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Fate and Disposition of Sucrose-*U*-^{14}C Acetate Isobutyrate in Humans, Rats, and Dogs

Ralph C. Reynolds,* Bernard D. Astill, Clarence J. Terhaar, and David W. Fassett

To determine the fate of sucrose acetate isobutyrate (SAIB) in mammals, SAIB-^{14}C, prepared from sucrose-*U*-^{14}C, was fed to humans, rats, and dogs and the elimination of radioactivity in breath, urine, and feces was studied. After a single oral dose of SAIB-^{14}C (1–1.2 mg/kg), humans eliminated within 30 days radioactivity in breath (41–66% of the dose), urine (15–21%), and feces (10%). Similarly, for two dogs fed 3 and 4.8 mg/kg, eliminations were 28 and 27% as $^{14}CO_2$, 7 and 5% in the urine, and 53 and 46% in the feces within 7 days, and for two rats fed 5.8 and 11.2 mg/kg, eliminations were 59 and 52% as $^{14}CO_2$, 11 and 13% in the urine, and 23 and 27% in the feces within 3 days. Urinary metabolites, detected solely by radiochromatography on paper, were apparently mostly partially esterified sucrose molecules with only traces of sucrose. They were similar in men and rats but possibly different in dogs. The results suggest that humans and rats handle SAIB similarly, the dog apparently differing both in the disposition of the dose and in the urinary excretory products.

Sucrose acetate isobutyrate (SAIB) is produced by the controlled esterification of sucrose with acetic and isobutyric anhydrides (Touey and Davis, 1960). The commercial material, more than 95% esterified with about 2 mol of acetate and 6 mol of isobutyrate per mol of sucrose, is an extremely viscous, colorless to light yellow liquid, insoluble in water, moderately soluble in aqueous ethanol, *n*-hexane, olive oil, and corn oil, and very soluble in ethanol and benzene. It has a very compact structure for its molecular weight (830–860). SAIB has potential use in soft drinks as a suspending agent for essential oils.

Octaesters of sucrose with short-chain fatty acids are well known and have some limited industrial uses, but little is known about their *in vivo* metabolism. Sucrose octaacetate, used to impart a bitter taste to animal feeds and rubbing alcohol to deter human consumption, had no adverse effect when fed to cows, ducks, chicks, and pigs and it could not be tasted after prolonged feeding in the flesh of fowl or animals or in cow's milk (Křiženecký, 1941a,b). Domingues *et al.* (1960) showed β-D-glucose pentaacetate to be completely absorbed and extensively utilized by the rat, undergoing some hydrolysis in the gut.

Feeding studies in rats (Krasavage *et al.*, 1973) showed SAIB to be without effect in 95-day feedings at up to 5% in the diet. Dogs had increased liver weights after feeding 0.6 and 2.0% in the diet (but not at 0.2%) and increased serum alkaline phosphatase activities and indocyanine green clearance times at the highest dose level. These effects were readily reversed when SAIB was withdrawn and were not seen in rats. We, therefore, investigated the fate

Health and Safety Laboratory, Eastman Kodak Company, Rochester, New York 14650.

Table I. Elimination of Radioactivity by Humans, Rats, and Dogs Fed a Single Dose of SAIB-^{14}C

Species	No. of subjects	Dose		Elimination, % of dose			Recovery, % of dose	
		Form[a]	mg/kg	CO_2	Urine	Feces	Carcass	Total
Human	6	A	1.0–1.2	41–64	15–21	~10		71–90
	1	A	0.2	66	18	10		95
Rat	2	O	89, 98	25, 27	13, 13	50, 55		90–93
	2	O	26, 28	47, 55	18, 19	18, 25		91–92
	1	A	11.2	52	13	27	6.0	99
	1	A	5.8	59	11	23	6.6	99
Dog	1	A	4.8	27	7	46		80
	1	A	3.0	28	6	53		86

[a] A = aqueous emulsion; O = solution in corn oil.

of SAIB in rats, dogs, and humans to assess the relevance of these findings in establishing the safety of SAIB in man. We also studied the fate of sucrose-^{14}C in humans and rats as a model for the fate of sucrose derived from SAIB in the gut.

MATERIALS AND METHODS

Labeled Compounds. Sucrose-*U*-^{14}C acetate isobutyrate (SAIB-^{14}C) was prepared by the method of Touey and Davis (1960). In a typical preparation 2.010 g of sucrose, 0.129 g of sucrose-*U*-^{14}C (New England Nuclear Corp., sp act. 4.91 mCi/mmol), 0.906 g of acetic anhydride, and 10.010 g of isobutyric anhydride gave 4.782 g of pale yellow SAIB-^{14}C having a saponification equivalent of 104.16 ± 0.19; the specification for food grade SAIB is 104–107. The infrared curve was virtually identical with that of a commercial sample and lacked any OH band. The specific activity was 0.359 μCi/mg. Sucrose-*U*-^{14}C (New England Nuclear Corp., sp act. 5.07 mCi/mmol), 16.9 mg, 0.25 mCi, was added to 612.6 mg of unlabeled sucrose and crystallized under ethanol. The specific activity was 0.389 μCi/mg.

Dosage. Single oral doses of SAIB-^{14}C were given at levels shown in Table I. In some rat experiments, SAIB-^{14}C was dissolved in corn oil and the solution was fed by intragastric intubation. In other experiments (rats, dogs, humans), SAIB-^{14}C was incorporated into a simulated noncarbonated soft drink. In a typical preparation, a mixture of 297 mg of citrus oil and 273.2 mg of SAIB-^{14}C was warmed and mixed with 3.183 g of mucilage (18.48 g of gum acacia in 84.45 g of water). The mixture was stirred for 1 hr and sonicated (Biosonic III cell disrupter, Bronwill Scientific, Inc.), to a fine, stable emulsion which was added to water containing sucrose (12%) and citric acid (0.2%). This drink was imbibed by humans (200 ml, 85–570 ppm of SAIB) or fed to rats (2.6–5 ml, 700 ppm) or dogs (100 ml, 400–540 ppm) by stomach tube.

Sucrose-^{14}C was given in aqueous solution to rats and humans at a level of 400 mg/kg. Sucrose-^{14}C and unlabeled sucrose were dissolved in water and the solutions were imbibed by two humans (25 or 28 g in 200 ml) or intubated into two rats (112 mg in 4.0 ml) by stomach tube.

Maintenance of Experimental Animals. *Humans.* After imbibing the dose, humans remained in the laboratory area for 16 hr performing sedentary tasks. After resuming normal routines they returned to the laboratory for breath collections. Breath and urine collections were generally made for 25–30 days and feces were collected for 5 days.

Rats were housed in glass metabolism chambers fitted for collection of CO_2, urine, and feces. Rats fed SAIB-^{14}C in corn oil were maintained 4 days; rats fed an aqueous emulsion of SAIB-^{14}C were kept 3 days.

Dogs were kept in stainless steel mesh metabolism cages fitted for collection of urine and feces. During breath collection periods the cages were placed inside an airtight stainless steel isolation chamber (640 l.) fitted for collection of CO_2.

Collections. *Humans.* Breath samples were collected at 1–1.5 hr intervals from 0.5 to 16 hr after dosing and at irregular intervals thereafter. Subjects breathed freely into 96 l. Saran bags through a double Douglas valve for 5.0 min. The entire sample was passed through 60 ml of a 1:2 v/v mixture of 2-aminoethanol and 2-methoxyethanol to absorb CO_2. Urine and feces were voided and collected *ad libitum* and frozen and stored at −10°.

Rats and Dogs. Radioactivity in excreta of rats fed SAIB-^{14}C in corn oil was determined by Geiger-counter assay. Air drawn through the chamber was passed through two gas washing bottles containing aqueous sodium hydroxide. These were changed every 24 hr. In the other rat and dog studies a 1:2 mixture of 2-aminoethanol and 2-methoxyethanol was used to absorb $^{14}CO_2$ for liquid scintillation spectrometer assay. The absorbers were changed every 1.5 hr for the first 15 hr and at 8–16-hr intervals thereafter. Urine and feces were collected when the CO_2 absorbers were changed and frozen until assayed.

Analysis of Excreta. *Geiger-Counting Assays.* Carbon dioxide was assayed by precipitating as $BaCO_3$. Urine and aqueous extracts were assayed by the lens paper technique. Feces were dried in an oven at 50–60°, pulverized, and extracted with benzene for 16 hr (Soxhlet). The insoluble material was homogenized (VirTis homogenizer) with absolute ethanol, the extract separated by centrifuging, and the homogenization and extraction were repeated. The insoluble material was similarly extracted with water. Benzene and ethanol extracts were plated directly, aqueous extracts by the lens paper technique, and insoluble material from suspension in an isopropyl alcohol–water mixture (1:3). Self-absorption corrections were obtained by adding sucrose-^{14}C to replicate plates or from curves prepared from control extracts containing known amounts of radioactivity.

Liquid Scintillation Spectrometer Assays. Carbon dioxide absorbers were made up to a convenient volume with 2-methoxyethanol and portions were added to 10 ml of scintillator composed of 8 g of 2,5-diphenyloxazole (PPO) and 0.2 g of 2,2′-*p*-phenylenebis(5-phenyloxazole) (POPOP) in 1000 ml of toluene. Urine samples (1 ml) were added to 15 ml of a scintillator composed of 120 g of naphthalene, 4 g of PPO, and 0.05 g of POPOP in 1000 ml of *p*-dioxane. Feces were homogenized (Waring Blendor or VirTis homogenizer) in 70% aqueous ethanol. The resultant slurry was centrifuged. The residues were resuspended in 70% aqueous ethanol and centrifuged. The combined ethanol extracts were made up to 100–1000 ml and 1-ml samples were added to 15 ml of the naphthalene–dioxane

scintillator. The dried residue was powdered in a ball mill and the powder was assayed by the combustion technique of Kalberer and Rutschmann (1961) using the flask of Kelly *et al.* (1961) and the Thomas-Ogg ignition apparatus. Rat gastrointestinal washings were similarly treated.

Rat Tissue and Carcass Assays. Rats dosed with sucrose-^{14}C in an aqueous emulsion were killed with carbon dioxide. Selected organs were removed, steeped in acetone (16 hr), and homogenized (VirTis homogenizer). The homogenate was centrifuged in 50-ml polypropylene tubes at 5000 rpm. The residue was resuspended in a small amount of acetone, the mixture was centrifuged, and the acetone combined with the first extract. The combined extracts were made up to 25 or 50 ml, and 1-ml samples were added to 15 ml of the napthalene–dioxane scintillator solution. The residue was dried at 45–55° and assayed by the combustion technique. Carcasses were ground in a meat grinder and homogenized in an explosion proof Waring Blendor with acetone (500 ml). The slurry was refluxed for several hours and the acetone decanted. The residue was homogenized with water and the slurry spread out to dry at 45–55° for 4–5 days. The dried residue was powdered in a ball mill. The acetone extract was assayed by addition of a sample to the naphthalene–dioxane scintillator. The powdered residue was assayed by the combustion technique.

Counting of Radioactivity. Planchets were counted with a Nuclear-Chicago Model D-47 gas-flow thin end window Geiger counter. Counts were standardized as described above. Liquid scintillation samples were counted with a Tri-Carb Model 3375 scintillation spectrometer (Packard Instrument Co.) with external standardization using curves prepared by the addition of standard toluene-^{14}C to samples quenched with Methyl Orange.

Paper Chromatography. Direct chromatography on paper was not successful due to the large quantities of interfering materials present. The radioactivity was therefore separated by extraction. Urine (5 ml) was neutralized with dilute NaOH (aqueous) and stripped *in vacuo* at 40°. The residue was refluxed with 25 ml of absolute ethanol for several hours and the extract was filtered through Whatman No. 1 paper. The residue and filter were washed several times with ethanol. The combined filtrate and washings were dried under a stream of nitrogen and the residue was dissolved in 1 ml of water. A sample (50–100 μl) was streaked on Whatman No. 1 paper (1.5 in. × 8 in.) and developed by ascending chromatography. Solvents were: 1-butanol–acetic acid–water (4:1:5, organic phase) (BAW), 1-butanol–ethanol–water (4:1:5, organic phase) (BEW), ethyl acetate–pyridine–water (2:1:2, organic phase) (EPW), and 1-propanol–ethyl acetate–water (7:1:2) (PEW). Developed strips were scanned for radioactivity with an Actigraph II Geiger-counting system (Nuclear-Chicago Corporation). Sugars were detected by aniline–diphenylamine spray (aerosol can, Sigma Chemical Co., St. Louis, Mo.) with which SAIB does not react.

RESULTS

Elimination of Radioactivity by Subjects Fed SAIB-^{14}C. The results of experiments in humans, rats, and dogs are shown in Table I. Dogs eliminated a much higher proportion of the dose in the feces than did humans or rats at dose levels below 28 mg/kg. Humans probably eliminated about one-half as much in the feces as rats but the doses were lower in humans. More than 50% of the absorbed dose was eliminated as $^{14}CO_2$ during each total collection period by all species, although one human subject eliminated slightly less than 50% over 30 days in each of two trials. Rats and humans eliminated 14–28% of the absorbed dose in the urine; dogs eliminated slightly less (11.6, 13.4%). Rat and dog data suggest that the proportion of the absorbed dose metabolized to $^{14}CO_2$ increases and the proportion eliminated in the urine slightly decreases as the dose decreases over the range studied. Elimination of radioactivity in the urine was very rapid in all species, although the dog seemed to be slightly slower (Figures 1 and 2). Elimination as $^{14}CO_2$ started rapidly in all species; the peak elimination was, however, delayed to 7–8 hr in rats and 8–16 hr in humans and dogs (Figures 1 and 2). The rates then fell off sharply. At times later than 2 days after dosing, elimination as $^{14}CO_2$ was 5–10 times the elimination rate in the urine in all species.

To test the effect on elimination of SAIB of various changes in the dosing routine, three human subjects were each given two or three single doses of SAIB-^{14}C at widely spaced intervals. The first dose was given at a level of *ca.* 1 mg/kg to each subject, none of whom had been previously exposed to SAIB. Two of these subjects were given a second dose at the same level 7 or 27 weeks after the first dose and following daily ingestion of a single dose of 100 mg of unlabeled SAIB (*ca.* 1 mg/kg) for 7 days. The shapes of the curves before and after dosing were quite similar, and it appears that there was no difference attributable to daily ingestion of SAIB preceding the dose. A third subject was given a single dose of SAIB-^{14}C at a level of 0.18 mg/kg 25 weeks after receiving a 1.14-mg/kg dose. There were no significant differences in the elimination patterns or in the proportions of the dose eliminated by each route (Table I). To determine the effect of changing the stomach emptying time on the shape of the elimination curve, one subject was given a third dose at a level of 1 mg/kg 10 weeks after the second dose and immediately after he ingested a high fat meal. There was no apparent difference between this elimination pattern and the previous one.

Tissue Levels of Radioactivity in Rats Fed SAIB-^{14}C. Two rats intubated with SAIB-^{14}C in an aqueous emulsion at levels of 5.8 and 11.2 mg/kg retained 6.0 and 6.6% of the dose in the carcass 3 days after dosing. Levels of radioactivity in individual tissues showed that no organ, including fat, had incorporated a significantly greater amount of radioactivity than the average (Figure 3). The levels obtained are roughly equivalent to 1 ppm of SAIB in the tissues at the higher dose level.

Radiochromatography of Fecal and Urine Extracts. Chromatography on paper of aqueous ethanol extracts of feces from all three species showed only radioactivity of high R_f, running near the front in all solvent systems and probably composed of SAIB-^{14}C or highly acylated sucrose molecules. Some radioactivity, however, was not extracted by the procedure.

Chromatography on paper of ethanol extracts of urine in solvents BEW, BAW, and EPW gave separations of radioactivity on the strips. Human and rat urines generally gave one or two large more or less well-defined peaks. Dog urines gave one large peak at R_f <0.2 and a large amount of radioactivity spread out over higher R_f values. Solvent PEW, however, spread out all the peaks giving a distribution of radioactivity over most of each strip in all three species (Figure 4). Although rat and human urines showed no radioactive material near the front, dog chromatograms showed material having the chromatographic properties of SAIB-^{14}C (Figure 4C).

The aniline–diphenylamine gave positive reactions corresponding to radioactive peaks of low R_f (<0.5) on chromatograms from rats dosed with 26–98 mg/kg of SAIB-^{14}C (solvent BEW). Extracts of urines from all species dosed with lower levels of SAIB-^{14}C contained too much interfering material to permit detection of sugars possibly derived from SAIB-^{14}C.

Fate of Sucrose-^{14}C in Rats and Humans. Rats intubated with sucrose-^{14}C in aqueous solution at a level of 400 mg/kg rapidly absorbed and metabolized the sucrose-^{14}C to $^{14}CO_2$ (Table II). Peak elimination occurred within 2 hr of dosing. A small amount of radioactivity was eliminated in urine and feces. At sacrifice, 3 days after dosing, the

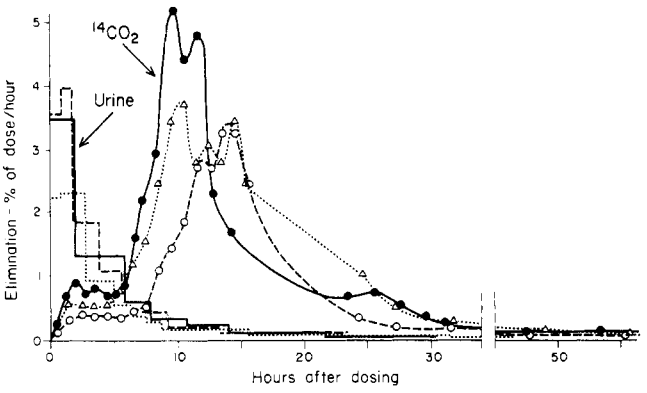

Figure 1. Elimination of radioactivity in breath and urine of three humans after ingestion of 83–115 mg of SAIB-^{14}C in an aqueous emulsion.

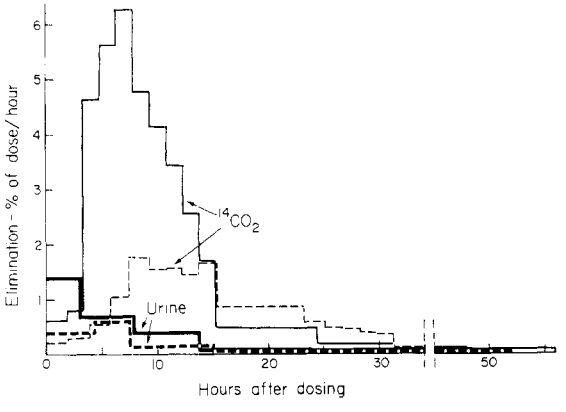

Figure 2. Elimination of radioactivity in breath and urine of a rat and a dog intubated by stomach tube with SAIB-^{14}C in an aqueous emulsion: (—) rat (1.9 mg/kg); (- - -) dog (4.8 mg/kg).

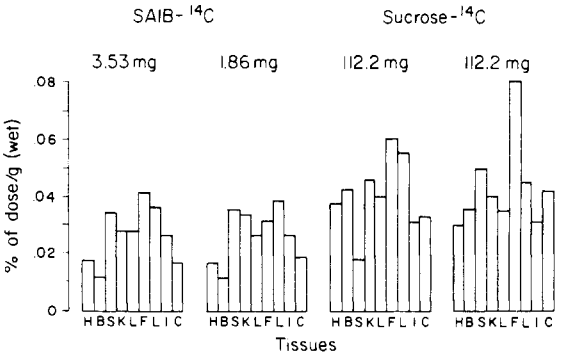

Figure 3. Levels of radioactivity in tissues of rats 3 days after a single dose of SAIB-^{14}C or sucrose-^{14}C. Tissues are heart, brain, spleen, kidneys, liver, fat, lung, gastrointestinal tract, and carcass after removal of organs.

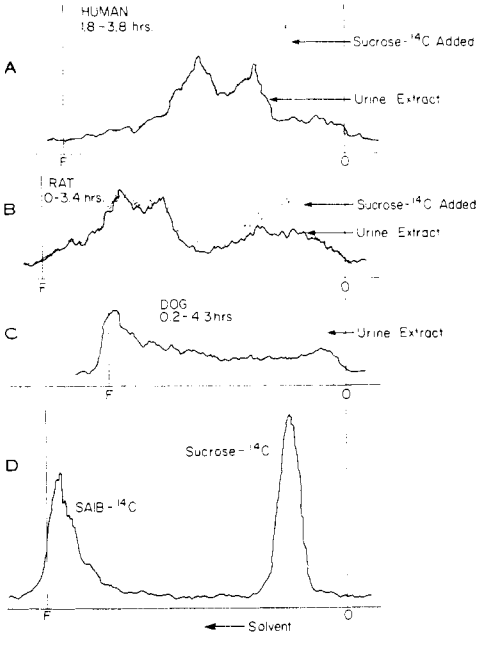

Figure 4. Distributions of radioactivity on paper chromatograms of ethanol extracts of urines from a human, a rat, and a dog fed an aqueous emulsion of SAIB-^{14}C. Doses were: (A) human, 1.2 mg/kg, (B) rat, 11.2 mg/kg, and (C) dog, 4.8 mg/kg. Dotted curves in A and B show distributions of radioactivity on chromatograms of urines to which sucrose-^{14}C was added before spotting; solvent, PEW.

carcasses retained 9.6 and 12.9% of the dose, distributed among selected tissues as shown in Figure 3. Humans fed sucrose-^{14}C at a level of 400 mg/kg eliminated $^{14}CO_2$ at a much slower rate than did rats at the same dose level (Table II), but the maximum rate occurred within 3 hr.

DISCUSSION

These results show that humans, rats, and dogs handle ingested SAIB-^{14}C by partially absorbing it from the gut and partially eliminating it in the feces, at dose levels ranging from 0.2–1.2 mg/kg (humans) to 6–100 mg/kg (rats). The absorbed dose in all three species is largely catabolized to $^{14}CO_2$ or incorporated into physiological body constituents, with only small amounts of radioactivity eliminated in the urine. The three species differ, however, both in the proportion of the dose eliminated in the feces and in the way the absorbed material is handled.

Rats absorb about three-fourths of low (6–11 mg/kg) doses, whereas dogs eliminated about half of comparable doses (3–5 mg/kg) in the feces. Humans at lower dose levels (1–1.2 mg/kg) absorb upwards of 88% of the dose and are thus closer to rats than dogs in this respect. The proportion of the absorbed dose eliminated in breath and urine is approximately the same in rats and humans; dogs eliminate slightly less in the urine. The proportion of the absorbed dose converted to $^{14}CO_2$ increases and elimination in the urine decreases slightly with decreasing dose. Some material, however, will be eliminated in the urine at all dose levels.

Paper chromatography shows that dogs initially eliminate SAIB-derived molecular species mostly of high R_f expected for SAIB or highly acylated sucrose molecules. This contrasts with rats and humans in which urinary elimination products appear to be more polar. The urine metabolites appear to be mostly sugar esters, with very little free sucrose in any species.

The low level of residual radioactivity in rats after SAIB-^{14}C intake, indicating virtually complete clearance, may arise from incorporation of carbon-14 into the physiological constituents. Rats fed SAIB-^{14}C still retained about 6% of the radioactive dose in the whole body at 3 days. These levels represent about 10% of the absorbed dose which was not eliminated in the urine. Rats fed sucrose-^{14}C incorporated about 11% of the dose, which indicated that the residual radioactivity in SAIB-^{14}C fed rats is probably incorporation of sucrose catabolites.

In vivo experiments in rats (R. C. Reynolds, unpublished work) showed that SAIB-^{14}C is hydrolyzed in the gut, apparently to sucrose-^{14}C and partially esterified sucrose-^{14}C. Radiochromatography on paper showed the presence in the gut of materials having chromatographic properties expected of molecules more polar than SAIB,

Table II. Elimination of Radioactivity by Humans and Rats Fed a Single Dose of Sucrose-U-^{14}C

Species	Dose, mg/kg	Time, days	Elimination, % of dose			Recovery, % of dose	
			CO_2	Urine	Feces	Carcass	Total
Human	391	31	50.1	2.7	<0.3		53.1
	400	2	59.0	1.7			60.7
Rat	405	3	82.6	3.4	2.2	9.6	97.8
	371	3	77.1	3.3	2.5	12.9	95.8

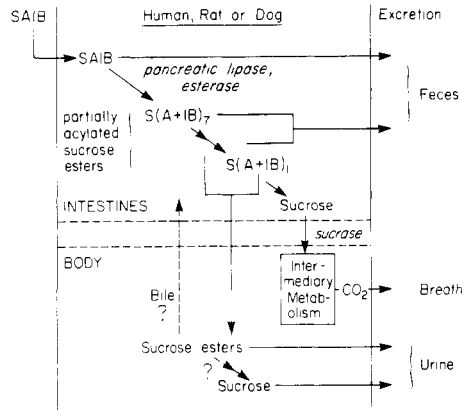

Figure 5. Pathways involved in the elimination of SAIB from humans, rats, and dogs.

but these molecules are found in feces only in very small amounts. In this study we found that the peak of SAIB-^{14}C catabolism to $^{14}CO_2$ occurs much later than the peak of sucrose-^{14}C catabolism to $^{14}CO_2$. These findings suggest that some hydrolysis is required before the ester can be absorbed. These and the other results presented in this report suggest that mammals handle SAIB-^{14}C by the pathways shown in Figure 5.

In handling SAIB, dogs clearly differ from rats and humans in two ways, *viz*, dogs absorb less and they excrete more highly acylated molecules in the urine. This suggests that dogs break down SAIB less readily in the gastrointestinal tract but absorb highly acylated molecules more readily than rats or humans. These highly acylated molecules may also return to the gastrointestinal tract *via* the enterohepatic circulation as well as appear in the urine. Since rats and humans handle SAIB more alike than do dogs and humans or dogs and rats, the rat is the preferred metabolic model in assessing SAIB safety in humans.

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