# DATA EVALUATION RECORD - SUPPLEMENT

XDE-570 (FLORASULAM)

Study Type: OPPTS 870.7485 [§85-1]; Metabolism Study in Rats

Work Assignment No. 4-1-128 S (MRID 46808301)

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## DATA EVALUATION RECORD

**STUDY TYPE:** Metabolism - Rat; OPPTS 870.7485 (§85-1); OECD 417.

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

**TEST MATERIAL (RADIOCHEMICAL PURITY):** XDE-570 (Florasulam; 99.3-99.5%)

**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:** Dryzga, M. D., S. S. Hiroko, S. C. Hansen, and K. A. Brzak (1996) XR-570: tissue distribution and metabolism of $^{14}$C-labeled XR-570 in Fischer 344 rats. The Toxicology Research Laboratory, Health and Environmental Sciences, The Dow Chemical Company, Midland, MI. Laboratory Project ID: HET DR 0312-6565-014, November 14, 1996. MRID 46808301. Unpublished.

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

**EXECUTIVE SUMMARY:** In a metabolism study (MRID 46808301), [$^{14}$C]-XDE-570 (Florasulam; 99.3-99.5% radiochemical purity; Lot Nos. B463-145 and B844-08A) in a suspension of 0.5% Methocel™ cellulose ethers was administered to 5 Fischer 344 rats/sex as a single gavage dose at 10 or 500 mg/kg bw. Additionally, 5 rats/sex were treated with 14 daily doses at 10 mg/kg bw/day of non-labeled XDE-570 followed by a single oral dose of [$^{14}$C]-XR-570 on Day 15. [$^{14}$C]-XDE-570 was uniformly labeled in the aniline ring for each of these test groups. In addition, 5 males were treated with a single gavage dose at 10 mg/kg bw with [$^{14}$C]-XR-570 (labeled at the 9 position in the triazolo-pyrimidine ring). All animals were killed 168 hours after the administration of the radiolabeled dose.

Absorption was rapid and extensive. Approximately 90-93% of the dose was absorbed in the 10 mg/kg rats, and 82-86% was absorbed in the 500 mg/kg rats (based on the sum of radioactivity detected in the urine, tissues/carcass, and cage rinse). Peak plasma concentrations (Cmax) were achieved within 0.5-1 hour following dose administration at 10 or 500 mg/kg. Cmax in the plasma did not increase proportionally with dose, possibly indicating a saturation of the absorption and/or excretion mechanisms at the high dose. The apparent volume of distribution was increased at the high dose, possibly indicative of increased tissue binding.

Total recoveries at 168 hours post-dose were 95.9-100.2% of the administered dose. Elimination

was rapid. The administered dose was mostly eliminated within 12 hours in the urine (>80% of the dose at 10 mg/kg and >60% of the dose at 500 mg/kg). Total radioactivity found in the urine was approximately 90-92% of the dose following single or repeated low-dose treatment, and 81-85% of the dose following treatment at 500 mg/kg. Radioactivity in the feces accounted for another 5-7% at 10 mg/kg and 14-17% at 500 mg/kg. Thus, compared to the low dose, excretion of the high dose was slightly slower, and more of the compound was excreted in the feces. At 24 hours, <0.5% of the dose was found in expired air. By 24 hours post-dose, plasma levels had declined to <0.1 µg eq/g plasma in both sexes at 10 mg/kg and <5.0 µg eq/g plasma in both sexes at 500 mg/kg. The highest residue levels were observed in the skin (single dose) and carcass (repeated dose), but the mean recovery of radioactivity in the tissues/carcass at sacrifice was <0.6% of the dose.

Identified compounds accounted for 87.6-91.6% of the administered dose in each group. In each group, the following compounds were isolated: parent accounted for 77.7-85.0% dose, OH-phenyl-XR-570 accounted for 3.1-9.0% dose, OH-phenyl-XR-570 sulfate conjugate accounted for 2.8-3.7% dose, and 2 unidentified metabolites accounted for <=0.32% dose. In the high dose, more of the parent was isolated in the feces and less in the urine compared to the low dose.

There were no sex-related differences in the metabolism or pharmacokinetics of the test compound. Similarly, the number of doses or the position of the radiolabel generally made no difference in the metabolism and pharmacokinetic profile.

This study is classified as **acceptable/guideline** and satisfies the guideline requirement for a metabolism study [OPPTS 870.7485, OECD 417] in rats.

**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 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.

46808301.PMRA.der
.pdf

Reviewer: Tom Morris , Date February 25, 2000.

**OECD 5.1.1 (single low dose - rat oral); 5.1.2 (single high dose - rat oral); 5.1.3 (repeat dose - rat oral)**

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

**TEST MATERIAL (PURITY):** XR-570 (Purity - 99.4%)

**SYNONYMS:** XDE-570, XRD-570, DE-570, florasulam

**CITATION:** Dryzga, M. D., Hiroko, S. S., Hansen, S. C. and Brzak, K. A. November 14, 1996. **XR-570: Tissue Distribution and Metabolism of $^{14}$C-Labeled XR-570 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 0312-6565-014. Unpublished

**SPONSOR:** Dow AgroSciences Canada Inc. (DAS).

**EXECUTIVE SUMMARY:** The absorption, distribution, metabolism and excretion of XR-570 (Purity - 99.4%) was investigated in Fischer 344 rats following gavage administration of $^{14}$C-XR-570 uniformly labelled in the aniline ring (aniline labelled; both sexes) or labelled at the 9 position on the triazolo-pyrimidine ring (pyrimidine labelled; males only). In a single low- and high-dose experiment, 5 animals/sex/dose received a single oral dose of either 10 or 500 mg/kg bw of $^{14}$C-aniline labelled XR-570. In a separate single low-dose experiment, 5 males received a single oral dose of 10 mg/kg bw $^{14}$C-pyrimidine labelled XR-570. In a repeat low-dose experiment, 5 animals/sex received a single oral dose of 10 mg/kg bw non-radiolabelled XR-570 daily for 14 consecutive days followed by a final oral dose of 10 mg/kg bw $^{14}$C-aniline labelled XR-570 on day 15. For all experiments, the animals were sacrificed at 168 hours post-dosing.

Following single or repeat oral low-dose or single oral high-dose administration, $^{14}$C-XR-570 was extensively and rapidly absorbed in both sexes. Peak plasma concentrations (Cmax) were achieved within 0.5-1 hour following either single low- or high-dose administration. Based on the available urinary data (radioactivity detected in the urine, tissues/carcass and cage rinse), the estimated proportion of the administered dose absorbed was approximately 90-93% following single or repeat low-dose administration and approximately 82-86% following single high-dose administration. Following single high-dose administration, Cmax was not increased proportionately to the administered dose and plasma clearance was reduced compared to the single low-dose exposure which may suggest a saturation of absorption and / or saturable renal excretion at the high dose. The higher plasma clearance following single low-dose administration suggest a more efficient and rapid removal of the test substance at the low dose. The apparent volume of distribution was increased following high-dose administration which may suggest increased binding to tissues at this dose level. The highest residue levels were observed in skin (single low- and high-dose) and carcass (repeat low-dose). However, the mean recovery of radioactivity in the tissues/carcass at sacrifice (at 168 hours post-dosing) was <0.6% of the administered dose for all dose groups indicating little potential for accumulation. Excretion was rapid, with a majority of the radioactivity being eliminated within 12 hours post-dosing via the urine (>80 and 60% of the administered dose following single or repeat low-dose administration and single high-dose administration, respectively) and within 24 hours via the faeces (3-6 and 11-15% of the administered dose following single or repeat low-dose administration and single high-dose administration, respectively). The urinary excretion rate (half-life) was approximately 3-4 hours at the low dose and approximately 5 hours at the high dose. By 24 hours post-dosing, plasma levels declined to <0.1 µg eq/g plasma in both sexes at the low dose and to <5.0µg eq/g plasma in both sexes at the high-dose. The major route of excretion was via the urine, accounting for approximately 90-92% of the administered dose following single or repeat low-dose administration and approximately 81-85% following single high dose administration. The corresponding values for

faecal excretion were approximately 5-7% following single or repeat low-dose administration and approximately14-17% following single high-dose administration. At 24 hours, less than 0.5% of the administered dose was excreted via expired air. No bile data was included with this study. The major component in the urine and faecal extracts was identified as the unchanged parent compound, XR-570, representing approximately 77-85% of the administered dose. Two other metabolites found in the excreta were characterized as OH-phenyl-XR-570 (≈3-10% of the administered dose) and a sulfate conjugate of OH-phenyl-XR-570 (≈2-4% of the administered dose). Two minor peaks were not identified, however, neither represented more than 0.32% of the administered dose. The sulfate conjugate of the OH-phenyl-XR-570 was not observed in the faecal extracts and was either not quantifiable or not detected in the urine of females. Metabolites in the urine and faeces revealed no evidence of hydrolysis of the sulphonamide bridge. A proposed metabolic pathway is summarized in Figure 1. There were no significant differences in absorption, distribution, metabolism or excretion or changes in pharmacokinetic parameters between the low-dose aniline labelled and pyrimidine labelled groups. Absorption, distribution, metabolism and excretion were not influenced by repeat low-dose oral administration. There were no significant sex-related differences in absorption, distribution, metabolism or excretion following single or repeat low-dose administration or single high-dose administration.

This metabolism study in the rat is classified acceptable / guideline and satisfies the guideline requirement for a metabolism study (OPPTS 870.7485; OECD 417) in rats.

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

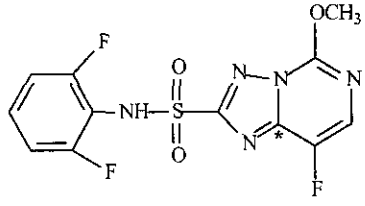
**I. MATERIALS AND METHODS**

## A. MATERIALS:

### 1. Test Compound:

| | |
|---|---|
| **Radiolabelled Test Material 1:** | $^{14}$C-XR-570 uniformly labelled in the aniline ring (XR-570-phenyl-UL-$^{14}$C) |
| **Radiochemical purity** | 99.3 ± 0.0% [determined by linear gradient reversed-phase HPLC with UV and $^{14}$C detection; ACL Report # 94-195] |
| **Specific Activity** | 54.6 mCi / mmole |
| **Lot/Batch #:** | Lot # B463-145 |
| ***Radiolabelled Test Material 2:*** | $^{14}$C-XR-570 (triazolo-pyrimidine) labelled at the 9 position on the triazolo-pyrimidine ring (see below) |
| **Radiochemical purity** | 99.5 ± 0.0% [determined by linear gradient reversed-phase HPLC with UV and $^{14}$C detection; ACL Report # 94-196] |
| **Specific Activity** | 24.2 mCi / mmole |
| **Lot/Batch #:** | Lot # B844-08A |
| **Non-Radiolabelled Test Material:** | XR-570 as named in the study. Chemical Name (CA nomenclature): N-(2,6-difluorophenyl)-8-fluoro-5-methoxy(1,2,4)triazolo(1,5-c)pyrimidine-2-sulphonamide |
| **Description:** | White powdery solid |
| **Lot/Batch #:** | Lot # 930910 / TSN 100298 |
| **Purity:** | 99.4% a.i.[determined by HPLC] |
| **CAS #:** | 145701-23-1 |

**Structure - $^{14}$C labelled in the 9 position on the triazolo-pyrimidine ring (* denotes position of radiolabel)**




2. **Vehicle and/or positive control:** The test substance was administered as a suspension in 0.5% Methocel™ cellulose ethers.

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 ≈155-220 g (♂) and 110-145 g (♀) at dosing. | |
| **Source:** | Charles River Breeding Laboratories, Kingston, New York. | |
| **Housing:** | Animals in the single dose groups were housed individually in glass Roth-type metabolism cages after dosing with radiolabel. In the repeat dose group, the animals were housed individually in wire-mesh cages for the first 11 daily doses, transferred to metabolism cages for the doses on days 12 and 13 and then transferred back to the wire-mesh cages until dosed with radiolabel after which they were transferred back to the metabolism cages. | |
| **Diet:** | Certified Rodent Chow #5002 (Purina Mills Inc., St. Louis, MO) *ad libitum* | |
| **Water:** | Municipal tap water *ad libitum* | |
| **Environmental conditions:** | **Temperature:** | 19-22 °C |
| | **Humidity:** | 46-61% |
| | **Air changes:** | Not provided |
| | **Photoperiod:** | 12 hrs dark/12 hrs light |
| **Acclimation period:** | Acclimatized to laboratory conditions for at least 1 week and to metabolism cages for a period of at least 2 days prior to administration of $^{14}$C-XR-570. | |

**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/or non-radiolabelled XR-570 to obtain target doses of 10 and 500 mg/kg bw. Radio-tracers were diluted with non-radiolabelled XR-570 to obtain target radioactivity for all dose groups of 400 µCi/kg (aniline ring) and 200 µCi/kg (triazolo-pyrimidine ring). Prior to dosing, aliquots of the dose solutions containing $^{14}$C-XR-570 were analysed by $^{14}$C analysis for confirmation of homogeneity and targeted radioactivity. A 21-day stability check was conducted utilizing the $^{14}$C-labelled 10 mg/kg dose solution (ACL Report # 94-276). Analytical determinations on day 0 and day 21 were 2.14 and 1.89 mg/g, respectively. A radiochemical purity was conducted on one of the day 21 aliquots which reported only one radiolabelled peak (parent XR-570) being observed at a detection limit of 1.77%.

## B. STUDY DESIGN AND METHODS:

**1. Group Arrangements** - Animals were randomly (computer driven randomization procedure) assigned to the test groups noted in Table 1.

**TABLE 1: Dosing groups for pharmacokinetic studies for $^{14}$C-aniline labelled XR-570 and $^{14}$C-pyrimidine labelled XR-570.**

| Test Group | Dose of labelled material (mg/kg bw) | Number/sex | Remarks |
|---|---|---|---|
| **Single Low Dose - aniline labelled** | 10 mg/kg bw | 5 animals/sex | Single oral dose of 10 mg/kg bw of $^{14}$C-XR-570 (uniformly labelled in the aniline ring). Sacrificed after 168 hours post-dosing. |
| **Single High Dose - aniline labelled** | 500 mg/kg bw | 5 animals/sex | Single oral dose of 500 mg/kg bw of $^{14}$C-XR-570 (uniformly labelled in the aniline ring). Sacrificed after 168 hours post-dosing. |
| **Repeat Low Dose - aniline labelled** | 10 mg/kg bw | 5 animals/sex | 14 daily doses of 10 mg/kg bw/d of non-radiolabelled XR-570 followed by a single oral dose of 10 mg/kg bw of $^{14}$C-XR-570 (uniformly labelled in the aniline ring). Sacrificed after 168 hours post-dosing. |
| **Single Low Dose - pyrimidine labelled** | 10 mg/kg bw | 5 males | A single oral dose of 10 mg/kg bw of $^{14}$C-XR-570 (labelled at the 9 position in the triazolo-pyrimidine ring). Sacrificed after 168 hours post-dosing. |

**2. Dosing and sample collection:**

**a. Pharmacokinetic studies** - The dose was administered by oral gavage using a syringe and stainless steel feeding needle. The quantity of $^{14}$C-XR-570 dose solution actually administered was determined by weighing the syringe prior to and following dosing. Animals giving multiple doses of non-radiolabelled were weighed every 3-4 days and their dose volumes adjusted accordingly. Animals in which the plasma $^{14}$C time-course was determined (for single low- and high-dose aniline labelled groups and single low-dose pyrimidine labelled group) had an indwelling jugular vein cannula implanted approximately one day prior to administration of the test substance. The dose solutions were administered at an amount of 5 g/kg bw.

Blood samples of approximately 0.1 mL were drawn from the jugular vein of the cannulated animals at 0.5, 1, 3, 5, 8, 12, 18, 24, 48, 72 and 168 hours post-dosing using a syringe. Following collection of each sample, approximately 0.1 mL of heparinized saline (13 U/mL) was used to flush the blood from the cannula and to provide a heparin "lock". The sample was then transferred into heparinized capillary tubes and centrifuged to obtain plasma. Weighed aliquots of plasma were then mixed with scintillation fluid and analysed for radioactivity. Red blood cells were solubilized and then analysed for radioactivity.

Following administration of the radiolabelled dose, all urine voided was collected on dry-ice cooled traps. Urine

was collected at 12, 24, 36, 48, 72 and 168 hours post-dosing. Each urine specimen and cage rinse was weighed, and a weighed aliquot was analysed for radioactivity.

Faeces were collected at 24, 48, 72 and 168 hours post-dosing in dry-ice chilled containers. An aqueous homogenate (~25% w/w) was prepared and weighed aliquots of these homogenates were placed in scintillation vials, solubilized and quantitated for radioactivity.

Following dosing with radiolabelled XR-570, animals (single low- and high-dose alanine labelled groups only) were returned to the metabolism cages and air was drawn through the cages at approximately 500 mL/min. Upon exiting the cage, the air was passed through a charcoal trap and then through a $CO_2$ trap. The charcoal and $CO_2$ traps were changed at 24 hours post-dosing. Radioactivity trapped on the charcoal trap was desorbed with a weighed amount of toluene and a weighed aliquot of the toluene was then analysed for radioactivity. The $CO_2$ traps were weighed and a weighed aliquot was also analysed for radioactivity. Since the $CO_2$ and charcoal traps accounted for <0.5% of the administered radioactivity at 24 hours, the traps were not used for the repeat low-dose alanine labelled group or for the low-dose pyrimidine labelled group.

After 7 days post-dosing (168 hours), 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 |

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** - Selected urine samples were pooled and stored frozen at -80 °C until evaluated by appropriate analytical techniques to determine the chemical identity of the radioactivity. Selected faecal specimens were also pooled and stored frozen at -80 °C until evaluated by appropriate analytical techniques to determine the chemical identity of the radioactivity. When >10% of the administered dose was excreted in the faeces an attempt was made to determine the chemical identity of the radioactivity. Urine samples were profiled using step-gradient conditions by reversed-phase HPLC with RAM (radioactivity monitoring) detection. Faecal samples were profiled using the same step-gradient conditions by reversed-phase HPLC with data reconstructed from 10-second collected fractions counted by LSC detection. Manual 50 µL injections were made into the HPLC system. Identification of metabolites was performed using HPLC separation, electrospray ionization, with mass spectrometric detection (HPLC / ESI / MS). Pooled urine and faecal samples were injected directly into the HPLC column.

**3. Statistics:** Descriptive statistics were calculated (mean ± SD) for all sets of data collected during the study. The concentration time course of $^{14}C$ in the plasma was described by a two-compartment model using the method of residuals and linear regression to estimate the half-life, $t_{1/2}\alpha$ and $t_{1/2}\beta$. The area under the plasma $^{14}C$-concentration-time curves (AUC) was calculated using the trapezoidal rule. The volume of distribution was calculated as the dose divided by the AUC and the overall rate of elimination ($k_{el}$). The clearance (Cl) was defined as the dose divided by the AUC.

## II. RESULTS

### A. Pharmacokinetic Studies:

1. **Absorption** - Concentration of radioactivity in the plasma and red blood cells are summarized in Table 2. Pharmacokinetic parameters which describe plasma time course are summarized in Table 3.

Following single oral low- or high-dose administration, $^{14}$C-XR-570 (aniline labelled) was extensively and rapidly absorbed in both sexes. In males, peak plasma concentrations (Cmax) were attained by 0.5 (23.7 µg eq/g plasma) and 1.0 (580.7 µg eq/g plasma) hour post-dosing at the low- and high-dose, respectively. In females, peak plasma concentrations (Cmax) were attained by 0.5 hours post-dosing at the low- and high-dose (21.9 and 405.7 µg eq/g plasma, respectively). By 24 hours post-dosing, plasma levels declined to <0.1 µg eq/g plasma in both sexes at the low dose and to <5.0µg eq/g plasma in both sexes at the high-dose. Based on the available urinary data (radioactivity detected in the urine, tissues/carcass and cage rinse), the estimated proportion of the administered dose absorbed was approximately 90-93% in the single low-dose males and females following single or multiple administration and approximately 82-86% in the single high-dose males and females (see Table 5). When the dose was increased from 10 to 500 mg/kg bw, Cmax was not increased proportionately to the administered dose and plasma clearance was reduced which may suggest a saturation of absorption and / or saturable renal excretion. The higher plasma clearance after a single low-dose suggests a more efficient and rapid removal of the test substance at the low dose. A slightly lower urinary excretion and higher faecal excretion (see Table 5) and a slightly higher level of unchanged parent compound in the faecal extracts (see Table 6) in high-dose group may also suggest a saturation of absorption at the high-dose. The increased apparent volume of distribution at the high-dose may suggest increased binding to tissues at this dose level. Changes in concentration of radioactivity in the red blood cells were similar across sexes within each dose group and reflected a pattern similar to that observed in the plasma. There were no significant differences in absorption or pharmacokinetic parameters between the low-dose aniline labelled and pyrimidine labelled groups. Absorption was not influenced by repeat low-dose oral administration and there were no significant sex-related differences in absorption. No bile data was included with this study.

**TABLE 2: Concentration of radioactivity in plasma and red blood cells at indicated times after oral administration of $^{14}$C-aniline labelled XR-570 or $^{14}$C-pyrimidine labelled XR-570. (a)**

| Time (hours) | Single low-dose - aniline labelled | | Single high-dose - aniline labelled | | Single low-dose - pyrimidine labelled |
|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male |
| **Plasma (µg eq / g plasma ± SD) (n = 5 animals/group)** | | | | | |
| 0.5 | 23.7 ± 4.10 | 21.9 ± 6.51 | 463.6 ± 22.4 | 405.7 ± 19.8 | 20.0 ± 4.02 |
| 1 | 6.93 ± 1.65 | 8.04 ± 2.37 | 580.7 ± 77.7 | 403.7 ± 51.7 | 6.69 ± 1.18 |
| 3 | 0.75 ± 0.14 | 0.69 ± 0.14 | 420.0 ± 56.1 | 310.6 ± 133.7 | 0.60 ± 0.08 |
| 5 | 0.37 ± 0.11 | 0.36 ± 0.09 | 157.0 ± 45.4 | 130.9 ± 74.2 | 0.31 ± 0.04 |
| 8 | 0.22 ± 0.04 | 0.17 ± 0.03 | 31.3 ± 7.43 | 32.4 ± 3.02 | 0.20 ± 0.03 |
| 12 | 0.15 ± 0.04 | 0.11 ± 0.01 | 24.2 ± 6.44 | 18.3 ± 5.50 | 0.13 ± 0.03 |
| 18 | 0.10 ± 0.02 | 0.06 ± 0.01 | 8.21 ± 1.44 | 6.88 ± 1.26 | 0.08 ± 0.01 |
| 24 | 0.07 ± 0.01 | 0.04 ± 0.01 | 4.06 ± 0.39 | 2.87 ± 1.01 | 0.06 ± 0.01 |
| 48 | 0.03 ± 0.00 | 0.02 ± 0.00 | 1.30 ± 0.19 | 1.00 ± 0.18 | 0.03 ± 0.01 |
| 72 | 0.02 ± 0.01 | 0.01 ± 0.00 | 0.80 ± 0.23 | 0.77 ± 0.36 | 0.02 ± 0.01 |
| 168 | NQ | NQ | NQ | NQ | NQ |
| **Red Blood Cells (µg eq / g RBC ± SD) (n = 5 animals/group)** | | | | | |
| 0.5 | 3.97 ± 2.96 | 5.72 ± 7.28 | 41.23 ± 50.0 | 40.6 ± 53.4 | 2.24 ± 0.29 |
| 1 | 0.70 ± 0.15 | 0.83 ± 0.28 | 283.5 ± 73.7 | 205.0 ± 46.2 | 1.16 ± 0.19 |
| 3 | 0.11 ± 0.03 | 0.12 ± 0.04 | 227.6 ± 92.4 | 161.0 ± 115.3 | 0.58 ± 0.12 |
| 5 | 0.08 ± 0.07 | 0.06 ± 0.01 | 96.5 ± 88.2 | 174.1 ± 77.0 | 0.45 ± 0.07 |
| 8 | 0.03 ± 0.00 | 0.02 ± 0.01 | 3.79 ± 0.42 | 5.41 ± 0.78 | 0.49 ± 0.23 |
| 12 | 0.02 ± 0.01 | NQ | 4.01 ± 0.90 | 2.99 ± 0.68 | 0.27 ± 0.06 |
| 18 | NQ | NQ | 1.10 ± 0.08 | 1.46 ± 0.28 | 0.18 ± 0.03 |
| 24 | NQ | NQ | NQ | NQ | 0.12 ± 0.02 |
| 48 | NQ | NQ | NQ | NQ | 0.04 ± 0.01 |
| 72 | NS | NQ | NQ | NQ | NQ |
| 168 | NQ | NQ | NQ | NQ | NQ |

(a) Data extracted from pages 55 and 56 of the study report
NQ - Not quantifiable.
NS - No sample.

**TABLE 3: Pharmacokinetic parameters for plasma time course for $^{14}$C-aniline labelled XR-570 or $^{14}$C-pyrimidine labelled XR-570 after oral administration. (a)**

| Parameter | Single low-dose aniline labelled | | Single high-dose aniline labelled | | Single low-dose pyrimidine labelled |
|---|---|---|---|---|---|
| | Male | Female | Male | Female | Male |
| Tmax (hr) | 0.5 | 0.5 | 1.0 | 0.5 | 0.5 |
| Cmax (µg eq /g plasma) | 23.7 | 21.9 | 580.7 | 405.7 | 20.0 |
| *T½ - distribution (hr)* | 0.6 | 0.6 | 1.1 | 1.2 | 0.4 |
| T½ - elimination (hr) | 9.8 | 7.6 | 5.1 | 4.5 | 8.1 |
| $AUC_{0\text{-}24\ hr}$ (µg eq hr/g) | 26.8 | 26.3 | 3328 | 2523 | 23.6 |
| Apparent Volume of distribution (mL/kg) | 449 | 439 | 852 | 1435 | 292 |
| Plasma Clearance (Cl) (mL/min/kg) | 7.2 | 7.1 | 2.6 | 3.3 | 6.8 |
| Urinary Excretion Rate (hr) | 3.4 | 3.6 | 4.8 | 4.9 | 3.4 |

(a) Data extracted from page 57 of the study report

## 2. Tissue distribution

**a) Single low dose (both sexes):** As summarized in Table 4, the residual tissue radioactivity was low at sacrifice, 168 hours after single oral low-dose administration, with <0.3% of the administered dose remaining in the carcass and tissues in both sexes. The highest tissue levels were observed in the skin at 0.24 and 0.11 % of the administered dose in males and females, respectively. In all other tissues, residual radioactivity levels represented <0.01% of the administered dose or were non-quantifiable. There were no significant sex-related differences in tissue distribution. These data suggest a low potential for accumulation.

**b) Low dose with pretreatment (both sexes)** As summarized in Table 4, the residual tissue radioactivity was low at sacrifice, 168 hours after repeat oral low-dose administration, with <0.2% of the administered dose remaining in the carcass and tissues in both sexes. In males, the highest tissue levels were observed in the carcass at 0.10 % of the administered dose. In all other tissues, the residual radioactivity represented <0.01% of the administered dose or were non-quantifiable. In females, the residual radioactivity levels in all tissues represented <0.01% of the administered dose or were non-quantifiable. There were no significant sex-related differences in tissue distribution. Tissue distribution was not significantly influenced by repeat low-dose administration compared to single low-dose administration. These data suggest a low potential for accumulation.

**c) Single high dose (both sexes)** As summarized in Table 4, the residual tissue radioactivity was low at sacrifice, 168 hours after single oral low-dose administration, with <0.6% of the administered dose remaining in the carcass and tissues in both sexes. The highest tissue levels were observed in the skin at 0.52 and 0.18 % of the administered dose in males and females, respectively. In all other tissues, residual radioactivity levels represented <0.01% of the administered dose or were non-quantifiable. There were no significant sex-related differences in tissue distribution. There were no significant differences in tissue distribution between the single high-dose and single low-dose aniline labelled groups. These data suggest a low potential for accumulation.

**d) Single low dose - pyrimidine labelled (males only)** As summarized in Table 4, the residual tissue radioactivity was low at sacrifice, 168 hours after single oral low-dose administration, with <0.1% of the administered dose remaining in the carcass and tissues. The residual radioactivity levels in all tissues represented <0.01% of the administered dose or were non-quantifiable. There were no significant differences in tissue distribution between the single low-dose aniline labelled and pyrimidine labelled groups. These data suggest a low potential for accumulation.

***TABLE 4: Distribution of radioactivity in rat tissues/organs 168 hours after oral administration of $^{14}$C-aniline labelled XR-570 or $^{14}$C-pyrimidine labelled XR-570. (a)***

| Tissue / organ | Residual Tissue Radioactivity (mean % of administered dose for 5 rats) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Single low-dose aniline labelled | | Repeated low-dose aniline labelled | | Single high-dose aniline labelled | | Single low-dose pyrimidine labelled |
| | Male | Female | Male | Female | Male | Females | Males only |
| Adrenals | NQ | NQ | <0.01 | <0.01 | NQ | NQ | NQ |
| Blood | NQ | NQ | <0.01 | <0.01 | <0.01 | NQ | NQ |
| Bone | NQ | NQ | <0.01 | <0.01 | NQ | NQ | NQ |
| Brain | NQ | NQ | NQ | NQ | NQ | NQ | NQ |
| Carcass | NQ | NQ | 0.10 | NQ | NQ | NQ | NQ |
| Duodenum | NQ | NQ | NQ | <0.01 | <0.01 | NQ | <0.01 |
| Fat | NQ | NQ | NQ | <0.01 | NQ | NQ | NQ |
| *GIT* | NQ | NQ | <0.01 | <0.01 | NQ | NQ | NQ |
| Gonads | NQ | NQ | NQ | <0.01 | <0.01 | NQ | NQ |
| Heart | NQ | NQ | NQ | NQ | NQ | NQ | NQ |
| Kidneys | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | NQ |
| Liver | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | NQ | NQ |
| Lungs | NQ | NQ | NQ | NQ | NQ | NQ | NQ |
| Lymph nodes | NQ | NQ | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 |
| Sk. muscle | NQ | NQ | NQ | NQ | NQ | NQ | NQ |
| *Pancreas* | NQ | NQ | NQ | NQ | NQ | NQ | NQ |
| Skin | 0.24 | 0.11 | NQ | NQ | 0.52 | 0.18 | NQ |
| Spleen | NQ | NQ | NQ | NQ | NQ | NQ | NQ |
| Thymus | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | <0.01 | NQ |
| Thyroid | NQ | NQ | NQ | NQ | NQ | NQ | NQ |
| Uterus | - | <0.01 | - | NQ | - | <0.01 | - |
| Total Tissue & Carcass (b) | 0.25 ± 0.11 | 0.15 ± 0.13 | 0.12 ± 0.14 | 0.02 ± 0.00 | 0.55 ± 0.33 | 0.18 ± 0.09 | 0.02 ± 0.02 |

(a) Data extracted from pages 64 -65 of the study report
(b) Data for total % of administered dose recovered in tissue/carcass extracted from pages 53-54 of the study report.
NQ - Not quantifiable.

### 3. Excretion

**a) Single low dose (both sexes):** As summarized in Table 5, the major route of excretion after single low-dose

administration was via the urine in both sexes. In males, approximately 90.2 and 6.8% of the administered dose was recovered in the urine and faeces, respectively. The corresponding values for females were approximately 91.7 and 6.5%, respectively. Excretion was rapid, with a majority of the radioactivity being eliminated within 12 hours post-dosing via the urine and within 24 hours post-dosing via the faeces. At 24 hours, less than 0.5% of the administered dose was observed in the expired air. At sacrifice (168 hours post-dosing) less than 0.3% of the administered dose was observed in the carcass and tissues. Less than 1% of the administered dose was recovered in the cage wash. Total recovery was approximately 98.1 and 99.2% of the administered dose for males and females, respectively. The urinary excretion rate (half-life) was 3.4 and 3.6 hr in males and females, respectively (Table 3). There were no significant sex-related differences in the excretion of $^{14}$C-XR-570 (aniline labelled).

**b) Low dose with pretreatment (both sexes):** As summarized in Table 5, the major route of excretion following repeat low-dose administration was via the urine in both sexes. In males, approximately 90.5 and 6.5% of the administered dose was recovered in the urine and faeces, respectively. The corresponding values for females were 90.1 and 5.3%, respectively. Excretion was rapid, with a majority of the radioactivity being eliminated within 12 hours post-dosing via the urine and within 24 hours post-dosing via the faeces. At sacrifice (168 hours post-dosing) less than 0.15% of the administered dose was recovered in the carcass and tissues. Less than 0.5% of the administered dose was recovered in the cage wash. Recovery in expired air was not determined. Total recovery was approximately 97.3 and 95.9% of the administered dose for males and females, respectively. There were no significant sex-related differences in the excretion of $^{14}$C-XR-570 (aniline labelled). Excretion was not significantly influenced by repeat low-dose administration compared to single low-dose administration.

**c) Single high dose (both sexes):** As summarized in Table 5, the major route of excretion following single high-dose administration was via the urine in both sexes. In males, approximately 81.5 and 16.7% of the administered dose was recovered in the urine and faeces, respectively. The corresponding values for females were 84.6 and 14.2%, respectively. Excretion was rapid, with a majority of the radioactivity being eliminated within 12 hours post-dosing via the urine and within 24 hours post-dosing via the faeces. At 24 hours, less than 0.5% of the administered dose was observed in the expired air. At sacrifice (168 hours post-dosing) less than 0.6 and 0.2% of the administered dose was recovered in the carcass and tissues in males and females, respectively. Less than 0.6 and 1.3% of the administered dose was recovered in the cage wash in males and females, respectively. Total recovery was approximately 99.2 and 100.2% of the administered dose for males and females, respectively. The urinary excretion rate (half-life) was 4.8 and 4.9 hr in males and females, respectively (Table 3). There were no significant sex-related differences in the excretion of $^{14}$C-XR-570 (aniline labelled). In the single high-dose group urinary excretion was slightly lower and faecal excretion was slightly higher compared to single low-dose administration.

**d) Single low dose - pyrimidine labelled (males only):** As summarized in Table 5, the major route of excretion following single low-dose administration (pyrimidine label) was via the urine. Approximately 85.9 and 6.7% of the administered dose was recovered in the urine and faeces, respectively. Excretion was rapid, with a majority of the radioactivity being eliminated within 12 hours post-dosing via the urine and within 24 hours post-dosing via the faeces. At sacrifice (168 hours post-dosing) less than 0.1% of the administered dose was recovered in the carcass and tissues. Less than 0.2% of the administered dose was recovered in the cage wash. Recovery in expired air was not determined. Total recovery was approximately 96.4% of the administered dose. The urinary excretion rate (half-life) was 3.4 hr (Table 3). At the low-dose, there were no significant differences in excretion between the $^{14}$C-aniline labelled XR-570 and $^{14}$C-pyrimidine labelled XR-570 groups.

**TABLE 5: Recovery of radioactivity in tissues and excreta of rats after oral administration of $^{14}$C-*aniline* labelled XR-570 or $^{14}$C-pyrimidine labelled XR-570. (a)**

| Time (hours) | Radioactivity Recovered (mean % of administered dose ± SD for 5 rats) | | | | | | |
|---|---|---|---|---|---|---|---|
| | Single low-dose aniline labelled | | Repeated low-dose aniline labelled | | Single high-dose aniline labelled | | Single low-dose pyrimidine labelled |
| | Male | Female | Male | Female | Male | Females | Males only |
| **Urine** | | | | | | | |
| **0 - 12** | 82.7 ± 10.0 | 86.1 ± 5.45 | 84.4 ± 4.35 | 85.0 ± 2.31 | 62.9 ± 3.98 | 63.1 ± 11.0 | 85.9 ± 1.44 |
| **12 - 24** | 2.62 ± 0.54 | 2.72 ± 0.74 | 4.46 ± 4.24 | 2.89 ± 0.55 | 14.0 ± 5.24 | 13.7 ± 5.31 | 2.07 ± 0.56 |
| **24 - 36** | 0.54 ± 0.27 | 0.80 ± 0.14 | 0.49 ± 0.07 | 0.95 ± 0.62 | 1.97 ± 1.25 | 2.06 ± 0.99 | 0.56 ± 0.31 |
| **36 - 48** | 0.39 ± 0.17 | 0.35 ± 0.12 | 0.26 ± 0.13 | 0.36 ± 0.11 | 0.55 ± 0.22 | 1.30 ± 1.55 | 0.33 ± 0.22 |
| **48 - 72** | 0.23 ± 0.15 | 0.45 ± 0.51 | 0.15 ± 0.06 | 0.25 ± 0.16 | 0.51 ± 0.26 | 1.09 ± 1.46 | 0.17 ± 0.08 |
| **72 - 168** | 3.74 ± 7.03 | 1.25 ± 1.98 | 0.69 ± 0.31 | 0.66 ± 0.16 | 1.52 ± 0.92 | 3.38 ± 3.48 | 0.47 ± 0.39 |
| **0 - 168** | **90.2 ± 2.8** | **91.7 ± 4.1** | **90.5 ± 0.4** | **90.1 ± 1.4** | **81.5 ± 3.2** | **84.6 ± 5.6** | **89.5 ± 0.6** |
| **Faeces** | | | | | | | |
| **0 - 24** | 5.26 ± 2.14 | 3.22 ± 1.25 | 4.82 ± 1.98 | 4.46 ± 0.75 | 14.85 ± 2.63 | 11.51 ± 4.58 | 5.88 ± 1.83 |
| **24 - 48** | 0.88 ± 0.68 | 2.03 ± 1.54 | 0.55 ± 0.30 | 0.45 ± 0.14 | 1.14 ± 0.32 | 1.53 ± 0.51 | 0.57 ± 0.39 |
| **48 - 72** | 0.12 ± 0.08 | 0.22 ± 0.28 | 0.13 ± 0.06 | 0.05 ± 0.02 | 0.21 ± 0.09 | 0.32 ± 0.28 | 0.17 ± 0.14 |
| **72 - 168** | 0.57 ± 0.37 | 0.99 ± 1.02 | 0.19 ± 0.21 | 0.09 ± 0.07 | 0.45 ± 0.40 | 0.79 ± 0.74 | 0.13 ± 0.11 |
| **0 - 168** | **6.8 ± 3.0** | **6.5 ± 3.1** | **6.5 ± 1.7** | **5.3 ± 0.8** | **16.7 ± 2.5** | **14.2 ± 4.0** | **6.7 ± 1.7** |
| **Expired Air** | <0.5 | <0.5 | - | - | <0.5 | <0.5 | - |
| **Tissue & Carcass** | 0.25 ± 0.11 | 0.15 ± 0.13 | 0.12 ± 0.14 | 0.02 ± 0.00 | 0.55 ± 0.33 | 0.18 ± 0.09 | 0.02 ± 0.02 |
| **Cage Wash** | 0.83 ± 0.81 | 0.96 ± 0.61 | 0.21 ± 0.27 | 0.45 ± 0.53 | 0.53 ± 0.42 | 1.24 ± 1.24 | 0.18 ± 0.13 |
| **Total Recovery** | **98.1 ± 1.0** | **99.2 ± 1.3** | **97.3 ± 1.4** | **95.9 ± 1.5** | **99.2 ± 1.2** | **100.2 ± 1.9** | **96.4 ± 2.0** |

(a) Data extracted from pages 53-54, 58-59 and 61-62 of the study report.

**B. Metabolite characterization studies**: Metabolic profile in excreta of rats dosed with $^{14}$C-aniline labelled XR-570 or $^{14}$C-pyrimidine labelled XR-570 is summarized in Table 6.

Three radiolabelled peaks were observed in the urine. The major peak was identified as the unchanged parent compound, XR-570, this represented >70% of the administered dose in all dose groups. For the aniline labelled $^{14}$C-XR-570, the parent compound represented 74.9/82.3% of administered dose for ♂/♀ following single low-dose administration, 75.4/80.7% of the administered dose for ♂/♀ following repeat low-dose administration and 71.1/74.4% of the administered dose for ♂/♀ following single high-dose administration. For the pyrimidine labelled $^{14}$C-XR-570, the parent compound represented 76.3% of the administered dose for males following single low-dose administration. The two minor peaks were identified as OH-phenyl-XR-570 and OH-phenyl-XR-570 sulfate conjugate, accounting for approximately 2-6 and 2-4% of the administered dose, respectively. The OH-phenyl-XR-570 sulfate conjugate metabolite was either not quantifiable or was not detected in the urine of females in all dose groups.

Four radiolabelled peaks were observed in the faecal extracts. The major peak was identified as the unchanged parent compound, XR-570, accounting for approximately 2-4% of the administered dose following single low-dose and repeat low-dose administration and approximately 10-12% of the administered dose following single high-dose administration. The second peak was identified as OH-phenyl-XR-570, accounting for approximately 0.4-3% of the administered dose for all dose groups. Two minor peaks were not identified, however, neither represented more than 0.32% of the administered dose. The sulfate conjugate of the OH-phenyl-XR-570 was not observed in the faecal extracts in either sex.

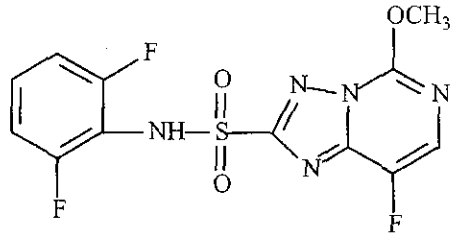
Metabolites in the urine and faeces revealed no evidence of hydrolysis of the sulphonamide bridge. There were no significant sex-related differences in the metabolic profile of $^{14}$C-XR-570 (aniline labelled) in any dose group, although the OH-phenyl-XR-570 sulfate conjugate metabolite was either not quantifiable or not detected in the urine of females in all dose groups. The metabolic profile was not significantly influenced by repeat low-dose administration compared to single low-dose administration. With the exception of slightly increased levels of the unchanged parent compound in the faecal extract, there were no significant differences in the metabolic profile between the single low- and high-dose group, no additional metabolites were observed in the single high-dose group. There were no significant differences in the metabolic profile between the single low-dose aniline labelled group and single low-dose pyrimidine labelled group. A proposed metabolic pathway for XR-570 (florasulam) is summarized in Figure 1.

**TABLE 6. Metabolite profile in excreta of rats after oral administration of $^{14}$C-aniline labelled XR-570 or $^{14}$C-pyrimidine labelled XR-570. (a)**

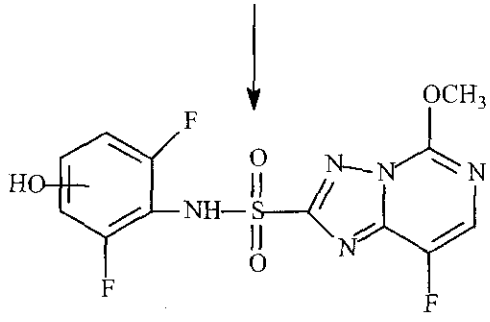
| Component | Percent of administered dose | | | | | |
|---|---|---|---|---|---|---|
| | Total Urine (b) | | Total Faeces (c) | | Total Urine + Faeces | |
| | Male | Female | Male | Female | Male | Female |
| **Single Low-Dose Aniline Labelled** | | | | | | |
| Parent XR-570 | 74.94 | 82.33 | 2.72 | 2.66 | 77.66 | 84.99 |
| OH-phenyl-XR-570 | 4.96 | 3.75 | 2.23 | 0.42 | 7.19 | 4.17 |
| OH-phenyl-XR-570 Sulfate Conjugate | 2.77 | ND | ND | ND | 2.77 | - |
| Unidentified Metabolite 1 | ND | ND | 0.18 | ND | 0.18 | - |
| Unidentified Metabolite 2 | ND | ND | 0.14 | 0.14 | 0.14 | 0.14 |
| **Repeat Low-Dose Aniline Labelled** | | | | | | |
| Parent XR-570 | 75.37 | 80.72 | 2.71 | 3.61 | 78.08 | 84.33 |
| OH-phenyl-XR-570 | 5.59 | 4.29 | 2.11 | 0.59 | 7.70 | 4.88 |
| OH-phenyl-XR-570 Sulfate Conjugate | 3.43 | NQ | ND | ND | 3.43 | - |
| Unidentified Metabolite 1 | ND | ND | ND | ND | - | - |
| Unidentified Metabolite 2 | ND | ND | NQ | 0.25 | - | - |
| **Single High-Dose Aniline Labelled** | | | | | | |
| Parent XR-570 | 71.13 | 74.49 | 11.56 | 10.53 | 82.59 | 85.02 |
| OH-phenyl-XR-570 | 2.17 | 2.30 | 2.97 | 0.83 | 5.14 | 3.13 |
| OH-phenyl-XR-570 Sulfate Conjugate | 3.62 | NQ | ND | ND | 3.62 | - |
| Unidentified Metabolite 1 | ND | ND | ND | ND | - | - |
| Unidentified Metabolite 2 | ND | ND | 0.32 | 0.16 | 0.32 | 0.16 |
| **Single Low-Dose Pyrimidine Labelled** | | | | | | |
| Parent XR-570 | 76.29 | - | 2.58 | - | 78.87 | - |
| OH-phenyl-XR-570 | 5.91 | - | 3.14 | - | 9.05 | - |
| OH-phenyl-XR-570 Sulfate Conjugate | 3.68 | - | ND | - | 3.68 | - |
| Unidentified Metabolite 1 | ND | - | ND | - | - | - |
| Unidentified Metabolite 2 | ND | - | 0.16 | - | 0.16 | - |

(a) Data extracted from pages 60 and 63 of the study report
(b) Urine sample time for single and repeat low-dose aniline labelled and single low-dose pyrimidine label was 0-12 hours. Urine sample time for single high-dose aniline label was 0-12 and12-24 hours, total urine values represented in the table are for 0-12 and 12-24 hours combined.
(c) Faecal sample time for all dose groups was 0-24 hours.
ND - Not detected.
NQ - Not quantifiable (Average LOQ = 1.03% of dose for urine and 0.13% of dose for faeces)

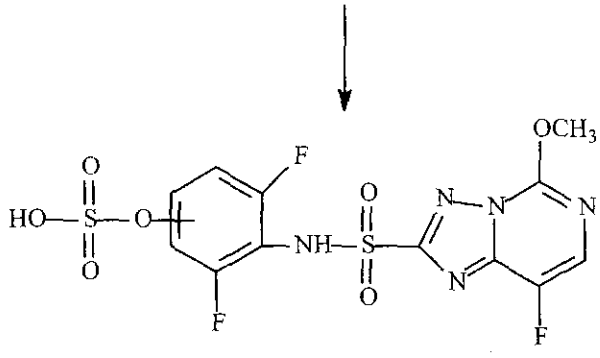
**Figure 1: Proposed Metabolic Pathway for XR-570 in Rats Following Oral Administration (extracted from page 50 of the study report, Laboratory Project ID - HET DR 0312-6565-014).**



**Parent XR-570 (Present in urine and faeces)**



**OH-phenyl-XR-570 (Present in urine and faeces)**



**OH-phenyl-XR-570 Sulfate Conjugate (Present in the urine)**

**III. DISCUSSION**

**A. Investigators' conclusions (extracted from pages 8-9 of study report)**: "A total of 96-100% of the administered radioactivity was recovered from all dose groups. The principle route of excretion was the urine,

which contained an average of 81-92% of the administered radioactivity. The faces contained 5-17% of the dose and the final cage wash accounted for <2% of the administered radioactivity. After 168 hr post-dosing, less than 0.6% of the administered dose was recovered in the tissues. Radioactivity was <0.1% of the dose or non-quantifiable in the majority of tissues and carcasses. Overall, the pharmacokinetic parameters which describe the 10 mg/kg doses were very similar and were nearly identical for male and female rats. Average plasma half-lives for the α (distribution) and β (elimination) phase were (0.4-0.6) and (8.1-8.7) hr, respectively, for rats administered 10 mg/kg $^{14}$C-XR-570. Equivalent area under the curve values for plasma of ~27 and 24 µg eq hr /g were calculated for rats administered aniline or pyrimidine labeled 10 mg/kg $^{14}$C-XR-570, respectively. In addition, clearance values were very comparable and ranged from 6.8-7.2 ml/min kg for the 10 mg/kg dose groups. Following the administration of 500 mg/kg $^{14}$C-XR-570, plasma half-lives for the α and β phases were ~1 and 5 hr, respectively. Rats given 500 mg/kg $^{14}$C-XR-570 had area under the curve values for male and female rats of 3328 and 2523 µg eq hr / g, respectively and clearance values of 2.6 hr (males) and 3.3 hr (females), indicating similarities across sexes. The rate of radioactivity excreted in the urine was essentially the same for rats given 10 mg/kg $^{14}$C-XR-570 with half-lives of 3.2-3.7 hr. Rats administered 500 mg/kg $^{14}$C-XR-570 had urinary half-lives of 4.8-4.9 hr. Up to 4 $^{14}$C-peaks were found in the feces and 3 in the urine via HPLC. The major peak was confirmed to be unchanged parent and represented >75% and 2-12% of the radioactive dose in the urine and feces, respectively. Two of the minor peaks were characterized as OH-phenyl-XR-570 and a sulfate conjugate of OH-phenyl-XR-570. In summary, these data indicate that XR-570 is extensively absorbed (92% and 85% for the 10 and 500 mg/kg dose groups, respectively), distributed nearly identically across dose groups, and then rapidly eliminated primarily in the urine as unchanged parent XR-570. Metabolites in the urine and feces revealed no evidence of hydrolysis of the sulfonamide bond. Dosing with 500 mg/kg of $^{14}$C-XR-570 and repeated administration of XR-570 resulted in no additional metabolites in the 0-24 hr feces. In addition, due to its rapid elimination, XR-570 has little potential to accumulate upon repeated administration."

**B: Reviewer comments:** Following single or repeat oral low-dose or single oral high-dose administration, $^{14}$C-XR-570 was extensively and rapidly absorbed in both sexes. Peak plasma concentrations (Cmax) were achieved within 0.5-1 hour following either single low- or high-dose administration. Based on the available urinary data (radioactivity detected in the urine, tissues/carcass and cage rinse), the estimated proportion of the administered dose absorbed was approximately 90-93% following single or repeat low-dose administration and approximately 82-86% following single high-dose administration. Following single high-dose administration, Cmax was not increased proportionately to the administered dose and plasma clearance was reduced compared to the single low-dose exposure which may suggest a saturation of absorption and / or saturable renal excretion at the high dose. The higher plasma clearance following single low-dose administration suggests a more efficient and rapid removal of the test substance at the low dose. The apparent volume of distribution was increased following high-dose administration which may suggest increased binding to tissues at this dose level. The highest residue levels were observed in skin (single low- and high-dose) and carcass (repeat low-dose). However, the mean recovery of radioactivity in the tissues/carcass at sacrifice (at 168 hours post-dosing) was <0.6% of the administered dose for all dose groups indicating little potential for accumulation. Excretion was rapid, with a majority of the radioactivity being eliminated within 12 hours post-dosing via the urine (>80 and 60% of the administered dose following single or repeat low-dose administration and single high-dose administration, respectively) and within 24 hours via the faeces (3-6 and 11-15% of the administered dose following single or repeat low-dose administration and single high-dose administration, respectively). The urinary excretion rate (half-life) was approximately 3-4 hours at the low dose and approximately 5 hours at the high dose. By 24 hours post-dosing, plasma levels declined to <0.1 µg eq/g plasma in both sexes at the low dose and to <5.0µg eq/g plasma in both sexes at the high-dose. The major route of excretion was via the urine, accounting for approximately 90-92% of the administered dose following single or repeat low-dose administration and approximately 81-85% following single high dose administration. The corresponding values for faecal excretion were approximately 5-7% following single or repeat low-dose administration and approximately14-17% following single high-dose administration. At 24 hours, less than 0.5% of the administered dose was excreted via expired air. No bile data was included with this study. The major component in the urine and faecal extracts was identified as the unchanged parent compound, XR-570, representing approximately 77-85% of the administered dose. Two other metabolites found in the excreta were characterized as OH-phenyl-XR-570 (≈3-10% of the administered dose) and a sulfate conjugate of OH-phenyl-XR-570 (≈2-4% of the administered dose). Two minor peaks were not identified, however, neither represented more than 0.32% of the administered dose. The sulfate conjugate of the OH-phenyl-XR-570 was not observed in the faecal extracts and was

either not quantifiable or not detected in the urine of females. Metabolites in the urine and faeces revealed no evidence of hydrolysis of the sulphonamide bridge. A proposed metabolic pathway is summarized in Figure 1. There were no significant differences in absorption, distribution, metabolism or excretion or changes in pharmacokinetic parameters between the low-dose aniline labelled and pyrimidine labelled groups. Absorption, distribution, metabolism and excretion were not influenced by repeat low-dose oral administration. There were no significant sex-related differences in absorption, distribution, metabolism or excretion following single or repeat low-dose administration or single high-dose administration.

C. **Study deficiencies:** - There were no deficiencies that would impact upon the outcome of the study. This metabolism study in the rat is classified acceptable and satisfies the guideline requirement for a metabolism study (OPPTS 870.7485; OECD 417) in rats.