DATA EVALUATION RECORD - SUPPLEMENT

XDE-570 (FLORASULAM)

Study Type: Non-guideline; Supplementary Metabolism Study in Rats

Work Assignment No. 4-1-128 T (MRID 46808303)

Prepared for
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DATA EVALUATION RECORD

STUDY TYPE: Non-guideline; supplementary metabolism study in rats

PC CODE: 129108 **DP BARCODE:** D331116
TXR #: 0054348

TEST MATERIAL (RADIOCHEMICAL PURITY): XDE-570 (Florasulam; 98.5%)

SYNONYMS: *N*-(2,6-Difluorophenyl)-8-fluoro-5-methoxy(1,2,4)triazolo(1,5-*c*)pyrimidine-2-sulfonamide; XR-570; XRD-570; DE-570

CITATION: Hansen, S.C. (1997) XDE-570: distribution and metabolism of ^{14}C-labeled XDE-570 in selected tissues at plasma Cmax and $C_{½}$max and in the bile following oral administration in Fischer 344 rats. The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI. Laboratory Project ID: HET DR 0312-6565-029, September 29, 1997. MRID 46808303. Unpublished.

SPONSOR: Dow AgroSciences Canada, Inc., 2100- 450 1 St. SW, Calgary, AB, Canada

EXECUTIVE SUMMARY: In a metabolism study (MRID 46808303), [^{14}C]-XDE-570 (Florasulam; 98.5% radiochemical purity; Lot No. B734-21) in a suspension of 0.5% Methocel™ cellulose ethers was administered to 3 Fischer 344 rats/sex/time point as a single gavage dose at 10 or 500 mg/kg bw. Animals were killed at Tmax or $T_{½}$max (0.5-4 h postdose). Tissue samples, carcass, and final cage wash were analyzed for radioactivity. Additionally, 3 males were fitted with indwelling bile-duct cannulas prior to dosing. Bile was periodically sampled, and urine and feces were collected for a 24 hour interval. The animals were killed 24 hours postdose, and blood, skin, carcass, and gastrointestinal tract/ingesta samples were collected. Data were reported for 2 animals in this group. [^{14}C]-XDE-570 was uniformly labeled in the aniline ring for each of these test groups. The stated purpose of this study was to provide additional information on the absorption, distribution, metabolism, and excretion of the test compound to support registration in Japan.

Total recovery was 98.7% in the bile duct cannulated group and 77.8-94.8% in the other test groups. The highest concentration of radioactivity was found in the kidney (570 µg-eq/g). On a percentage of the dose basis, excluding the carcass and GIT/ingesta, the blood, kidneys, liver, and skin had relatively high amounts of radioactivity; however, the radioactivity isolated in the skin may have been due to urinary contamination. Excluding the skin, the amount (% dose) isolated was generally highest in the blood, but all amounts were low (0.5-5.0% dose), regardless of dose,

time point, or sex. Parent accounted for >91% of the radioactivity in the kidney, liver, and blood for each dose, time point, and sex. At 24 hours postdose, biliary excretion accounted for only 1.0% of the administered dose, while urinary excretion (81.0% dose) accounted for the majority of the dose. The remaining administered radioactivity in the bile duct cannulated test group was isolated in the feces (3.9% dose), tissues, GIT/ingesta, and carcass (8.3% dose), and final cage wash (4.6% dose). There were no sex-related differences in the metabolism or pharmacokinetics of the test compound.

This study is classified as **acceptable/non-guideline**. An acceptable metabolism study (MRID 46808301) was concurrently submitted.

COMPLIANCE: Signed and dated GLP Compliance, Quality Assurance, and Data Confidentiality statements were provided.

NOTE: This DER summarizes EPA conclusions regarding effects observed in the non-guideline metabolism study in rats. A detailed DER completed by the Canadian Pest Management Regulatory Agency (PMRA) is attached.

COMMENTS: EPA concurs with the PMRA toxicology evaluation, no conclusions have been changed.

46808303.PMRA.der
.pdf

Reviewer: Tom Morris , Date February 29, 2000

OECD 5.1.1 (single low dose - rat oral); 5.1.2 (single high dose - rat oral).

STUDY TYPE: Metabolism - [rats]; OPPTS 870.7485; OECD 417.

TEST MATERIAL (PURITY): XDE-570 (Purity - 99.2%)

SYNONYMS: XR-570, XRD-570, DE-570, florasulam

CITATION: Hansen, S. C. September 29, 1997. **XDE-570: Distribution and Metabolism of ^{14}C-Labeled XDE-570 in Selected Tissues at Plasma Cmax and C½max and in Bile Following Oral Administration in Fischer 344 Rats**. Performing Laboratory: The Toxicology Research Laboratory, Health and Environmental Research Laboratories, The Dow Chemical Company, Midland, Michigan, 48674. Laboratory Project ID: HET DR-0312-6565-029. Unpublished

SPONSOR: Dow AgroSciences Canada Inc. (DAS).

EXECUTIVE SUMMARY: The absorption, distribution, excretion and metabolism of XDE-570 was investigated in male and female Fischer 344 rats following gavage administration of ^{14}C-XDE-570 uniformly labelled in the aniline ring. The core study included five test groups. In the first four test groups, 3 animals/sex/group received a single dose of 10 or 500 mg/kg bw of ^{14}C-XDE-570 to determine tissue distribution of total radioactivity at plasma C_{max} and $C_{½\ max}$ (as determined by Dryzga, et al, 1996; see DACO 4.5.9.1, Laboratory Project ID: HET DR 0312-6565-014). A fifth group consisting of 3 males, fitted with indwelling bile cannulas, received a single dose of 10 mg/kg bw of ^{14}C-XDE-570, with bile collected at various time intervals and urine collected at 24 hours post-dosing. Animals in groups 1-4 were sacrificed at the appropriate time intervals (for sex/dose/time interval). Animals in group 5 were sacrificed at 24 hours post-dosing.

Following single oral low- or high-dose administration, ^{14}C-XDE-570 was extensively and rapidly absorbed in both sexes. By 24 hours, bile absorption accounted for 1% of the administered dose with the 0-2 hour post-dosing interval containing the highest percentage of the administered dose suggesting rapid absorption. For both sexes and dose levels, the highest residue levels were observed in the GIT/ingesta at Cmax and C½max. After the GIT/ingesta, the highest tissue levels were observed in the carcass, skin, blood, kidneys and liver at both Cmax and C½max. For all tissues, residue levels were decreased at C½max compared to Cmax levels. The data also suggest that ^{14}C-XDE-570 was rapidly excreted in both sexes following single oral low- and high-dose administration. ^{14}C-XDE-570 was metabolised only slightly in the liver, kidney and blood for each sex, dose and time point. In the liver and kidney, there were a total of 8 peaks detected for each sex, dose and time point, however, no single liver or kidney sample contained all 8 peaks. In the blood 2 peaks were detected. The major peak in the liver, kidney and blood was identified as the unchanged parent compound, XDE-570, accounting for greater than 90% of the radioactivity recovered in the respective tissue at Cmax and C½max at both dose levels for both sexes, however, the total radioactivity recovered in either the liver, kidney or blood did not exceed 5% of the administered dose in any tissue at either Cmax or C½max at either dose level. In the bile, a total of 9 peaks were detected. The largest peak, accounting for 0.11% of the administered dose, was unidentified. The unchanged parent compound, XDE-570, represented 0.09% of the administered dose. There were no significant differences in absorption, distribution, metabolism, excretion or HPLC profile of the select tissues between the sexes.

This metabolism study in the rat is classified supplementary and does not satisfy the guideline requirement for a

metabolism study (OPPTS 870.7485; OECD 417) in rats.

The objective of this study was to evaluate ^{14}C distribution and metabolism (via HPLC profiling) in target organs (liver and kidney) and blood at plasma Cmax and C½max and to obtain information on the absorption, distribution, metabolism and excretion of ^{14}C-XDE-570 in the bile, to supplement data obtained in the previous ^{14}C-XDE-570 rat metabolism study (see DACO 4.5.9.1 - Dryzga, M. D. et al, November 14, 1996. XR-570: Tissue Distribution and Metabolism of ^{14}C-Labeled XR-570 in Fischer 344 Rats. Laboratory Project ID: HET DR 0312-6565-014. Unpublished) and to support registration of this compound in Japan. The same strain of rat (Fischer 344), route of exposure (single oral dose) and dose levels (10 and 500 mg/kg bw as an aqueous Methocell suspension) were used. The animals were dosed with ^{14}C-aniline labelled XDE-570 since the pervious study showed that the metabolites in the urine and faeces revealed no evidence of hydrolysis of the sulfonamide bond. This metabolism study in the rat is classified supplementary and does not satisfy the guideline requirement for a metabolism study (OPPTS 870.7485; OECD 417) in rats, however, this study is adequate for the purpose for which it was intended. The guideline requirement for a metabolism study (OPPTS 870.7485;OECD 417) in rat, was adequately satisfied with the previous metabolism study in rats utilizing ^{14}C-XDE-570 (Dryzga et al, 1996).

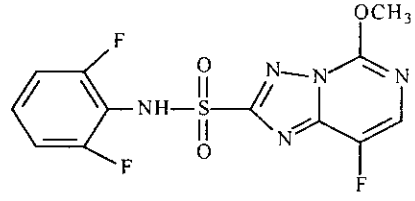
COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Compound:

Radiolabelled Test Material:	^{14}C-XDE-570 uniformly labelled in the aniline ring (XR-570-phenyl-UL-^{14}C)
Radiochemical purity	98.5% [determined by HPLC,: Freshour, N.L., 1996. Radiochemical purity determination of ^{14}C-XDE-570. Report of the Dow Chemical Company, Midland, MI]
Specific Activity	54.9 mCi/mmole
Lot/Batch #:	Lot # B734-21
Non-Radiolabelled Test Material:	XDE-570 as named in the study. Chemical Name (CAS nomenclature) - N-(2,6-diflurophenyl)-8-fluoro-5-methoxy(1,2,4)triazolo(1,5-c)pyrimidine-2-sulphonamide
Description:	White powdery solid
Lot/Batch #:	930910 (TSN100298)
Purity:	99.2% a.i. [determined by HPLC, Boothroyd, S.J., et al, 1996, Characterization of Technical Batch TSN100298, GHE-P-4702: Summary report, Report of DowElanco Europe, Letcombe Regis]
CAS #:	145701-23-1
Structure	



2. Vehicle and/or positive control:

The test substance was prepared as an aqueous suspension in Methocel™ cellulose ethers (≈0.5%).

3. Test animals:

Species:	male and female rats
Strain:	Fischer 344
Age/weight at study initiation:	At dosing, the animals were ≈9 to 10 weeks of age with a body weight range of ≈198-229 g for males and 114-132 g for females.
Source:	Charles River Breeding Laboratories, Raleigh, North Carolina.
Housing:	Animals were housed individually in glass Roth-type metabolism cages after dosing with radiolabel.
Diet:	Certified Rodent Chow #5002 (Purina Mills Inc., St. Louis, MO) *ad libitum*. For groups 1-4, food withdrawn ≈16 hours prior to dosing. For group 5, 1 pellet of food was left 16 hours prior to dosing. Feed was returned to the animals 4 hours post-dosing.
Water:	Municipal tap water *ad libitum*
Environmental conditions:	**Temperature:** 22-24 °C **Humidity:** 45-50% **Air changes:** Not provided **Photoperiod:** 12 hrs dark/12 hrs light
Acclimation period:	Animals were acclimatized to laboratory conditions for at least 1 week and to metabolism cages for at least 2 days prior to administration of ^{14}C-XDE-570. Animals destined for bile duct cannulation were acclimatized to metabolism cages for ≈5 days prior to surgery.

4. Preparation of dosing solutions: The oral dosing solutions were prepared as an aqueous suspension in

Methocel™ cellulose ether (~0.5%) by adding appropriate amounts of ^{14}C-labelled and non-radiolabelled XDE-570 to obtain target doses of 10 and 500 mg/kg bw. Radio-tracers were diluted with non-radiolabelled XDE-570 to obtain target radioactivity for all dose groups of 80 µCi/kg. The dose solutions were administered at an amount of 5 g/kg bw. The quantity of ^{14}C-XDE-570 dose solution actually administered was determined by weighing the syringe prior to and following dosing. Prior to dosing, aliquots of the dose solutions containing ^{14}C-XDE-570 were analysed by ^{14}C analysis for confirmation of homogeneity and targeted radioactivity. The targeted and actual concentrations of radioactivity and XDE-570 in each of the oral dosing solutions are summarized in the following table.

^{14}C-XDE-570 Dose Solutions	Target Radioactivity (µCi/g)	Actual Radioactivity (µCi/g)	Target XDE-570 (mg/g)	Actual XDE-570 (mg/g)
10 mg/kg bw	80	98.4 (123%)	2	1.31 (66%)
500 mg/kg bw	80	81.0 (101%)	100	87.4 (87%)

B. STUDY DESIGN AND METHODS:

1. Group Arrangements Animals were randomly assigned, utilizing a computer driven randomization procedure, to the test groups noted in Table 1.

TABLE 1: Dosing groups for pharmacokinetic studies for ^{14}C-aniline labelled XDE-570.

Test Group	Dose of labelled material (mg/kg bw)	Number/sex	Remarks/Investigations
Single Low Dose Deposition - Plasma C_{max}	10 mg/kg bw	3 animals/sex	Single oral dose of 10 mg/kg bw of ^{14}C-XDE-570. Animals sacrificed at C_{max} corresponding to 0.5 hours post-dosing for both sexes. Radioactivity in selected tissues[a] and ^{14}C-XDE-570 metabolites in pooled samples[b] were determined.
Single High Dose Deposition - Plasma C_{max}	500 mg/kg bw	3 animals/sex	Single oral dose of 500 mg/kg bw of ^{14}C-XDE-570. Animals were sacrificed at C_{max} corresponding to 1.0 and 0.5 hrs post-dosing for ♂ & ♀, respectively. Radioactivity in selected tissues[a] and ^{14}C-XDE-570 metabolites in pooled samples[b] were determined.
Single Low Dose Deposition - Plasma $C_{½max}$	10 mg/kg bw	3 animals/sex	Single dose of 10 mg/kg bw of 10 mg/kg bw of ^{14}C-XDE-570. Animals were sacrificed at $C_{½max}$ corresponding to 1.0 hours post-dosing for both sexes. Radioactivity in selected tissues[a] and ^{14}C-XDE-570 metabolites in pooled samples[b] were determined.
***Single High Dose* Deposition - Plasma $C_{½max}$**	500 mg/kg bw	3 animals/sex	Single oral dose of 500 mg/kg bw of ^{14}C-XDE-570. Animals were sacrificed at $C_{½max}$ corresponding to 4.0 hours post-dosing for both sexes. Radioactivity in selected tissues[a] and ^{14}C-XDE-570 metabolites in pooled samples[b] were determined.
Bile Cannulated Group	10 mg/kg bw	3 males	Animals fitted with indwelling bile-duct cannulas prior to dosing. Single oral dose of 10 mg/kg bw of ^{14}C-XDE-570. Animals were sacrificed at 24 hours post-dosing. Radioactivity in selected tissues[c] and ^{14}C-XDE-570 metabolites in pooled samples[d] were determined.

(a) adrenals, blood, bone, brain, duodenum, fat, gastro-intestinal tract/ingesta, gonads, heart, kidneys, liver, lung, lymph nodes, pancreas, skeletal *muscle, spleen, skin, thymus,* thyroid, uterus, remaining carcass; any urine and/or faeces voided were included in final cage wash.
(b) pooled blood, liver and kidney.
(c) bile (2, 4, 6, 8, 12 and 24 hours), carcass, skin, gastro-intestinal tract/ingesta, urine and faeces (0-24 hours).
(d) bile (0-2 hours) and pooled urine (0-24 hours), plus pooled urine (0-24 hours) from previous ADME study (DACO 4.5.9.1 - Dryzga, et al, 1996,, Laboratory Project ID: HET DR 0312-6565-014).

2. Dosing and sample collection:

a. Pharmacokinetic studies - The oral dose was administered by gavage using a stainless steel feeding needle. The

quantity of the ^{14}C-XDE-570 dose solution administered was determined by weighing the syringe prior to and following dosing. For animals destined for the bile duct cannulation (bile cannulated group), continuous flow bile duct cannulas were implanted under methoxyflurane anaesthesia. Following surgery, the animals were fitted with rodent jackets and allowed to recover in their cages containing corn cob bedding for approximately 3 days prior to administration of ^{14}C-XDE-570. The bile duct was exteriorized behind the neck of the animal and was connected to a duodenal cannula for continuous circulation of bile during the recovery period. Prior to dosing, the bile duct cannula was threaded through a rotating spring mount which was attached to the jacket. The duodenal cannula was plugged with copper wire. Final selection of animals for the biliary excretion segment was based on adequate function of the bile duct cannula, general healthy appearance and food and water consumption.

At the times corresponding to plasma Cmax and plasma C½max for each sex and dose (see Table 1), the animals were sacrificed with CO_2, exsanguinated via cardiac puncture and the tissues marked with an (X) in the following table were collected and analysed for radioactivity.

X	adrenals	X	gonads	X	skeletal muscle
X	blood	X	heart	X	spleen
X	bone	X	kidneys	X	skin
X	brain	X	liver	X	thymus
X	duodenum	X	lung	X	thyroid
X	fat (peri-renal)	X	lymph nodes	X	uterus
X	gastro-intestinal tract (with contents)	X	pancreas	X	remaining carcass

Due to the short time span (0.5 to 4 hours) from dosing to sacrifice for animals in groups 1-4, all urine and/or faeces voided were included in the final cage wash (FCW) and analysed for radioactivity.

Following dosing, bile was collected from the bile cannulated animals at 2, 4, 6, 8, 12 and 24 hours in individual dry-ice traps. Bile from untreated donor rats was administered to the animals on test via the duodenal cannula to supplement bile loss. The individual bile samples were weighed and aliquots analysed for radioactivity by liquid scintillation counting (LSC). Equal-volume aliquots of bile with the highest percent of administered dose volume (0-2 hours) were pooled and analysed via HPLC. At sacrifice (24 hours), blood, skin, carcass and GIT/ingesta were homogenized and/or solubilized and analysed for radioactivity via LSC. Urine and faeces were collected (0-24 hours) in dry-ice cooled traps. Each urine specimen was weighed and an aliquot was analysed for radioactivity. Equal volume aliquots of urine were pooled and stored at -80 °C until analysed by HPLC. Each faecal specimen was weighed and an aqueous homogenate (≈25% w/w) of faeces was prepared. Weighed aliquots of faecal homogenates were placed in scintillation vials, solubilized and quantitated for radioactivity. Once the study was terminated (24 hours post-dosing) the cages were washed with water, the weight of the final cage wash (FCW) obtained and a weighed aliquot analysed for radioactivity via LSC.

Radioactivity was quantitated using liquid scintillation counting (LSC). Counts per minute (cpm) were corrected for quench (H# technique) to obtain disintegrations per minute (dpm) and the dpm of the concurrently run blank subtracted. At least one sealed ^{14}C standard was counted with each group of samples to monitor the liquid scintillation spectrometer. Samples with dpm's less than twice the concurrently run background (blanks) were considered to contain insufficient radioactivity to reliably count.

b. Metabolite characterization studies - Prior to preparation, all samples were removed from the -80 °C freezer and allowed to thaw to laboratory temperature and mixed well. For pooled blood, kidney and liver samples (male and female, dosed at 10 and 500 mg/kg bw, collected at Cmax and C½max) approximately 2 g aliquots were mixed with 10 mL aliquots of ethyl acetate (EtAc) and centrifuged for 10 minutes. The top layers were removed and transferred to weighed 2 oz jars. The procedure was repeated with 2 x 10 mL EtAc and concentrated to dryness under nitrogen. Weighed amounts (~2.0 mL) of 75:25 AcN:H_2O with 1% acetic acid (HpOAc) were added to the dry extracts, sonicated for 1 min and mixed well. For pooled bile (0-2 hours from 2/3 males) and individual bile (0-2 hours from remaining male) approximately 750 µL aliquots of the pooled and individual bile samples were each mixed with approximately 300 µL weighed aliquot of AcN (1% acetic acid) and mixed well. Weighed aliquots of the AcN-

diluted pooled and the AcN-diluted individual bile were then mixed in appropriate ratios in order to make up an equivalent pooled bile sample from the three animals.

The pooled urine (0-24 hours) collected from the bile-cannulated males (2 males) and individual males urine from 0-12 hr, and for comparative purposes, the pooled 12-24 hr urine from the previous ADME study (Dryzga, et al, 1996, DACO 4.5.9.1, Laboratory Project ID: HET DR 0312-6565-014) were also analysed by HPLC. The individual 0-12 urine samples were pooled and a portion of it combined with the 12-24 hour pooled urine to create a 0-24 hour pooled sample.

All biological samples prepared for HPLC analysis were filtered via respective 0.2 µm Anotop 25 Plus syringe filters prior to injection. Bile, blood, liver, kidney and urine samples were profiled using step gradient conditions by reversed-phase HPLC. A fraction collector was used to collect the 20-second (2.0 min post injection) which were counted by LSC. DPM values from LSC analysis of the HPLC fractions were converted into chromatographic data files. Metabolite profiles were then calculated by manual integration of the reconstructed radiochromatograms for these samples. An LDC Spectrometer UV detector was used to determine the retention time of an analytical standard of XDE-570.

3. Statistics: Descriptive statistics were conducted (i.e., mean ± standard deviation). No standard deviation was calculated for a sample set with less than 3 animals.

II. RESULTS

A. Pharmacokinetic Studies:

1. Absorption Data for recovery of radioactivity in the tissues and excreta of rat after oral administration of ^{14}C-aniline labelled XDE-570 are summarized in Table 2. Summary of bile excretion data from male rats after oral administration of 10 mg/kg bw ^{14}C-aniline labelled XDE-570 are summarized in Table 3.

a) Single low dose at plasma Cmax and C½max: Following single oral low dose administration, the GIT/ingesta accounted for approximately 32/20% (♂/♀) of the administered dose at Cmax. At C½max this was decreased to approximately 17/11% (♂/♀). The total recovery at the low dose was approximately 86/83% (♂/♀) of the administered dose at Cmax and approximately 83/78% (♂/♀) at C½max. When based on the total recovery and the amount of radioactivity recovered in the GIT/ingesta (assuming the radioactivity recovered in the GIT/ingesta has not been absorbed) at Cmax or at C½max, the estimated proportion of the administered dose absorbed was approximately 54/63% (♂/♀) at Cmax. At C½max, the estimated proportion absorbed was increased to approximately 66/67% (♂/♀). There were no significant sex-related differences in absorption.

a) Single high dose at plasma Cmax and C½max: Following single oral high dose administration, the GIT/ingesta accounted for approximately 35 and 42% (♂/♀) at Cmax. At C½max this was decreased to approximately 31/26%. The total recovery at the high dose was approximately 94/87% (♂/♀) of the administered dose at Cmax and approximately 94/88% (♂/♀) at C½max. When based on the total recovery and the amount of radioactivity recovered in the GIT/ingesta (assuming the radioactivity recovered in the GIT/ingesta has not been absorbed) at Cmax or at C½max, the estimated proportion of the administered dose absorbed was approximately 59 /45% (♂/♀) at Cmax. At C½max, the estimated proportion absorbed was increased to approximately 64/62% (♂/♀). There were no significant sex-related differences in absorption.

c) Bile cannulated group Following single oral low dose administration, the majority of the radioactivity was recovered in the urine and rinse at 24 hours post-dosing, representing approximately 81% of the administered dose. The final cage wash (FCW) accounted for approximately 4.59% of the administered dose. The tissues and carcass accounted for approximately 8.28% of the administered dose. In the tissues and carcass, the GIT/ingesta accounted for approximately 5.14% of the administered dose. The total recovery was approximately 98.71% of the administered dose. Bile was collected over a 24 hour period (at various time intervals) and represented 1.0% of the

administered dose. The 0-2 hour post-dosing interval contained the highest percentage (0.37% of the administered dose) of the administered dose (Table 3). When based on the total recovery and the amount of radioactivity recovered in the GIT/ingesta and faeces (assuming the radioactivity recovered in the GIT/ingesta and faeces has not been absorbed) at 24 hours, the estimated proportion of the administered dose absorbed was approximately 90%.

TABLE 2: Recovery of radioactivity in tissues and excreta of rats after oral administration of ^{14}C-aniline labelled XDE-570. (a)

Tissue/organ	Recovery of Radioactivity (% of Administered Dose)								
	Single low-dose Cmax		Single low-dose C½max		Single high-dose Cmax		Single high-dose C½max		Bile Cannulated Group
	♂ n = 3	♀ n = 3	♂ n = 3	♀ n = 3	♂ n = 3	♀ n = 3	♂ n = 3	♀ n = 3	♂ n = 2
Sacrifice Time	0.5 h	0.5 h	1.0 h	1.0 h	1.0 h	0.5 h	4.0 h	4.0 h	24 h
Faeces	-	-	-	-	-	-	-	-	3.87
Tissues/Carcass (GIT/Ingesta)	61.74 (32.34)	44.18 (19.88)	31.99 (16.85)	18.19 (10.68)	82.19 (35.14)	76.73 (42.19)	59.45 (30.62)	38.14 (26.25)	8.28 (5.14)
Urine and Rinse	-	-	-	-	-	-	-	-	80.97
Bile	-	-	-	-	-	-	-	-	1.00
FCW (b)	24.22	38.80	51.04	59.63	12.12	10.74	35.38	49.75	4.59
Total Recovery	85.96	82.97	83.03	77.81	94.31	87.47	94.83	87.89	98.71
Estimated absorption (c)	53.62	63.09	66.18	67.14	59.17	45.28	64.21	61.64	89.70

(a) Data extracted from pages 45-47 of the study report.
(b) FCW - Final cage wash, includes any urine and faeces voided.
(c) Based on the total recovery and the amount of radioactivity recovered in the GIT/ingesta (assuming the radioactivity recovered in the GIT/ingesta has not been absorbed) at Cmax or at C½max. For the bile cannulated group, estimated absorption was based on total recovery and amount of radioactivity in the GIT/ingesta and faeces (assuming the radioactivity recovered in the GIT/ingesta and faeces has not been absorbed).

TABLE 3. Summary of bile excretion data from male rats after oral administration of 10 mg/kg bw ^{14}C-aniline labelled XDE-570. (a)

Time (hour)	Bile Cannulated Group (% of Administered Dose) (n = 3)
2	0.37
4	0.14

Time (hour)	Bile Cannulated Group (% of Administered Dose) (n = 3)
6	0.06
8	0.05 (b)
12	0.09 (b)
24	0.04 (b)

(a) Data extracted from page 59 of the study report. Biliary Interval Excretion, 3 males received single oral dose of 10 mg/kg bw of ^{14}C-aniline labelled XDE-570. Animals were sacrificed at 24 hours post-dosing.
(b) Mean value based on data from 2 animals

2. Tissue distribution

a) Single low dose at plasma Cmax and C½max: As summarized in Table 4, the tissue/carcass accounted for approximately 62/44% (♂/♀) of the administered dose at plasma Cmax. At plasma C½ max, tissue/carcass levels were decreased to approximately 32/18% (♂/♀) of the administered dose. At Cmax and C½max, the highest residue levels were observed in the GIT/ingesta, representing approximately 32/20% (♂/♀) of the administered dose at Cmax and approximately 17/11% (♂/♀) at C ½max. After the GIT/ingesta, the highest tissue levels were observed in the carcass, skin, blood, kidneys and liver at Cmax and C½max. There were no significant sex-related differences in tissue distribution.

b) Single high dose at Cmax and C½max: As summarized in Table 4, the tissue/carcass accounted for approximately 82/77% (♂/♀) of the administered dose at plasma Cmax. At plasma C½max, tissue/carcass levels were decreased to approximately 60/38% (♂/♀) of the administered dose. At Cmax and C½max, the highest residue levels were observed in the GIT/ingesta, representing approximately 35 /42% (♂/♀) of the administered dose at Cmax and approximately 31/26% (♂/♀) at C½max. After the GIT/ingesta, the highest tissue levels were observed in the carcass, skin, blood, liver and kidneys at Cmax and C½max. There were no significant sex-related differences in tissue distribution.

c) Bile cannulated group: As summarized in Table 4, the tissue/carcass accounted for approximately 8.28% of the administered dose at 24 hours post-dosing. The highest residues were observed in the GIT/ingesta, representing approximately 5.14% of the administered dose, while the skin, carcass and blood accounted for 2.67, 0.46 and 0.01% of the administered dose, respectively.

TABLE 4: Distribution of radioactivity in rat tissues/organs after oral administration of ^{14}C-aniline labelled XDE-570. (a)

TABLE 5. Metabolite profile in liver, kidney, blood and bile in rats following oral administration of ^{14}C-aniline labelled XDE-570. (a)

Metabolite	Percent of administered dose								
	Single low-dose Cmax		Single low-dose C½max		Single high-dose Cmax		Single high-dose C½max		Bile Cannulated Group
	♂ n = 3	♀ n = 3	♂ n = 3	♀ n = 3	♂ n = 3	♀ n = 3	♂ n = 3	♀ n = 3	♂ n = 2
Sacrifice Time	0.5 h	0.5 h	1.0 h	1.0 h	1.0 h	0.5 h	4.0 h	4.0 h	24 h
Liver HPLC Reconstructed Profile Data (ND - Not detected at ≥0.01% of administered dose)									
Un-identified Metabolite 1	ND	ND	ND	ND	ND	0.00	ND	ND	-
Un-identified Metabolite 2	0.03	ND	ND	ND	ND	ND	ND	ND	-
Un-identified Metabolite 3	ND	ND	0.02	ND	0.03	ND	0.03	0.01	-
Un-identified Metabolite 4	0.03	ND	ND	ND	0.04	ND	ND	ND	-
Un-identified Metabolite 5	0.06	ND	ND	ND	0.11	0.00	ND	ND	-
Un-identified Metabolite 6	0.07	0.04	0.04	ND	0.15	0.01	0.04	0.02	-
Un-identified Metabolite 7	ND	ND	ND	ND	0.02	ND	ND	ND	-
Parent - XDE-570	2.51	1.42	1.15	0.46	4.66	0.24	2.39	0.67	-
Kidney HPLC Reconstructed Profile Data (ND - Not detected at ≥0.01% of administered dose)									
Un-identified Metabolite 1	ND	ND	ND	ND	ND	ND	ND	ND	-
Un-identified Metabolite 2	0.01	ND	ND	ND	ND	ND	ND	ND	-
Un-identified Metabolite 3	0.01	0.01	0.01	ND	0.01	ND	ND	ND	-
Un-identified Metabolite 4	0.02	ND	0.01	ND	0.02	ND	ND	ND	-
Un-identified Metabolite 5	0.03	ND	0.01	ND	0.02	ND	0.01	ND	-
Un-identified Metabolite 6	0.01	ND	0.01	ND	0.01	ND	ND	ND	-
Un-identified Metabolite 7	0.18	0.09	0.06	0.03	0.04	0.03	0.02	0.02	-
Parent - XDE-570	3.16	2.64	1.23	0.65	0.95	0.65	0.72	0.49	-
Distribution of Radioactivity in Blood (LOD = 0.01% of administered dose)									
Un-identified Metabolite 1	0.09	0.05	0.04	0.02	0.06	0.09	0.02	0.02	-
Parent - XDE-570	3.49	2.80	1.30	0.78	4.20	3.13	1.84	0.95	-
Distribution of Radioactivity in Bile (ND - Not detected at ≥0.01% of administered dose)-									
Un-identified Metabolite 1	-	-	-	-	-	-	-	-	0.01
Un-identified Metabolite 2	-	-	-	-	-	-	-	-	0.03
Un-identified Metabolite 3	-	-	-	-	-	-	-	-	0.11
Un-identified Metabolite 4	-	-	-	-	-	-	-	-	0.03
Un-identified Metabolite 5	-	-	-	-	-	-	-	-	0.02
Un-identified Metabolite 6	-	-	-	-	-	-	-	-	0.01
Un-identified Metabolite 7	-	-	-	-	-	-	-	-	ND
Un-identified Metabolite 8	-	-	-	-	-	-	-	-	0.01

Metabolite	Percent of administered dose								
	Single low-dose Cmax		Single low-dose C½max		Single high-dose Cmax		Single high-dose C½max		Bile Cannulated Group
	♂ n = 3	♀ n = 3	♂ n = 3	♀ n = 3	♂ n = 3	♀ n = 3	♂ n = 3	♀ n = 3	♂ n = 2
Parent - XDE-570	-	-	-	-	-	-	-	-	0.09

(a) Data extracted from pages 60-66 of the study report

Urine from the bile cannulated males dosed at 10 mg/kg bw was pooled and analysed (Table 6). The largest peak in the urine 0-24 hour sample corresponded to the unchanged parent compound, XDE-570, representing approximately 75% of the administered dose. This was similar to values observed in 0-12 hour and 0-24 hour urine samples obtained from the single low dose males from the previous rat metabolism study (see DACO 4.5.9.1 - Dryzga, et al, 1996,, *Laboratory Project ID: HET DR 0312-6565-014).*

TABLE 6. Metabolite profile in urine of rats following oral administration of ^{14}C-aniline labelled XDE-570. (a)

Metabolite	Percent of administered dose			
Time Period (hr)	0-24 (b)	0-24 (c)	0-12 (d)	0-12 (e)
Distribution of Activity in Urine (ND - Not detected at or below the number in the parenthesis)				
Un-identified Metabolite A	ND (0.60)	0.39	0.41	ND (1.03
Un-identified Metabolite B	0.69	*ND (0.31)*	*ND (0.21)*	ND
Un-identified Metabolite 1	1.21	2.83	2.46	2.77
Un-identified Metabolite 2	4.23	5.01	4.74	4.96
Parent - XDE-570	74.84	77.06	75.06	74.94

(a) Data extracted from page 67 of the study report
(b) Pooled urine from bile cannulated animals
(c) Pooled urine from Dryzga, et al, (DACO 4.5.9.1, 1996, Laboratory Project ID: HET DR 0312-6565-014), analysed 1/97.
(d) Pooled urine from Dryzga, et al, (DACO 4.5.9.1, 1996, Laboratory Project ID: HET DR 0312-6565-014), re-analysed 1/97.
(e) Results based upon percent of administered radioactivity, 0-12 hr male urine, Appendix Table 3, Dryzga, et al, (DACO 4.5.9.1, 1996, Laboratory Project ID: HET DR 0312-6565-014).
ND - Not detected at or below the number indicated in the parentheses.

III. DISCUSSION

A. Investigators' conclusions (extracted from page 12 of the study report): "The purpose of this study was to obtain additional information on the absorption, distribution, metabolism and excretion of ^{14}C-XDE-570, in selected tissues at plasma C_{max} and $C_{½max}$ and in the bile, in the rat to support registration of this compound in Japan. Groups of 3 rats/sex were orally dosed at 10 and 500 mg ^{14}C-XDE-570/kg BW for the tissue analyses and a group of three

male rats was dosed at 10 mg ^{14}C-570/kg BW for the bile analyses. Selected tissues were collected at each dose/sex at plasma C_{max} and $C_{½max}$ and were analyzed for radioactivity. Overall, the blood contained greater amounts of radioactivity (3-4% of the administered dose) than the kidney and liver at plasma C_{max} and $C_{½max}$ for each dose/sex. However, the kidney had the largest amount of radioactivity as µg-eq ^{14}C-570/g, at plasma C_{max} and $C_{½max}$ relative to blood and liver. All tissues analyzed had maximum concentrations of radioactivity at C_{max} (at each dose/sex) and decreased at a rate proportional to or greater than that of the blood at plasma $C_{½max}$. In addition, respective blood, kidney, and liver samples were pooled and extracted, and the extract subjected to high-performance liquid chromatography (HPLC). Parent XDE-570 accounted for greater than 91% of the radioactivity in the kidney, liver, and blood for each dose/time point/sex. Bile from male rats (dosed at 10 mg/kg BW) was collected over a 24-hr period (at various time intervals) and accounted for 1.0% of the administered dose. The 0-2 hr post-dosing interval contained the highest percentage of the administered dose (0.37%). Parent XDE-570 represented 0.09% of the administered dose in bile. Orally administered ^{14}C-XDE-570 was readily absorbed and rapidly eliminated in the tissues from the F344 rat. There were no major differences in disposition, rate of tissue clearance, and HPLC profiles of the select tissues between the sexes."

B: Reviewer comments: Following single oral low- or high-dose administration, ^{14}C-XDE-570 was extensively and rapidly absorbed in both sexes. The estimated proportion of the administered dose absorbed (based on total recovery and recovery of radioactivity in the GIT/ingesta, assuming radioactivity recovered in the GIT/ingesta was not absorbed) at plasma Cmax was approximately 54/63% (♂/♀) at the low dose (at 0.5 hrs) and approximately 59/45% (♂/♀) at the high dose (at 1.0 and 0.5 hrs for ♂ and ♀, respectively). At plasma C½max the corresponding values increased to approximately 66/67% at the low dose (at 1.0 hr) and to approximately 64/62% (♂/♀) at the high dose (at 4.0 hrs). In the bile cannulated group (♂ only) approximately 90% of the administered dose was absorbed by 24 hours (based on total recovery and recovery of radioactivity in the GIT/ingesta, assuming radioactivity recovered in the GIT/ingesta was not absorbed). Bile absorption accounted for 1% of the administered dose with the 0-2 hour post-dosing interval containing the highest percentage of the administered dose (0.37%) suggesting rapid absorption. For both sexes and dose levels, the highest residue levels were observed in the GIT/ingesta at Cmax and C½max accounting for approximately 32/20% (♂/♀) and 35/42% (♂/♀) at Cmax at the low and high dose, respectively. At C½max the levels decreased to approximately 17/11% and 31/25% at the low and high dose, respectively. After the GIT/ingesta, the highest tissue levels were observed in the carcass, skin, blood, kidneys and liver at both Cmax and C½max. For all tissues, residue levels were decreased at C½max compared to Cmax levels. In the bile cannulated animals the highest residue levels were found in the GIT/ingesta accounting for ≈5% of the administered dose at 24 hours. The data suggest that excretion was rapid in both sexes at both dose levels. The proportion of the administered dose excreted in the final cage wash (urine + faeces) at plasma Cmax was approximately 24/39% (♂/♀) at the low dose and approximately 12/11% (♂/♀) at the high dose. By C½max, radioactivity recovered in the final cage wash was increased to approximately 51/60% of the administered dose at the low dose and to approximately 35/50% at the high dose. In the bile cannulated animals, the majority of the administered dose was excreted via the urine, accounting for approximately 80% by 24 hours. The faeces and final cage wash accounted for approximately 4 and 5% of the administered dose, respectively. Approximately 1% of the administered dose was excreted in the bile by 24 hours. ^{14}C-XDE-570 was metabolised only slightly in the liver, kidney and blood for each sex, dose and time point. In the liver and kidney, there were a total of 8 peaks detected for each dose, sex and time point, however, no single liver or kidney sample contained all 8 peaks. In the blood 2 peaks were detected. The major peak in the liver, kidney and blood was identified as the unchanged parent compound, XDE-570, accounting for greater than 90% of the radioactivity recovered in the respective tissue at Cmax and C½max at both dose levels for both sexes, however, the total radioactivity recovered in either the liver, kidney or blood did not exceed 5% of the administered dose in any tissue at either Cmax or C½max at either dose level. In the bile, a total of 9 peaks were detected. The largest peak, accounting for 0.11% of the administered dose, was unidentified. The unchanged parent compound, XDE-570, represented 0.09% of the administered dose. There were no significant differences in absorption, distribution, metabolism, excretion or HPLC profile of the select tissues between the sexes.

C. Study deficiencies: The objective of this study was to evaluate ^{14}C distribution and metabolism (via HPLC profiling) in target organs (liver and kidney) and blood at plasma Cmax and C½max and to obtain information on the absorption, distribution, metabolism and excretion of ^{14}C-XDE-570 in the bile, to supplement data obtained in the previous ^{14}C-XDE-570 rat metabolism study (see DACO 4.5.9.1 - Dryzga, M. D. et al, November 14, 1996. XR-570: Tissue Distribution and Metabolism of ^{14}C-Labeled XR-570 in Fischer 344 Rats. Laboratory Project ID: HET

DR 0312-6565-014. Unpublished) and to support registration of this compound in Japan. The same strain of rat (*Fischer* 344), *route of exposure (single oral dose)* and dose levels (10 and 500 mg/kg bw as an aqueous Methocell suspension) were used. The animals were dosed with ^{14}C-aniline labelled XDE-570 since the pervious study showed that the metabolites in the urine and faeces revealed no evidence of hydrolysis of the sulfonamide bond. This metabolism study in the rat is classified supplementary and does not satisfy the guideline requirement for a metabolism study (OPPTS 870.7485; OECD 417) in rats, however, this study *is adequate for the purpose for which* it was intended. The guideline requirement for a metabolism study (OPPTS 870.7485;OECD 417) in rat, was adequately satisfied with the previous metabolism study in rats utilizing ^{14}C-XDE-570 (Dryzga et al, 1996).