of *A. parasiticus* containing 0.2 ml acetone and 9.8 ml of RC medium are compared to control cultures containing 10.0 ml RC medium, there are differences in aflatoxins and/or versicolorin pigment production. In table 1 data are presented showing total aflatoxins and versicolorin pigment production with and without acetone in RC medium containing 4 different levels of glucose. Production of both aflatoxins and versicolorins increases with higher levels of glucose. At all glucose concentrations tested more aflatoxin was produced in cultures without acetone than in those with acetone. No versicolorins were detected in cultures lacking glucose, with or without acetone. However, versicolorin pigment production was greatly enhanced by acetone in cultures containing glucose. With 1.62 g glucose/l RC medium (90 μmol glucose per 10 ml medium), no versicolorins were produced in the absence of acetone, whereas

Table 1. Aflatoxin and versicolorin production by resting cell cultures of *A. parasiticus* at 4 glucose concentrations, with and without acetone.

Medium* (total 10 ml)		Aflatoxin in μg/flask				Versicolorins in μg/flask	
glucose g/l	acetone ml	B_1	B_2	G_1	Total	A	C
0	0.0	81.5	ND	15.6	97.1	ND**	ND
	0.2	43.6	ND	5.6	49.2	ND	ND
1.62	0.0	102.3	ND	17.3	119.6	ND	ND
	0.2	89.8	ND	21.5	111.3	3.0	3.5
15	0.0	154.0	16.7	58.7	229.4	5.0	6.3
	0.2	145.6	11.4	41.8	198.8	20.0	23.0
50	0.0	124.8	102.7	43.8	271.3	50.0	58.0
	0.2	153.3	65.2	40.0	258.2	100.0	75.0

* All cultures were grown in 10 ml of medium using 1g wet weight of mycelial pellets as inoculum.

** N.D. = none detected

levels were produced in the presence of acetone. With 15 g glucose/l RC medium, four times as much both versicolorin A and versicolorin C were elaborated by the fungus in the medium containing acetone. With 50 g glucose/l RC medium, versicolorin A production was double and versicolorin C production was one-third higher in the presence of acetone.

The results of experiments in which different concentrations of other low molecular weight carbon compounds were compared with acetone, using equimolar concentration of each compound, are presented in table 2. All compounds tested at the 1.0 M level inhibited aflatoxin and versicolorin pigment production with and without glucose. Acetic acid inhibited aflatoxins and versicolorin pigment production at all concentrations tested, with and without glucose. No versicolorin pigments were detected in cultures grown in RC medium lacking glucose with any of the 4 compounds tested.

However, in the presence of glucose, both acetone and ethanol stimulated aflatoxin production at the 0.1 and 0.01 M concentrations. In acetone-treated cultures aflatoxin content was 800 μg/flask as compared to 3500 μg/flask for the controls; for ethanol treated cultures the aflatoxin content was 550 μg/flask as compared to 350 μg/flask for the controls. Acetone stimulated versicolorin production at 0.1, 0.01 and 0.001 M levels, but in the presence of ethanol no versicolorin pigments were detected except at the 0.001 M level. Sodium acetate had little effect on aflatox production in the presence of glucose, although versicolorin production was stimulated at the 0.1 M level.

Without glucose, acetone at the 0.01 and 0.001 M levels had no effect on aflatoxin production. Ethanol at the 0.1, 0.01, and 0.001 M levels increased aflatoxin production slightly in this medium. Sodium acetate at the 0.01 and 0.001 M levels also had a mildly stimulatory effect on aflatoxin production in the absence of glucose. In the experiments in which larger (100 ml) volumes of RC medium were used and 0.2 ml acetone was added (0.025 M), 4600 μg of aflatoxins were produced per flask compared to 1600 μg for the control. Aflatoxin production was increased over 100%, therefore these results are in good agreement with those at a lower volume and a similar concentration (0.1 or 0.01 M).

Table 2. The effect of acetone, acetic acid, ethanol and sodium acetate on aflatoxin and versicolorin production by resting cell cultures of *A. parasiticus* with and without glucose.

Medium		RC medium with 15g glucose/l		RC medium without glucose	
Added compound	Molarity	Total aflatoxin in μg/flask	Total versicolorin in μg/flask	Total aflatoxin in μg/flask	Total versicolorin in μg/flask
acetone	1.0	3.5	ND*	10.0	ND
	0.1	800.0	12.0	40.0	ND
	0.01	800.0	45.0	80.0	ND
	0.001	266.0	12.0	80.0	ND
acetic acid	1.0	Tr**	ND	Tr	ND
	0.1	Tr	ND	Tr	ND
	0.01	150.0	ND	Tr	ND
	0.001	150.0	ND	Tr	ND
ethanol	1.0	17.0	ND	17.5	ND
	0.01	550.0	ND	120.0	ND
	0.01	550.0	ND	120.0	ND
	0.001	350.0	3.1	120.0	ND
sodium acetate	1.0	36.5	ND	17.5	ND
	0.1	282.0	20.0	80.0	ND
	0.01	282.0	ND	130.0	ND
	0.001	350.0	ND	130.0	ND
control		350.0	3.1	80	ND

* ND = none detected
** Tr = trace

Discussion

Secondary metabolites are generally produced during the idiophase (a phase following the growth phase or trophophase) of fungi grown in submerged liquid culture (4). The RC medium used in these experiments lacks a nitrogen source, which prevents the respiring mycelial pellets from growing (12). Hence this medium is conducive to the production of secondary metabolites such as aflatoxins and versicolorin pigments.

Our experiments indicate that the quantity of glucose supplied to resting cell cultures of *A. parasiticus* in RC medium affects the quantity of secondary metabolites produced. Higher concentrations of glucose in RC medium yield higher quantities of aflatoxins and versicolorins.

Adding acetone to a glucose-containing resting cell system may have an inhibitory or a stimulatory effect on secondary biosynthesis, depending on the concentration of added acetone. The resting cell system developed by Lin et al. (12) contains 0.2 ml acetone in 9.8 ml of RC medium. This volume of acetone is roughly equivalent to a 0.25 M solution. Under the conditions of our experiments, this acetone concentration mildly inhibits aflatoxin synthesis

but stimulates production of versicolorin pigments. Lower concentrations of acetone (0.1, 0.025, and 0.001 M) stimulate production of aflatoxin in the presence of glucose. Since aflatoxin production is not affected by acetone in RC medium lacking glucose (see table 2), it seems likely that acetone does not serve as a carbon source, but perhaps in some way enhances the uptake and/or utilization of glucose.

In these experiments, acetic acid inhibited secondary biosynthesis at the levels tested. Gupta et al. (6) studied the effect of carboxylic acids as carbon sources for aflatoxin production, using spores as inoculum in a liquid synthetic growth medium. They found that medium containing acetic acid supported no growth of *A. parasiticus*, and commented that the fungistatic effect of acetic acid is well known, although the mode of action is not clear.

At the 0.1 and 0.01 M levels, both with and without glucose, ethanol stimulated production of aflatoxin, but not versicolorins. Basappa et al. (2) reported that 2% ethanol increased aflatoxin production by nearly five times compared to controls in growth cultures. However, in another publication using a resting cell culture of *A. flavus*, Basappa et al. (3) reported that ethanol at 100 mol ml is not a useful substrate for aflatoxin production. Hsieh & Matales (9, 10) have reported that acetate can serve as a precursor for aflatoxins when used as a sole carbon source for resting cell cultures. Our findings that at the 0.01 to 0.001 M level of acetate in the absence of glucose, aflatoxin production was increased over the control corroborate this work.

In conclusion, low levels of acetone (0.1 and 0.01 M) in glucose-containing RC medium may be useful in enhancing secondary biosynthesis in resting cell cultures of *A. parasiticus*. Since this increase in secondary metabolism is not observed in RC medium that lacked glucose, and since increasing concentrations of glucose in RC medium stimulate secondary biosynthesis, it seems likely that the acetone effect is due to an improved uptake or utilization of glucose. Moreover, in all experiments containing acetone it is important to have appropriate acetone-containing controls. Experiments incorporating radioactivity into aflatoxin and versicolorin pigments from [^{14}-C]glucose, with and without acetone, are planned to test this hypothesis.

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