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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 phosphite
(LS 74.783) ; Excretion study in Rat.

CONTRACTING LAB : MAY and BAKER, Dept. of Metabolism and Residues.
Dagenham Essex England

SPONSOR : RHONE-POULENC AGROCHIMIE, LYON, FRANCE

REPORT NO. : May and Baker RES/2732 of September 1976
EPA Reg. No. Acc. No. 247183-B

REVIEWED BY : A. F. PELFRENE, MD, PhD, ATS
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RHONE-POULENC INC. *pelprene*
09/17/82 *C. Gullorio*
9-13-82

REVIEWED ON : July 12, 1982

TEST TYPE : Metabolism study

TEST MATERIAL Fosetyl-Al (radiolabelled: ^{14}C)
Specific activity 13.48 mCi/mM
Batch No. KNC 461

1075

MATERIAL AND METHOD

ANIMALS AND MAINTENANCE

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

TEST COMPOUND

Isotopically-labelled Fosetyl-Al (LS 74.783) was prepared in the Radio-chemistry Laboratories of May and Baker from phosphorus trichloride and ^{14}C -ethanol, $\text{CH}_3^{16}\text{CH}_2\text{OH}$, 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 radio-labelled 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 obtained, 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 seven days in single doses of 250 mg/kg/day in approximately 1ml volume.

QUANTITATIVE ASSAY PROCEDURES

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, brain, spleen, lung, heart, intestinal tract intotality, carcass and skin and fur separately) were taken for evaluation of their radioactivity content by liquid scintillation counting in a Tracerlab Corumatic Zoo Spectrometer using n-hexadecane- ^{14}C as an internal reference standard. 2

RESULTS

Radioactivity in urine : The recovery of administered radioactivity shows that approximately 26.27% were excreted in urine. The results obtained on a daily basis indicate that excretion of radioactivity of single doses of radiolabelled test material takes place within 24 hours of administration.

Radioactivity in feces : Only minor amounts (2 - 3%) of the administered radioactivity appeared in the feces.

Radioactivity in exhaled air : Results show that the major portion (60%) of the administered radioactivity was excreted in exhaled air as ^{14}C -labelled carbon dioxide.

Radioactivity in tissue : Results obtained show that approximately 3 to 4.5% of the total administered radioactivity is recovered from the carcasses, 1.7 to 2.7% from the skin and fur and approximately 1.2% from the entire intestinal tract. Less than 1% of the total radioactivity is recovered from various organs: approximately 0.7% from the liver, 0.2% from the kidney, 0.03 - 0.04% from the brain and heart.

DISCUSSIONS

The excretion of large amounts of radioactive carbon dioxide indicates removal of the labelled ethyl group from ^{14}C -Fosetyl-Al with its subsequent metabolism to carbon dioxide presumable via acetaldehyde and acetate. The formulation of isotopically -labelled carbon dioxide and acetate, both precursors of a wide range of naturally-occurring molecules suggest that tissue residual radioactivity is likely to be due to normal tissue components into which the isotopic label had been incorporated.

CONCLUSION

Aluminum tris (0-ethyl- ^{14}C phosphonate) is rapidly metabolized in the rat to give mainly (60%) carbon dioxide which is recovered from exhaled air. The second major route of excretion is via urine in which 26.27% of the administered radioactivity is found. The formation of isotopically-labelled carbon dioxide together with acetate as a likely intermediate probably results in the incorporation of radioactivity in tissue by normal biosynthetic pathways.

CLASSIFICATION : Not Applicable

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first dose for the duration of the study.

Radioactivity Counting: The amount of radioactivity in various samples was determined by liquid scintillation counting in a Trace lab Corumatic 200 Spectrometer using an aqueous solution of sodium dihydrogen phosphate- ^{32}P as an interval reference standard.

RESULTS: All results were calculated with respect to radioactivity at the start of the experiment to allow for natural decay of ^{32}P (half life of ^{32}P =14 days).

Radioactivity in Urine: The results expressed as percentage of total radioactivity administered show that for both males and females the major portion of the radioactivity is recovered from the urine: 65% in females and 59% in males.

Radioactivity in Faeces : The results (expressed as percentage of the total radioactivity administered) show that approximately 32 % of the radioactivity is recovered from the faeces of male rats and approximately 30 % is recovered from the faeces of female rats.

Radioactivity in tissues: Negligible amounts of the total radioactivity administered have been recovered in the tissues: liver 0.05% - kidney 0.01% - lung 0.01%. No radioactivity has been found in the brain and heart.

Limited amounts have been recovered from the carcasses. 1% in males and 1.35% in females. 0.14% and 0.2% respectively in the skin and fur and 0.16% and 0.33% respectively in the intestinal tract of males and females.

However the results showed that the highest levels of radioactivity were found in the spleen (0.06 and 0.04 microcuries in males and females respectively, corresponding to an average of 10.9 to 12.2 ppm of phosphorous acid equivalent. Lower levels were found in other tissues (1 to 10 ppm of phosphorous equivalent.

It must be noted that although the amounts of radioactivity present in the tissues at the time of sacrifice of the animals, can be expressed in terms of ppm phosphorous acid equivalent, these residues may also arise from radiolabelled phosphorous incorporated into tissue components, possibly via phosphate by normal synthetic pathways.

Radioactivity in blood: The results after the initial dose for blood radioactivity levels indicate that the maximum level was reached 1 to 2.5 hours after the initial ingestion of sodium phosphite- ^{32}P . The results give an estimated half life of 1 to 3 hours with an initial rapid phase of elimination.

The levels of blood radioactivity found 24 hours after each dose indicate that the elimination of radioactivity gave rise to a gradual accumulation of radioactivity in the blood as induced by the levels measured 24 hours after each dose. It must be noted however that the

radioactivity in blood will arise not only from the parent compound but also from any radiolabelled phosphorous incorporated into blood components possibly via phosphate by normal synthetic pathways.

CONCLUSION: When orally administered as sodium phosphite- ^{32}P , to male and female rats, phosphorous acid is mainly excreted in urine (59 - 65%) with a smaller amount found in feces (30-32%). Minor amounts (1.2%) of the administered radioactivity are still present in the body 72 hours after cessation of dosing with the highest amount found in the spleen. The level of radioactivity in blood reaches a maximum 1 to 2.5 hours after the initial dose of sodium phosphite- ^{32}P . The disappearance of radioactivity from the blood seems to occur in two stages, first a fairly rapid one (half-life 1-3 hours) and a second much slower one.

CLASSIFICATION : not applicable.

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