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DATA EVALUATION RECORD

CHEMICAL : Aluminum tris (O. ethyl phosphonate)
Trade Name : Fosetyl-Al

FORMULATION : ^{14}C-radio-labelled material

CITATION : UNSWORTH, J.B. 1976. Aluminum ethyl phosphate (LS 74.783). Metabolism study in Rats.

CONTRACTING LAB : May and Baker Ltd. Research Laboratories
Dagenham, Essex, England

SPONSOR : RHONE-POULENC AGROCHIMIE, Lyon , France

REPORT NO. : RES. 2741 of October 1976

EPA Reg. No. Acc. No. 247183-A

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9/13/82

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9-13-82

REVIEWED ON : July 13, 1982

TEST TYPE : Metabolism study

TEST MATERIAL : Fosetyl-Al (^{14}C-radiolabelled)
Specific activity 13.84 mCi/mM
Batch No. KWC 461

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MATERIAL AND METHODS

The work reported here has been performed as a follow-up of a previously reported study (UNSWORTH, J.B. 1976. Aluminum ethyl phosphite (LS 74.783): Excretion study in the rat. May and Baker report No. RES/2732). Therefore the ^{14}C-labelled test material, the animals used, doses administered are those already reported and the biological samples used; urine, feces, exhaled carbon dioxide, tissues, are those collected during the initial phase of the study.

Animals and maintenance: Sprague-Dawley rats from the May and Baker breeding colony were used. They weighed approximately 200g each at initiation of the study. The rats were housed for the duration of the experiment as single sex groups of 3 in metabolism cages (Jencons Metabowls MK III) which allowed total collection of urine, feces, exhaled carbon dioxide. The animals were allowed food and water ad libitum throughout the study.

Test Compound: Isotopically- labelled Fosetyl-Al was prepared in the Radiochemistry Laboratories of May and Baker from phosphorus trichloride and ^{14}C-ethanol ($CH_3\ ^{14}CH_2OH$) via sodium ethyl phosphite. The material was shown to be radiochemically homogeneous by thin Layer Chromatography and had a specific activity of 13.48 mCi/mM.

Test Compound Administration: The radiolabelled Fosetyl-Al (approximately 9mg) was dissolved in 5ml of water and the solution added to non-radio active Fosetyl-Al (approximately 2.5g). The material thus obtain, specific activity 0.048 mCi/mM was made up to 50 ml with water to give the dosing solution. The test compound was administered orally for 7 days in single doses of 250 mg/kg/day in approximately 1ml volume.

Collection of Biological Samples: Urine and feces were collected for 24 hours after each dose. The ethanol and carbon dioxide traps were similarly sampled whilst a second CO_2 trap was sampled at 3 and 7 days after initial dosing. Twenty-four hours after the final dose the animals were sacrificed by carbon dioxide asphyxiation. Samples (0.1 - 0.4g) of wet tissues (liver, kidney, spleen, lung, heart, brain, intestinal tract intotality, carcass and skin with fur) were taken.

Isolation of Metabolites; Metabolites were in general extracted from biological material with water. Aliquots of the aqueous solution detained were added to 2-methoxy ethanol and the mixture reduced to a small volume on a rotary evaporator at 45-50°C. The solution remaining was washed into a 25 ml volumetric flask with acetonitrite (approximately 5 ml) to remove the water still present. This facilitated the subsequent methylation and analysis by BLC of the metabolites. (Perkin-Elmer F17 GC Fitted with a specific phosphorus detector).

RESULTS

Metabolites in Urine: The percentages of the total dose of Fosetyl-Al administered (938.2mg in males/ 1008.5 mg in females) recovered in the urine either unchanged or as phosphite were respectively 26.28% and 73%.

Metabolites in feces: The percentages of the total administered dose of Fosetyl-Al were: 0.01-0.02% as unchanged and 3.78%(in males) , 0.67% (females) as phosphite.

Metabolites in body components:

Carcass and intestinal tract- No unchanged compound was recovered from the carcasses and intestinal tracts in either male or female rats. Only limited amounts were recovered as phosphite in the carcasses: 0.30%, 0.41% in the carcasses of males and females respectively and 0.09%, 0.47% in the intestinal tracts of males and females respectively.

Tissues- The percentages of tissue radioactivity recovered by aqueous extraction show that there was no evidence of the presence of unchanged ethyl phosphite in any of the tissues examined, similarly no phosphite could be detected in those tissues.

DISCUSSION

Although it might be expected that the phosphite moiety would be extensively oxidized to phosphate in vivo, the results obtained indicate that it was excreted without prior oxidation. The major excretory route of the orally administered phosphorus was in urine with only negligible amounts of feces.

Although the animals were dosed at high rate (250 mg/kg body weight/day) for 7 days, there was no evidence for any residues

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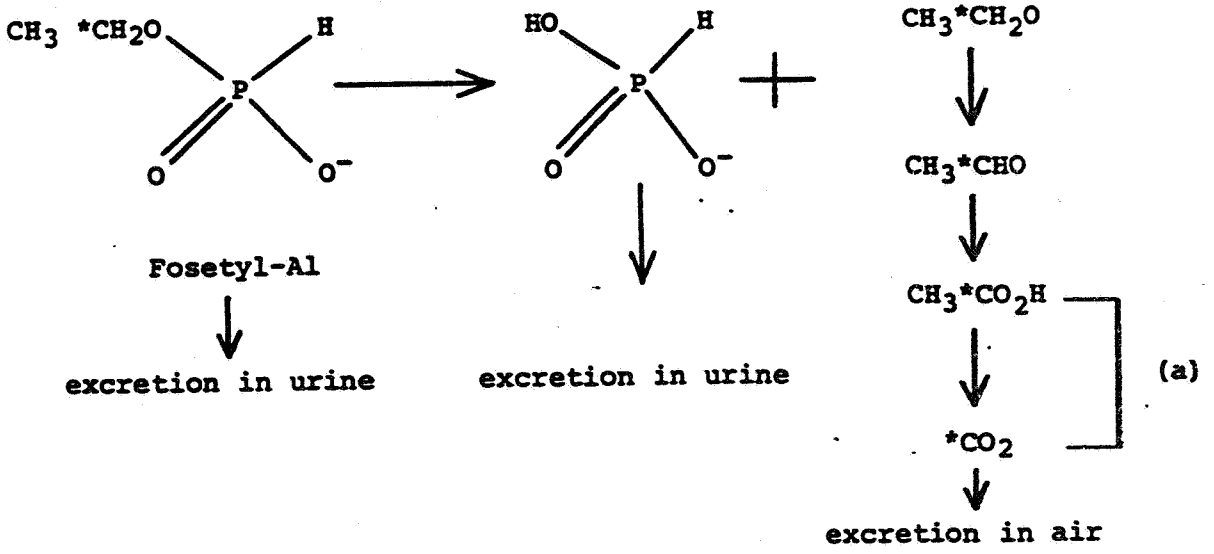
of Fosetyl-Al itself in any of the body components taken 24 hours after the last dosing. Residues of phosphite (phosphorus acid) were found in the carcasses and intestinal tracts of both sexes but only in very low levels (0.4 - 0.9% of the total administered dose). Residues of phosphorous acid were generally absent from the tissues examined (with the exception of samples of kidney and fat from the female group of rats (equivalent of 6ppm GP and 50ppm respectively).

From these results together with those for excretion (May and Baker report RES/2732: Excretion study in rats), it is possible to formulate a metabolic pathway for ^{14}C-Fosetyl-Al in the rat. After ingestion the compound is virtually completely absorbed and is extensively hydrolyzed to give ethanol-^{14}C and phosphite. The phosphite produced is then excreted directly in urine without further oxidation to phosphate. The major portion of the ethanol-^{14}C liberated in this way is rapidly oxidized via acetaldehyde and acetate to carbon dioxide-^{14}C which is excreted in the expired air.

However, a smaller amount of the radio-labelled material becomes incorporated into naturally occurring molecules via acetate-^{14}C and carbon dioxide-^{14}C, both of which are biosynthetic precursors, thus leading to the relatively high residue levels of radioactivity found in the tissues as shown in report RES/2732 (Excretion study in the rat).



(a) also incorporated in naturally occurring molecules.

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CONCLUSION

Aluminum tris(O-^{14}C-ethyl phosphonate), Fosetyl-^{14}C-AL, is rapidly hydrolized in the rat to give ethanol and phosphite. The ethanol is oxidized to mainly carbon dioxide which is excreted in the expired air. However a small proportion of the radioactive label is incorporated via acetate and carbon dioxide into naturally occurring molecules. The phosphite produced is excreted in the urine, without oxidation to phosphate, and there is no evidence for the accumulation of any phosphite residues in tissues.

Classification: not applicable

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