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STUDY TITLE

Report

¹⁴C-4,4'-sulphonyldiphenol
Study on kinetics in Wistar rats
after oral administration

TEST GUIDELINE(S)

OECD Guideline No. 417
OPPTS 870.7485
Commission Regulation (EC) No 440/2008
Japan/MAFF

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STUDY COMPLETION DATE

04 Sep 2019

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STATEMENT OF THE QUALITY ASSURANCE UNIT

The Quality Assurance Unit (QAU) inspected the study and reported any inspection results to the Study Director and to Test Facility Management.

The final report reflects the raw data.

Phase of study:	Date of inspection (mm-dd-yyyy)	Reported to Study Director and to Test Facility Management (mm-dd-yyyy)
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Conduct of study:	01-29-2018	01-29-2018
	02-13-2018	02-13-2018
	02-15-2018	02-15-2018
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	03-13-2018	03-13-2018
	03-15-2018	03-15-2018
	04-05-2018	04-05-2018
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	05-28-2018	05-28-2018
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Ludwigshafen,

03 Sep 2019

GLP CERTIFICATE (FROM THE COMPETENT AUTHORITY)



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gemäß/according to § 19b Abs. 1 Chemikaliengesetz

Eine GLP-Inspektion zur Überwachung der Einhaltung der GLP-Grundsätze gemäß Chemikaliengesetz bzw. Richtlinie 2004/9/EG wurde durchgeführt in: Assessment of conformity with GLP according to Chemikaliengesetz and Directive 2004/9/EC at:

Prüfeinrichtung / Test facility

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Prüfung nach Kategorien / Areas of Expertise

(gemäß / according ChemVwV-GLP Nr. 5.3/OECD guidance)

1,2,3,4,5,8,9

Kat. 9 – Biochemische und pathologische Untersuchungen zu Wirkmechanismen /
Biochemical and pathological examinations concerning mode of action

Datum der Inspektion / Date of Inspection

(Tag.Monat.Jahr / day.month.year)

12. bis 14.09.2016

Die genannte Prüfeinrichtung befindet sich im nationalen GLP-Überwachungsverfahren und wird regelmäßig auf Einhaltung der GLP-Grundsätze überwacht.

Auf der Grundlage des Inspektionsberichtes wird hiermit bestätigt, dass in dieser Prüfeinrichtung die oben genannten Prüfungen unter Einhaltung der GLP-Grundsätze durchgeführt werden können.

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The above mentioned test facility is included in the national GLP Compliance Programme and is inspected on a regular basis.

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Verification of the compliance of the test facility with the Principles of the GLP has to be applied for not later than three years after the last inspection. Elapsing this term, the test facility will be taken out of the German GLP-Monitoring Programme and this GLP Certificate becomes invalid.

Unterschrift, Datum / Signature, Date

Dr.-Ing. Stefan Hill - Präsident -

(Name und Funktion der verantwortlichen Person /
name and function of responsible person)

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Name and address of the GLP Monitoring Authority)

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9. APPENDICES

Appendix 1: Certificate of Analysis of the radio-labeled test substance
 ^{14}C -4,4'-sulphonyldiphenol

Appendix 2: Certificate of Analysis of the ^{13}C -labeled test substance
 ^{13}C -4,4'-Dihydroxydiphenylsulfon

Appendix 3: Characterization of "4,4'-dihydroxydiphenylsulfone"

Appendix 4: Sample HPLC-radio-chromatogram of test-substance preparation
(concentration control before administration, experiment 2)

Appendix 5: Sample HPLC-radio-chromatogram of test-substance preparation
(concentration control after administration, experiment 2)

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1. SUMMARY

This report outlines the results of an investigation on the absorption, distribution, elimination and plasma kinetics of ^{14}C -4,4'-sulphonyldiphenol in male and female Wistar rats.

For plasma kinetics, four animals per gender and dose group were treated with ^{14}C -4,4'-sulphonyldiphenol and blood samples were taken in general from the vena saphena at the following time points: 1, 2, 4, 8, 24, 48, 72, 96, 120, 144 and 168 hours after oral dosing.

For mass balance, four animals per gender and dose group were treated with ^{14}C -4,4'-sulphonyldiphenol and urine was collected after 6, 12 and 24 hours and subsequently at 24-hour time intervals up to 168 hours and feces at 24-hour time intervals up to 168 hours. In the low dose balance experiment (experiment 4), the first two male animals were placed in closed metabolism cages in order to additionally collect exhaled air for 48 hours to demonstrate that less than 2 % of the total radioactive dose were detected in exhaled air and to justify that balance experiments were carried out in open systems.

For experiments performed to investigate biliary excretion, bile ducts of animals were cannulated and six animals per gender and dose group were treated orally with ^{14}C -4,4'-sulphonyldiphenol. After treatment, the animals were placed in metabolism cages, and bile was collected at 3 h intervals as well as urine and feces at 24 h intervals up to 72 h, depending on the health state of the animals and the bile flow.

For tissue distribution experiments, three animals per gender, dose group and time point were treated orally. To achieve information on a potential time-dependent decrease of radioactivity in blood, organs and tissues, animals were sacrificed at four different time points, which were selected based on the results of the plasmakinetic experiments (experiments 1 and 2) and corresponded to the time points of maximum plasma concentration (MPC), second MPC (due to assumed enterohepatic recirculation), 1/2 MPC and 1/4 MPC.

The concentrations of the radioactive residues in the target matrices were analysed by liquid scintillation counting after appropriate sample work-up.

In plasmakinetics, maximum plasma concentrations occurred 1 and 4 hours after oral administration of the high and low dose. The presence of two maxima in plasmakinetics may be explained by a potential enterohepatic recirculation. Radioactivity declined rapidly post dosing and mean concentration below loq were generally found 72 hours post dosing. The AUC values indicate a sex independent internal exposure. Increasing the dose by a factor of about 10 (from target dose level of 30 to 300 mg/kg bw) an increase of the AUC-values by a factor of about 14 for male and female animals was measured. Taken together, plasma kinetics of ^{14}C -4,4'-sulphonyldiphenol within the current study demonstrated high absorption, potential enterohepatic recirculation, fast excretion and a supra-linear correlation of the internal exposure to oral dose. A comparable time course of radioactivity was found for blood as for plasma in both sexes.

The parameters derived from the plasma kinetics are presented in the following table:

Sex	target dose [mg/kg bw]	mean actual nominal dose [mg/kg bw]	C _{MAX} [µg Eq/g]	T _{MAX} [h]	half life [h]	AUC _{0--∞} [µg Eq*h/g]
male	300	305.5	58.16; 27.48	1; 4	10.3	1005
male	30	30.2	8.66; 3.81	1; 4	9.2	74
female	300	304.7	104.93; 26.47	1; 4	14.7	1083
female	30	30.3	6.59; 4.55	1; 4	8.9	80

After a single oral administration of the target doses of 300 mg/kg bw and 30 mg/kg bw of ¹⁴C-4,4'-sulphonyldiphenol as well as after 14 doses with unlabelled DHDPS followed by one oral dose of ¹⁴C-4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw mean total recoveries of radioactivity between 90 % and 110 % of the dose for all experiments.

For the high dose group, mean total urinary excretions accounted for 48.05 % (male) and 39.02 % of the dose (female). Mean excretions via feces were 44.20 % and 55.71 % of the dose in male and female rats, respectively. For rats treated once or repeatedly with the low dose, mean urinary excretions amounted to 60.13 % (single dosing) and 51.09 % (repeated dosing) of the dose for males and for 51.45 % (single dosing) and 51.82 % (repeated dosing) of the dose for females. Mean excretions via feces accounted for 43.00 % and 42.33 % of the dose for males treated once or repeatedly, respectively, and were 40.85 % and 43.99% of the dose for females treated once and repeatedly, respectively. These data indicate a rapid excretion occurring predominantly within two days after single or multiple administration. The total amounts of excreted radioactivity reflected more than 90 % of the administered dose for both genders. Furthermore, neither gender- nor dose-dependent differences in excretion patterns were observed.

The bile excretion study was performed after bile duct catheterization as a balance experiment and bile, urine and feces were collected up to 72 hours from rats that were dosed with ¹⁴C-4,4'-sulphonyldiphenol at target doses of 300 mg/kg bw and 30 mg/kg bw. Based on the data of excreted radioactivity via bile and urine as well as on the remaining radioactive residue in carcass, the oral absorption of ¹⁴C-4,4'-sulphonyldiphenol was calculated. The total recoveries in the bile excretion experiments demonstrated the validity of the applied study design. Within 72 hours after administration of ¹⁴C-4,4'-sulphonyldiphenol at a dose level of 300 mg/kg bw, mean excretion via bile was found to be 43.81 % and 45.65 % of the administered radioactivity in males and females, respectively. Mean total excretion of radioactivity via urine after 72 hours was 47.52 % for males and 48.91 % for females. At the low dose level (30 mg/kg bw.), excretion via bile was found to be 56.39 % and 38.21 % of the administered radioactivity in males and females, respectively. Total excretion of radioactivity via urine after 72 hours was 37.72 % for males and 46.37 % for females.

Based on the amounts of radioactivity excreted via bile and urine, as well as the radioactive residues found in cage wash and carcass, the oral absorption of ¹⁴C-4,4'-sulphonyldiphenol

in rats was calculated to be about 93 % and 96 % of the administered dose for males and females at a dose of 300 mg/kg bw as well as 95 % and 87 % of the administered dose for males and female rats at a dose level of 30 mg/kg bw, respectively.

Following a single oral dose of ^{14}C -4,4'-sulphonyldiphenol at a dose level of 300 mg/kg bw, tissue distribution was measured 1, 4, 36 and 46 hours post-dosing in males and 1, 4, 37 and 50 hours post-dosing in females. At the low dose level of 30 mg/kg bw, the corresponding radioactivity measurements were performed 1, 4, 18 and 25 hours as well as 1, 4, 17 and 22 hours after administration in males and females, respectively.

1 hour after administration of 300 mg/kg bw ^{14}C -4,4'-sulphonyldiphenol to male and female rats highest tissue concentrations (means) were found in the GI-tract/GI-tract contents. With the exception of the GI-tract (including its content), highest residues (means) in male rats were found in kidney, liver, plasma, carcass, lung and skin and lowest mean radioactive residues at this time point were measured in adipose tissue, brain and bone. With the exception of the GI-tract (including its content), highest residues (means) of the high dose group in female rats 1-hour post dosing were found in brain, plasma liver, thyroid, pancreas, lung, skin and carcass. Lowest mean radioactive residues at this time point were measured in adipose tissue, bone and kidney.

At 1 hour after oral administration of 30 mg/kg bw ^{14}C -4,4'-sulphonyldiphenol to male and female rats, highest tissue concentrations (means) were found in the GI tract/GI-tract contents. With the exception of the GI-tract (including its content), highest residues (means) in male rats were found in liver and kidney. For male animals, lowest mean radioactive residues at this time point were measured in brain, adipose tissue and bone. With the exception of the GI-tract (including its content), highest residues (means) in female rats 1 hour post oral dosing of 30 mg/kg bw ^{14}C -4,4'-sulphonyldiphenol were found in liver, kidney and thyroid. For female animals, lowest mean radioactive residues at this observation time point were measured in brain, bone, adipose tissue and muscle.

For both sexes and in both dose groups, radioactive residue concentrations generally declined in organs and tissues from the 1 h time point on and parallel to the radioactive residues in plasma. In contrast to this general trend, radioactive residues in carcass decreased slower than the general trend in other organs and tissues, especially in the high dose group tested. With the exception of radioactive residues in carcass samples, tissue distribution experiments showed a generally sublinear correlation between the radioactive residues in organs and tissues and the administered dose. For carcass samples, the radioactive residues are overproportional to dose. This overproportional ratio is more pronounced at later sampling time points.

Taken together, ^{14}C -4,4'-sulphonyldiphenol was rapidly absorbed from the gastrointestinal tract. Calculations based on the bile excretion experiments showed that about 93 and 96 % of the administered dose were absorbed at a dose level of 300 mg/kg bw for male and female rats, respectively, whereas about 95% of the administered dose were absorbed for males and 87 % of the administered dose were absorbed for females at a dose level of 30 mg/kg. The excretion of radioactivity occurred mainly within two days after dosing, generally with a high excretion via urine and bile. Plasma kinetics confirmed high oral absorption and demonstrated potential enterohepatic recirculation, fast excretion and a slight supra-linear correlation of the internal exposure to the oral dose. Tissue distribution experiments showed generally sublinear correlation between radioactive residues in organs and tissues, but supralinear correlation between radioactive residues in carcass and the external dose.

2. INTRODUCTION

2.1. OBJECTIVES

¹⁴C-4,4'-sulphonyldiphenol is used in curing fast-drying epoxy glues and as a corrosion inhibitor. It is also commonly used as a reactant in polymer reactions. The aim of this study was to generate information on the kinetics of radio-labeled test substance in rats. Studies on the biokinetics of a test substance provide relevant information for the evaluation of test results from toxicological studies and for the extrapolation of data from animals to man.

Another objective of the study was to generate samples for metabolism investigations. These samples were investigated at Consumer Safety within the test facility "Crop Protection - Global Metabolism & Structure of BASF SE, Speyerer Straße 2, 67117 Limburgerhof, Germany" under the responsibility of a separate study director under the AP study ID 858428.

2.2. SELECTION OF DOSES/CONCENTRATIONS

At request of the sponsor, the following dose levels were selected for the present study:

Oral administration:	dose 1 (high dose)	300	mg/kg bw
	dose 2 (low dose)	30	mg/kg bw

The administration route and doses were selected in agreement with the sponsor and in relation to already performed studies.

2.3. TEST GUIDELINES

The study was conducted according to following test guidelines:

- Commission Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), Part B: Methods for the determination of toxicity and other health effects: Toxicokinetics; Official Journal of the European Union, No. L 142
- OECD Guidelines for Testing of Chemicals; Method No. 417 Toxicokinetics, Version dated 23 July 2010
- U.S. EPA, Health Effects Test Guidelines, OPPTS 870.7485, Metabolism and Pharmacokinetics, August 1998
- Japan/MAFF: Guidelines on the Compiling of Test Results on Toxicity; Tests on In Vivo Fate In Animals, 2001

2.4. STUDY DATES / TIME SCHEDULE

Test dates:	Study initiation date:	06 Nov 2017
	Experimental starting date: (arrival of test animals)	16 Jan 2018
	Experimental completion date: (last LSC measurement)	10 Aug 2018

2.5. RETENTION OF RECORDS

GLP-relevant records and materials are archived at BASF SE for at least the period of time specified in the GLP principles. This includes the study plan, any amendments, raw data, test/ positive/ reference item samples (if applicable in this study), specimens (according to test facility SOPs and as appropriate for this study type) and the study report. Details concerning responsibilities or locations of archiving can be seen from the respective SOPs as well as from the raw data.

Defined samples that were produced within this study (urine, feces and bile) were investigated within a metabolism study. This metabolism study was performed by Consumer Safety within the Test facility "Crop Protection - Global Metabolism & Structure of BASF SE, Speyerer Straße 2, 67117 Limburgerhof, Germany". This study was conducted under a separate GLP study (AP study ID 858428) under the responsibility of a study director of this test facility.

2.6. ANIMAL WELFARE

This study was performed in an AAALAC-approved laboratory in accordance with the German Animal Welfare Act and the effective European Council Directive.

3. MATERIALS AND METHODS

3.1. TEST ITEM

The analyses of the labeled test items (= test substances) were carried out at the Crop Protection - Ecology and Environmental Analytics of BASF SE, Speyerer Straße 2, 67117 Limburgerhof, Germany

The analyses of the non-labeled test item (= test substance) was carried out at the Competence Center Analytics of BASF SE, 67056 Ludwigshafen, Germany

3.1.1. ¹⁴C-labeled test substance

Name of test substance: ¹⁴C-4,4'-sulphonyldiphenol

Test substance No.: 17/0423-1

Batch identification: 1248-1101

Radiochemical purity: > 98 %

Identity: confirmed (Certificate of Analysis (CoA), Study code: IL1248_1017)

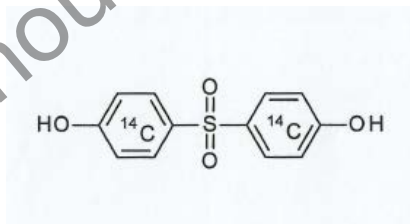
Homogeneity: given

Storage stability: see 4.1.

ADDITIONAL TEST SUBSTANCE INFORMATION

Chemical name: ¹⁴C-4,4'-sulphonyldiphenol

Molecular structure:



Molecular weight (non-labeled): 250.3 g/mol

Synonym: 14C-Reg.No. 63265; Bisphenol S; BPS; dihydroxydiphenylsulfone; DHDPS

Radio label: phenyl-U-C14

Specific activity of AI: 13.2 MBq/mg

Specific activity: 59.6 MBq/g in acetonitrile
Concentration of AI: 4.45 mg/g in acetonitrile
Chemical purity: 90.3 %
Storage conditions freezer

3.1.2. ^{13}C -labeled test substance

Name of test substance: ^{13}C -4,4'-Dihydroxydiphenylsulfon
Test substance No.: 17/0532-1
Batch identification: 1248-2101
Purity: 94.0 %
Identity: confirmed (Certificate of Analysis (CoA), Study code: IL1248_2001)
Homogeneity: given
Storage stability: see 4.1.

ADDITIONAL TEST SUBSTANCE INFORMATION

IUPAC-Name: 4,4' Sulfonyldiphenol
Synonym: ^{13}C -Reg.No. 63265
Label: phenyl-1,2,3,4,5,6- ^{13}C
Storage conditions freezer

3.1.3. Non-labeled test substance

Name of test substance: DHDPS
Test substance No.: 05/0066-8
Batch identification: 03508136W0
CAS No.: 80-09-1
Content: 99.9 g/100 g (Final Report, Study code: 16L00571)

Identity: confirmed (Final Report, Study code: 16L00571)

Homogeneity: given

Storage stability: 23 Nov 2019

The stability of the test substance under storage conditions over the test period was guaranteed by the sponsor, and the sponsor holds this responsibility

The test facility is organizationally independent from the BASF SE sponsor Division.

ADDITIONAL TEST SUBSTANCE INFORMATION

Chemical name: 4,4'-Sulfonyldiphenol

Synonym: BIS-(4-HYDROXYPHENYL)-SULFON 98%, DHDPS, 4,4'-Sulfonyldiphenol, 4,4'-Dihydroxydiphenylsulfon, 4,4'-Sulfonyldiphenol, 4,4'-Dihydroxyphenylsulfon; Bisphenol S; 4,4'-dihydroxydiphenylsulfone

Physical state / appearance: solid / white

Storage conditions: ambient(RT)

3.2. TEST SYSTEM

Test species and strain: rat, Crl:WI (Han)

Reason for selection of the test species: Recognized by international guidelines as the recommended test system. Study data have to be interpreted in the context of other data from the same test system.

Age at start of acclimatization: 8 - 14 weeks

Sex: males and females

Supplier: Charles River Laboratories, 97633 Sulzfeld, Germany

Arrival in the test facility: Acclimatization period at least 5 days before the beginning of the experimental phase; during the acclimatization period, the animals were accustomed to the environmental conditions of the study and to the diet.

Body weight:	about g 245 – 356 g and 190 – 269 prior to dosing for male and female animals, respectively. (body weight was determined on the day of dosing shortly before administration and prior operation procedure (bile experiment)).
Selection of animals:	Animals were generally selected based on health status and to provide a narrow range of body weights ($\pm 20\%$ per experiment). For bile experiments, all delivered animals were cannulated and animals with sufficient bile flow were selected for the experiment. Therefore, the body of male animals of experiment 6 differ about 25 % which has no influence on the data of the bile excretion experiment (see 4.2.2.).
Health status, clinical examinations and mortality:	The health status of the animals was checked prior to and during the experiment at least once daily. Observations during necropsy were documented in the raw data.
Total animals in study:	<u>Plasmakintic experiment:</u> total 18 animals (16 animals in data assessment, 2 animals served as retain animals and were not dosed with test substance) <u>Balance experiment:</u> total 30 animals single high dose: 8 animals single low dose: 8 animals 14+1 high dose experiment: 10 animals (one substitute per sex, 8 animals dosed with radio-labeled test substance) (4 animals served as retain animals and were not dosed with test substance)

Bile experiment:

total 48 animals

high dose: 24 animals
(12 animals in data assessment)

low dose: 24 animals
(12 animals in data assessment)

(48 animals were catheterized, 12 animals per dose group were taken for the bile excretion experiment, 12 animals per dose group served as retain animals and were not dosed with test substance)

Catheterized animals that were not dosed with test substance were sacrificed under isoflurane anaesthesia.

Tissue distribution:

total 52 animals

high dose: 24 animals
(24 animals in data assessment)

low dose: 24 animals
(24 animals in data assessment)

(4 animals served as retain animals and were not dosed with test substance)

total animals in study: 148

3.3. HOUSING AND DIET

Room temperature /
relative humidity:

Animals were held under conventional hygienic conditions in an air-conditioned room at 20 - 24°C and 45 - 65% relative humidity and 15 air changes per hour. These parameters were maintained under central control.

Photoperiod:	12 hours light (6:00 h - 18:00 h) 12 hours darkness (18:00 h - 6:00 h) (light during working hours if needed)
Identification, number of animals per cage and type of cage:	<p>During acclimatization and prior to the experiment animals housed in groups (up to five animals) in polysulfonate cages (H-Temp [PSU]) supplied by TECNIPLAST, Hohenpeißenberg, Germany (floor area about 2065 cm²).</p> <p>After the surgery procedure until administration for bile experiments and multiple dosing of unlabeled test substance for balance experiments, animals were kept individually in polycarbonate type III cages supplied by Becker & Co., Castrop-Rauxel, Germany (floor area of about 800 cm²).</p> <p>During plasmakinetic and tissue distribution experiments, animals were kept individually in polycarbonate type III cages (1291H; PC, 820 cm², Tecniplast) with steel wire mesh ground (11 x 11 mm mesh wire); from radio-labeled dosing on animals for the balance experiments were kept in plastic metabolism cages (Tecniplast, Italy), except for the two male animals where the exhaled air was checked and animals in the bile excretion experiments which were kept individually in all-glass metabolism cages type Metabowl (Jencons Leighton Buzzard, U.K.), labeled with the project number, animal number, section and time of (first) administration.</p>
Diet:	<p>Kliba lab diet (mouse / rat "GLP") either pelleted or meal (depending on the experimental conditions e.g. meal for balance experiments and pellets for plasmakinetics).</p> <p>Origin: Provimi Kliba SA (new name: Granovit AG), 4303 Kaiseraugst, Switzerland ad libitum prior to and during the experiment.</p>
Drinking water:	tap water ad libitum
Bedding:	Dust-free wooden bedding was used in this study (the present supplier is documented in the raw data).
Enrichment:	<p>During acclimatization</p> <p>Play Tunnel large (Art. 14153), PLEXX b.v., Elst, Netherlands</p> <p>During acclimatization and pretreatment (non-labeled dosing for 14 days) and regeneration period (after bile surgery until administration with radio-labeled test substance):</p> <p>Lignocell Block Large; J. Rettenmaier & Söhne GmbH + Co KG, Rosenberg, Germany</p>

3.4. TEST SUBSTANCE PREPARATIONS

In order to achieve the required specific activity, appropriate amounts of the radio-labeled test substance were taken and the solvent (acetonitrile) was evaporated under N_2 . Non-labeled and, if foreseen ^{13}C -labeled test substance were taken and the aqueous vehicle (0.5% sodium carboxymethyl cellulose (CMC) in tap water) was added. For calculations, a density of 1 g/mL is assumed for the preparations in 0.5% CMC in tap water.

Due to the possibility to facilitate structure elucidation of formed metabolites in balance and bile excretion experiments (experiments 3 - 7), ^{13}C -DHDPS and non-labeled test substance were added to the preparation in a ratio of 1:2 (w:w).

The preparations were homogenized by continuous stirring for 20 to 60 minutes, additional ultra-sonication for 15 to 30 min and eventually ongoing stirring for 10 min up to 2 hours and were kept in the refrigerator until the administration day (in general for bile experiments three days, for plasmakinetics, balance and tissue distribution experiments over night). On the administration day, the preparations were stirred and/or ultrasonicated before aliquots were taken for analyses. Additional ultrasonication and/or stirring was performed when LSC results of the aliquots indicated inhomogeneity or if the activity measured was too low compared to the nominal amount (calculated by the amount of added radio-labeled test substance).

The test-substance preparation for the low dose bile experiment with male animals was prepared on the morning before administration. After stirring for 20 min, the preparation was ultrasonicated for another 15 min with additional stirring for about 10 min before aliquots were taken for analysis.

At least before start and at the end of the administration, samples were taken under stirring to determine the amount of specific activity in the preparations and to demonstrate the correct concentration of the test substance, its homogeneity, stability and as well its radiochemical purity.

Non-labeled test-substance preparations for the experiment with multiple administration were stirred for about 3 hours after preparation and were kept in the refrigerator over night. On each administration day, preparations were brought at room temperature under stirring for at least 45 min.

Homogeneity and concentration control analyses of the test substance in the non-labeled test-substance preparation was performed before the first and after the last test-substance administration of each test-substance preparation by HPLC-UV.

Plasmakinetics:

Test-substance preparations yielded nominal concentrations of 30.0 mg/g and 3.0 mg/g for the dose groups of 300 and 30 mg/kg bw, respectively (corresponding to 30 and 3 mg/mL, details are shown in table 3.4.1.). The nominal specific activity was 1.0 MBq/g for test-substance preparation for the high and low dose group.

Balance/excretion experiments:

For balance experiments, the nominal concentrations of the test substance in the preparations yielded in values of 30.0 mg/g and 3.0 mg/g for the high and low dose group, respectively (details are shown in table 3.4.2). The nominal specific activity was 1.5 MBq/g for test-substance preparation for the high and low dose group.

For dosing unlabeled test substance in the "14+1 experiment", two test-substance preparations were prepared for a maximum of 7 administration days in 0.5% CMC in drinking water with a target concentration of 3.0 mg/g. For both test-substance preparations, nominal concentrations were 3.0 mg/g.

Bile experiments:

Test-substance preparations of the high dose group yielded nominal concentrations of 30.0 mg/g for male and female animals and test-substance preparations of the low dose group yielded 3.0 mg/g for male and female animals (details are shown in table 3.4.3). The nominal specific activities of the test-substance preparations of the high dose groups yielded in 1.3 MBq/g for the male and female animals. The nominal specific activities of the test-substance preparations of both low dose groups were 1.2 MBq/g.

Tissue distribution:

For tissue distribution experiments, nominal concentrations of the test substance in the preparations were 30.0 mg/g for the animals of the high dose group and 3.0 mg/g for the animals of the low dose group (details are shown in table 3.4.4). The nominal specific activities yielded in values of 0.3 MBq/g and 0.7 MBq/g for the the high and low dose goup test-substance preparations, respectively.

Further details are described in the raw data.

Table 3.4.1.: Plasmakinetic experiments – test-substance preparations

Item prepared		component	300 mg/kg bw	30 mg/kg bw
experiment No.			1	2
			weight [g]	
test-substance preparation		¹⁴ C-4,4'-sulphonyldiphenol in solution (MBq)	0.6142 (36.6)	0.6166 (36.7)
	corresponding to	¹⁴ C-4,4'-sulphonyldiphenol	0.002733	0.002744
	including impurities		0.003027	0.003039
	added	non-labeled DHDPS	1.0829	0.1059
	added	0.5 % CMC in tap water	35.0986	36.0500
test-substance preparation			36.1845	36.1589
amount of DHDPS			1.0856	0.1086

Table 3.4.2.: Balance/excretion experiments – test-substance preparations

Item prepared		component	300 mg/kg bw	30 mg/kg bw
experiment No.			3	4 + 5
			weight [g]	
test-substance preparation		¹⁴ C-4,4'-sulphonyldiphenol in solution (MBq)	0.9235 (55.0)	1.6782 (100.0)
	corresponding to	¹⁴ C-4,4'-sulphonyldiphenol	0.004110	0.007468
	including impurities		0.004551	0.008270
	added	¹³ C-4,4'-Dihydroxydiphenylsulfon	0.3847	0.0696
	corrected with purity		0.3616	0.0654
	added	non-labeled DHDPS	0.7158	0.1286
	added	0.5 % CMC in tap water	34.9291	66.8479
test-substance preparation			36.0342	67.0544
amount of DHDPS			1.0815	0.2015

Table 3.4.3.: Bile experiments – test-substance preparations

Item prepared		component	300 mg/kg bw		30 mg/kg bw	
experiment No.			6 males	6 females	7 males	7 females
			weight [g]			
test-substance preparation		¹⁴ C-4,4'-sulphonyldiphenol in solution (MBq)	0.5991 (40.1)	0.6068 (36.2)	0.7191 (42.9)	0.5062 (30.2)
	corresponding to	¹⁴ C-4,4'-sulphonyldiphenol	0.002995	0.002700	0.003200	0.002253
	including impurities		0.003317	0.002990	0.003544	0.002495
	added	¹³ C-4,4'-Dihydroxydiphenylsulfon	0.3190	0.2884	0.0356	0.0259
	corrected with purity		0.2999	0.2711	0.0835	0.0243
	added	non-labeled DHDPS	0.5991	0.5406	0.0688	0.0485
	added	0.5 % CMC in tap water	29.1450	26.3081	35.0292	24.9245
test-substance preparation			30.0664	27.1401	35.1371	25.0014
amount of DHDPS			0.9020	0.8144	0.1055	0.0751

Table 3.4.4.: Tissue distribution – test-substance preparations

Item prepared		component	300 mg/kg bw	30 mg/kg bw
experiment No.			8	9
			weight [g]	
test-substance preparation		¹⁴ C-4,4'-sulphonyldiphenol in solution (MBq)	0.5122 (30.5)	1.0276 (61.2)
	corresponding to	¹⁴ C-4,4'-sulphonyldiphenol	0.002279	0.004573
	including impurities		0.002524	0.005064
	added	non-labeled DHDPS	2.7009	0.2657
	added	0.5 % CMC in tap water	87.3053	89.7311
test-substance preparation			90.0087	90.0019
amount of DHDPS			2.7032	0.2703

3.5. STUDY DESIGN AND TEST GROUPS

3.5.1. Administration of test material

10 mL/kg body weight of a preparation was administered orally to rats by gavage.

The test-substance preparations were brought to room temperature if stored in a refrigerator and were kept under stirring to guarantee homogeneity during the dosing period.

3.5.2. Blood/plasma concentration

In this experiments, animals were placed in steel wire mesh cages after treatment with ^{14}C -4,4'-sulphonyldiphenol and blood samples (20 – 80 μl) were taken generally mutually from the vena saphena in the region of the femoral of the rat that was shaved at least before the first blood sampling. For two animals (animal 39 at the 8- and 24-hours time point and animal 54 at the 24-hour time point), blood samples were taken under isoflurane anesthesia from the retroorbital sinus since it was not possible to get blood samples from the vena saphena.

Blood sampling was performed at the following time points:

1, 2, 4, 8, 24, 48, 72, 96, 120, 144, 168 hours (all dose groups)

Animals were sacrificed by decapitation under isoflurane anesthesia after 168h without further examination.

3.5.2.1. Experiment 1

Animals:	4 males and 4 females
Radioactivity per animal:	about 3 MBq (calculated with an animal weight of 300 g)
Dosing:	1 oral dose, 300 mg/kg bw (high dose)
Analysis:	total radioactivity in blood cells and plasma

3.5.2.2. Experiment 2

Animals:	4 males and 4 females
Radioactivity per animal:	about 3 MBq (calculated with an animal weight of 300 g)
Dosing:	1 oral dose, 30 mg/kg bw (low dose)
Analysis:	total radioactivity in blood cells and plasma

3.5.3. Balance/excretion

In this set of experiments, animals were dosed and then placed in metabolism cages in order to collect urine cooled after 6, 12 and 24 hours and subsequently in time intervals of 24 hours up to 168 hours and feces cooled in intervals of 24 hours up to 168 hours. For the first experiment with the low dose group (single dosing, experiment 4), two male animals were placed in closed metabolism cages in order to additionally collect exhaled air for 48 h. The detection of less than 2% of the total radioactive dose in exhaled air justified to perform all balance/excretion experiments in open systems.

After 168 hours, animals were sacrificed by exanguination (under isoflurane anaesthesia) and the following tissues were checked for remaining radioactivity:

heart	carcass	adipose tissue	gut
liver	muscle	stomach	gut contents
spleen	kidney	stomach contents	bone marrow
bone	testes	thyroid gland	
skin	brain	adrenal glands	
lung	pancreas	blood cells	
ovaries	uterus	plasma	

For balance estimates the cage wash was also checked for radioactivity.

3.5.3.1. Experiment 3

Animals:	4 males and 4 females
Specific activity:	0.05 MBq/mg test substance
Dosing:	1 oral dose, 300 mg/kg bw (high dose)
Analysis:	total radioactivity

3.5.3.2. Experiment 4

Animals:	4 males and 4 females
Specific activity:	0.5 MBq/mg test substance
Dosing:	1 oral dose, 30 mg/kg bw (low dose)
Analysis:	total radioactivity

3.5.3.3. Experiment 5

Animals:	4 males and 4 females
Specific activity:	0.5 MBq/mg test substance
Dosing:	orally / non-labeled once per day for 14 days (5 animals per sex); radio-labeled once on day 15 (4 animals per sex, 30 mg/kg bw (low dose))
Analysis:	total radioactivity

3.5.4. Excretion via bile

In this set of experiments, the bile duct of the rats was cannulated in a surgery. The surgery was performed under isoflurane anesthesia and analgesia. For analgesia, Rimadyl® was given before surgery (at least 30 minutes before surgery started) and on the following days until 1 day before test substance administration. The dose was about 5 mg/kg bw and day. For antibiotics animals were treated each day with 1% Baytril® after the surgery until 1 day before administration. In addition, about 1 mL/100 g bw of 0.05% Baytril® was administered to the animals during surgery.

A second catheter was set in the duodenum to supplement the animal with a solution of synthetic bile acids by continuous infusion. The bile catheterized animals were placed in polycarbonate cages type III supplied by Becker & Co., Castrop-Rauxel, Germany (floor area of about 800 cm²). To guarantee a continuous correct technical set up, animals were checked regularly during the experiment and if necessary, the technical equipment was rearranged (eg. distorted catheters). For this purpose, animals were kept under isoflurane anesthesia if necessary (details are described in the raw data).

Before administration, the cannulated animals were placed in metabolism cages in order to collect bile at three-hour intervals as well as urine and feces at 24-hour intervals up to 72 hours, depending on the health state of the animals and the excretion rate. After 72 hours, animals were sacrificed by exsanguination (under isoflurane anaesthesia) and the following samples were checked for remaining radioactivity:

- bile samples of each sampling interval of each animal
- urine samples
- feces samples
- stomach
- stomach contents
- gut
- gut contents
- carcass
- For balance estimates the cage wash will also be checked for radioactivity

3.5.4.1. Experiment 6

Animals:	6 males and 6 females
Specific activity:	0.044 MBq/mg test substance
Dosing:	1 oral dose, 300 mg/kg bw (high dose)
Analysis:	total radioactivity

3.5.4.2. Experiment 7

Animals:	6 males and 6 females
Specific activity:	0.4 MBq/mg test substance
Dosing:	1 oral dose, 30 mg/kg bw (low dose)
Analysis:	total radioactivity

3.5.5. Tissue distribution

In this set of experiments animals were treated and then placed in steel wire mesh cages. Three animals were sacrificed at 4 defined time points after dosing that were selected based on the results of the blood and plasma kinetic experiments. The time points selected correspond to the following time points in plasmakinetics: maximum plasma concentration MPC, second MPC (based on assumed enterohepatic recirculation, 1/2 MPC and 1/4 MPC and 1/8 MPC at the high and low dose level for both sexes). After sacrifice by exanguination (under isoflurane anaesthesia) remaining radioactivity was measured in the following organs and tissues:

heart	bone	blood cells	stomach
liver	muscle	plasma	stomach contents
spleen	kidney	pancreas	bone marrow
brain	carcass	thyroid glands	
skin	adipose tissue	adrenal glands	
lung	testes	gut	
uterus	ovaries	gut contents	

3.5.5.1. Experiment 8

Animals:	12 males and 12 females
Radioactivity per animal:	1-2 MBq
Dosing:	1 oral dose, 300 mg/kg bw (high dose)
Time points:	1h, 4h, 36h and 46h for males; 1h, 4h, 37h and 50h for females
Remarks:	each 3 males and 3 females per time point
Analysis:	total radioactivity

3.5.5.2. Experiment 9

Animals:	12 males and 12 females
Radioactivity per animal:	1-2 MBq
Dosing:	1 oral dose, 30 mg/kg bw (low dose)
Time points:	1h, 4h, 18h and 25h for males; 1h, 4h, 17h and 22h for females
Remarks:	each 3 males and 3 females per time point
Analysis:	total radioactivity

3.6. ANALYSES

The analyses of the radioactive test-substance preparations were carried out at the Molecular Toxicology and Kinetics Laboratory of Experimental Toxicology and Ecology of BASF SE, Ludwigshafen, Germany.

The weights of all other samples except of total blood samples of plasmakinetics, were determined. All samples of biological material were prepared for analysis using conventional methods described in standard operating procedures. Radioactivity was counted in a LSC. Total radioactivity was measured (details see 3.6.3.)

All urine, feces and bile samples were transferred to the test facility "Crop Protection - Global Metabolism & Structure of BASF SE, Speyerer Straße 2, 67117 Limburgerhof, Germany" in order to investigate the metabolism of ^{14}C -4,4'-sulphonyldiphenol in a separate GLP study under the responsibility of a study director of the respective test facility. These results are described in a separate study report (AP study ID 858428). Additionally, the total radioactivity in feces was determined and 0-24h fractions of urine samples of animals 18-20 (experiment 4) were reanalysed at the test facility "Crop Protection - Global Metabolism & Structure of BASF SE, Speyerer Straße 2, 67117 Limburgerhof, Germany". The results were send to the Molecular Toxicology and Kinetics Laboratory for calculation and reporting.

3.6.1. Homogeneity/concentration control

The amounts of radioactivity, the amounts of ^{14}C -4,4'-sulphonyldiphenol and the total amount of DHDPs (sum of all isotopes) in the test-substance preparations were determined by LSC, Radio-HPLC as well as HPLC-UV in samples that were taken at least before and after administration of the test-substance preparations. The samples were prepared for analysis using conventional methods described in standard operating procedures. The analyses of these samples allow to demonstrate the homogeneity, correctness of the concentration and the stability of the test substance(s) in the test-substance preparations over the administration period. The stability of the test-substance in sodium carboxymethyl cellulose in drinking water with a comparable batch of the non-labeled test substance over a period of 7 days stored in the refrigerator is given (01Y0066/05Y009).

Aliquots of the respective radio-labeled test-substance preparations were shipped to the test facility "Crop Protection - Global Metabolism & Structure of BASF SE, Speyerer Straße 2, 67117 Limburgerhof, Germany" to be used within the performed metabolism investigations (eg. for the detection of the isotope pattern).

3.6.2. Methods of analysis

The analyses of the test-substance preparation were performed by HPLC (Agilent 1200 system and Thermofisher Ultimate 3000) according to the following conditions:

Column: XBridge C18, 5 μ m; 150 x 4.6 mm
Eluent: A: HPLC - water + HCOOH (1000 + 1 mL)
B: acetonitril + HCOOH (1000 + 1 mL)
Flow: 1.0 mL/min, isocratic %B: 25
Detection: UV-extinction 260 nm
radioflow detector Berthold LB 513 FlowStar and LB 514
FlowStar (cell: YG 75)

Recording and evaluation for HPLC analyses was performed with Chromeleon (Dionex) software Version 6.8.

3.6.3. Total radioactivity in biological material and cage wash

Whole blood samples were inverted several times to ensure homogeneity and then separated into plasma and blood cells by centrifugation.

All-glass metabolism cages were washed with 10% RBS® cleaner in drinking water and acetone at the end of each experiment, whereas Plastic Metabolism Cages (Tecniplast, Italy) were washed with 10% RBS® cleaner in drinking water only.

After weighing, aliquots of liquid samples (bile, urine, plasma and cage wash) were mixed with scintillation cocktail (Hionic Fluor, Perkin Elmer) and analyzed for radioactivity without any additional treatment.

Soluene®-350 (Perkin Elmer) was added to blood cells. The samples were incubated over night at 37° C followed by the addition of isopropanol. Then the samples were bleached by the addition of perhydrol solution (30%). After further incubation Hionic Fluor cocktail (Perkin Elmer) was added and the samples were measured by liquid scintillation counting.

Contents of gut and stomach, carcass, lung, heart, spleen, kidney, testes, brain and liver were suspended in deionized water and were homogenized using a WARING Blender.

Aliquots of the suspensions of contents of gut and stomach and carcass were dried by lyophilisation, dissolved with Soluene®-350, filled up with isopropanol, bleached with perhydrol solution (30% H₂O₂) and Hionic Fluor was added before the measurement of radioactivity by LSC.

To aliquots of the suspensions of lung, heart, spleen, kidney, testes, brain and liver and the whole samples of muscle, adipose tissue, uterus/ovaries, thyroid gland, adrenal gland, pancreas, skin, bone marrow, stomach and gut, Soluene®-350 and isopropanol were added, bleaching was performed with perhydrol solution (30% H₂O₂) and Hionic Fluor was added before measurement of radioactivity by LSC.

Bone samples were treated with hydrochloric acid (4M) and Hionic Fluor was added before measurement of radioactivity by LSC.

Detailed information on the conventional methods used for the preparation of the samples and LSC measurement are described in standard operation procedures and in the raw data.

Feces samples of balance and bile experiments were weighed and were send to Crop Protection - Global Metabolism & Structure of BASF SE, Speyerer Straße 2, 67117 Limburgerhof without further examinations. The total radioactivity in these feces samples was determined in each sample in a separate study under the responsibility of a study director of this test facility under GLP conditions. Additionally, 0-24 h fractions of urine samples of animals 18-20 of experiment 4 were reanalyzed at Crop Protection - Global Metabolism & Structure of BASF SE, Speyerer Straße 2, 67117 Limburgerhof to check if an interchange of samples has taken place. The results of theses analyses were used for further calcuations within the current study.

3.6.4. Food analyses

The food used in the study was assayed for chemical and microbial contaminants. On basis of the duration of use and analytical findings with respect to chemical and microbiological contaminants, the food was found to be suitable. The EPA Fed. Reg. of 09 May 1979 (Vol. 44, No. 91, p 27354) served as a guideline for maximum tolerable contaminants. The levels of phytoestrogens did not exceed 350 µg of genistein equivalents/g food and the amount of microorganisms did not exceed 1*10⁵ per g food. Individual results can be found in the archives of the Experimental Toxicology and Ecology of BASF SE

In view of the aim and duration of this study, the level and type of contaminants found in commercial feed was considered not to influence the results of the study.

3.6.5. Drinking water analyses

The drinking water is regularly assayed for chemical contaminants both by the municipal authorities of Frankenthal and by the Environmental Analytics Water/Steam Monitoring of BASF SE as well as for bacteria by a contract laboratory. The Drinking Water Regulation served as the guideline for maximum tolerable contaminants.

3.6.6. Bedding and enrichment analyses

The items used for bedding and enrichment were regularly assayed for contaminants (chlorinated hydrocarbons and heavy metals). The values given in Lab Animal, Nov.–Dec. 1979, pp 24–34, served as the guideline for maximum tolerable contaminants.

3.7. EXPERIMENTAL PROCEDURE

3.7.1. Clinical examinations

3.7.1.1. Mortality

A check for moribund and dead animals was conducted at least once daily.

3.7.1.2. Clinical signs

A cageside examination was conducted at least once daily for any signs of morbidity, pertinent behavioral changes and signs of overt toxicity. Abnormalities and changes were be documented for each animal.

3.7.1.3. Body weight

The body weight was determined on the days of administration prior to dosing in the plasmakinetic, balance and tissue distribution experiments.

In the bile experiments the body weight was determined on the day of surgery and before administration.

3.7.1.4. Necropsy

Findings during necropsy were documented.

3.8. DATA PROCESSING

Tables presented in the report are computer generated. The group mean and individual data are rounded appropriately for inclusion in the report. As a consequence, calculation of group mean data from the individual data presented in the report will, in some instances, yield a minor variation in value.

- Calculations

Depending on the preparation of the samples the appropriate formulas were chosen. Calculations were performed using formula I and III (see below) for all these samples, which were dried by freeze drying technique. The results for the other samples were obtained using formula II and IV (see below).

All values calculated for the plasmakinetic experiments are background corrected. Quantification limit (loq) was set twice the background (in cpm). For further calculations (e.g. mean values and standard deviations) samples <loq were set to 0 ($\mu\text{g Eq/g}$).

The results of feces samples and defined urine samples (total dpm of each sample) were send (signed by the study director of the corresponding study of Crop Protection - Global Metabolism & Structure of BASF SE) to the Molecular Toxicology and Kinetics Laboratory of Experimental Toxicology and Ecology of BASF SE and were archived with the raw data of the current study. The data were used in tables to calculate the % dose values of each sample. The results of the reanalyses of urine samples, performed under special focus to the correct assignment of the labelling and measurement, confirmed the interchange of samples (plausible recoveries and confirmed attribution of the samples to samples names / sample labels) and were used for data assessment within the current study.

Key of abbreviations		dimension
DPM	= disintegrations per minute	[DPM]
LSC	= weight of LSC sample	[g]
SOL	= weight of soluene	[g]
FRE	= weight of freeze drying sample	[g]
SAM	= weight of organ/tissue sample	[g]
AQU	= weight of ultrapure water	[g]
ACT	= specific activity of test material	[DPM/ μg]
EQUITIS	= equivalents of test material per tissue weight	[$\mu\text{g/g}$]
D _{rad}	= dose of radioactivity administered	[DPM]

Formula I

$$\% \text{ of } D_{rad} = \frac{\sum_{n=1}^n DPM_n / LSC_n}{n} \times \frac{SOL}{FRE} \times (SAM + AQU) \times \frac{100}{D_{rad}}$$

Formula II

$$\% \text{ of } D_{rad} = \frac{\sum_{n=1}^n DPM_n / LSC_n}{n} \times (SAM + AQU) \times \frac{100}{D_{rad}}$$

Formula III

$$EQU_{TIS} = \frac{\sum_{n=1}^n DPM_n / LSC_n}{n} \times \frac{SOL}{FRE} \times \frac{SAM + AQU}{SAM \times ACT}$$

Formula IV

$$EQU_{TIS} = \frac{\sum_{n=1}^n DPM_n / LSC_n}{n} \times \frac{SAM + AQU}{SAM \times ACT}$$

For the tissues of which aliquots were taken during necropsy (e.g. adipose tissue, bone) calculation of % of dose administered (Formula II) is based on sample amount taken for the measurement. For all other tissues, the calculation is based on the weight of the whole tissue.

Analysis of kinetic data:

Analysis of kinetic data was performed based on the group mean values using the PC program system WinNonLin Version 8.0.

4. RESULTS AND DISCUSSION

4.1. STABILITY, HOMOGENEITY AND CONCENTRATION CONTROL ANALYSES OF THE TEST-SUBSTANCE PREPARATIONS

Stability of the radio-labeled test substance: The radiochemical purity of the radio-labeled test substance was verified by radio-HPLC.

Stability of the test-substance preparations: The stability of the test substance (all isotopes) in the test-substance preparations over the test period was verified by analysis. Details are shown in table 4.1.1.

Concentration control and homogeneity analysis of the test-substance preparations: The concentrations and the homogeneous distribution of the test substance in the test-substance preparations were confirmed by analysis.

Table 4.1.1. Nominal and analytical concentrations compared to target concentrations

Experiment	target concentration [mg/mL]	nominal concentration [mg/mL]	analytical results % of nominal concentration (mean \pm RSD)
1	30.0	30.0	102.0 \pm 0.7
2	3.0	3.0	100.7 \pm 1.7
3	30.0	30.0	100.9 \pm 1.1
4 and 5	3.0	3.0	102.2 \pm 2.1
6 males	30.0	30.0	101.9 \pm 0.7
6 females	30.0	30.0	98.1 \pm 1.9
7 males	3.0	3.0	93.8 \pm 2.5
7 females	3.0	3.0	99.3 \pm 2.1
8	30.0	30.0	102.9 \pm 3.5
9	3.0	3.0	101.0 \pm 2.5

The nominal concentrations were calculated from the weights of ingredients used for producing the test-substance preparations.

As shown in table 4.1.1., the nominal concentrations reflect their target values. Concentration control analysis confirm the nominal concentrations with means between 90 and 110% related to the nominal values. Relative standard deviations below 5% demonstrate the homogenous distribution of the test substance in its preparation.

Mean values of the concentration control analysis of the non-labeled test-substance preparations 1 and 2 (applied for the "14+1"-balance experiment) were 94.7 and 98.0 % of the nominal concentrations with relative standard deviations between 3.8%-3.9%.

Table 4.1.2. Target specific activity of the test-substance preparations compared to measured results

experiment	target specific activity		measured specific activity	
	[MBq/mL]	[dpm/mL]	[MBq/mL]	[dpm/mL]
1	1.0	6×10^7	1.0	6.0×10^7
2	1.0	6×10^7	1.0	5.8×10^7
3	1.5	9.0×10^7	1.5	9.2×10^7
4 and 5	1.5	9.0×10^7	1.5	9.2×10^7
6 males	1.3	7.9×10^7	1.4	8.2×10^7
6 females	1.3	7.9×10^7	1.3	8.0×10^7
7 males	1.2	7.2×10^7	1.2	7.4×10^7
7 females	1.2	7.2×10^7	1.2	7.3×10^7
8	0.3	2.0×10^7	0.4	2.2×10^7
9	0.7	4.0×10^7	0.7	4.1×10^7

The measured specific activities of the test-substance preparations compared to their target values are assessed to be acceptable within the precision of the method. Radio-HPLC analyses generally confirmed the stability of the radio-labeled test substance over the application period for all dose groups by radiochemical purities of ^{14}C -4,4'-sulphonyldiphenol > 98 % (see appendix 4 and 5).

4.2. CLINICAL EXAMINATIONS

4.2.1. Mortality and clinical observations

One female animal of bile experiment 7 (low dose experiment) was found dead in the metabolism cage 48 h post dosing. The death of this animal was assessed not to be test substance related.

4.2.2. Body weight

No abnormalities in body weights were observed during multiple dosage and prior to the start of the experiments.

Body weights were in the expected range, except male animals of experiment 6 (high dose bile experiment) where the body weight of male animals varied more than $\pm 20\%$. Although animal 32 (animal with the highest body weight) excreted the lowest amount of bile regarding bile flow and percent of dose, this animal was taken into statistical evaluation since other male animals with a similar bile flow (animal 38) or body weight (animal 32) excreted more activity

via bile. Therefore, the higher body weights in the current bile experiment is assessed to have no significant influence on the obtained results.

4.2.3. Necropsy

During necropsy of two female animals of experiment 7 (low dose group) and one female animal of experiment 6 (high dose group), suppurations were observed in the abdomen of the bile experiment that were attributed to the surgery procedure and assessed not to be test substance related.

4.3. KINETICS OF ^{14}C -4,4'-SULPHONYLDIPHENOL

4.3.1. Blood/plasma concentration

Summarized data and single animal data discussed in the following sections are presented in tables 2,3 and 14 to 18.

Mean plasma concentrations of radioactivity in male and female rats after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at target dose levels of 300 and 30 mg/kg are presented in table 2. Representative plasma curves of these experiments are shown in figures 4 and 5. Single animal data of blood cells and plasma concentrations are included in tables 14 - 17. Table 18 gives the ratio of the blood cells/plasma concentrations for all dose groups. Presented results and calculated pharmacokinetic data are based on mean values. The pharmacokinetic data are summarized in table 3.

- Dose level: 300 mg/kg bw
(experiment 1, tables 2 – 3, 14 – 15, 18, figure 4)

In rats exposed to a single oral dose of 300 mg/kg bw ^{14}C -4,4'-sulphonyldiphenol, mean actual nominal doses of 305.5 and 304.7 mg/kg bw were achieved for males and females, respectively.

The maximum plasma concentrations of 58.16 and 27.48 $\mu\text{g Eq/g}$ in males occurred 1 and 4 hours post dosing, respectively, declined to 21.66 $\mu\text{g Eq/g}$ at 24 hours post dosing and 0.85 $\mu\text{g Eq/g}$ 72 hours post dosing and were below loq for all animals after 96 hours and the subsequent time points. In female rats the maximum plasma concentrations of 104.93 and 26.47 $\mu\text{g Eq/g}$ were reached 1 and 4 hours post dosing. Thereafter the plasma concentrations declined to 1.98 $\mu\text{g Eq/g}$ at 72 hours post dosing was below loq for all animals from 96 hours on and subsequent time points. Terminal half-lives were 10.3 and 14.7 hours, for males and females, respectively.

The area under the plasma concentration time curve $\text{AUC}_{0 \rightarrow \infty}$ was calculated to be 1005 $\mu\text{g Eq}\cdot\text{h/g}$ and 1083 $\mu\text{g Eq}\cdot\text{h/g}$ for males and females respectively. These calculations are based on group mean values.

Generally, blood cell/plasma increased to about the 2-fold amount at 72 hours after administration compared to the initial value with high variations over this period. After 72 hours, values were below loq.

- Dose level: 30 mg/kg bw
(experiment 2, tables 2 – 3, 16 - 18, figure 5)

In rats exposed to a single oral dose of 30 mg/kg bw ^{14}C -4,4'-sulphonyldiphenol, mean actual nominal doses of 30.2 and 30.3 mg/kg bw were achieved for males and females, respectively. The maximum plasma concentrations of 8.66 and 3.81 $\mu\text{g Eq/g}$ in males occurred 1 and 4 hours post dosing, declined to 0.13 $\mu\text{g Eq/g}$ at 48 hours post dosing and were below loq for all animals at 72 hours post dosing and the subsequent time points. In female rats, maximum plasma concentrations of 6.59 and 4.55 $\mu\text{g Eq/g}$ were reached 1 and 4 hours post dosing. Thereafter the concentration declined to 0.01 $\mu\text{g Eq/g}$ at 72 hours post dosing whereas for three of four animals the plasma levels were below loq at that time point and were dropped below loq for all animals after 96 hours and subsequent time points. Terminal half-lives were 9.2 and 8.9 hours, for males and females, respectively.

The area under the plasma concentration time curve $\text{AUC}_{0 \rightarrow \infty}$ was calculated to be 74 $\mu\text{g Eq}\cdot\text{h/g}$ and 80 $\mu\text{g Eq}\cdot\text{h/g}$ for males and females respectively. These calculations are based on group mean values.

The mean blood/plasma ratio at the low dose level of 30 mg/kg bw was between 0.16 and 0.18. Generally, ratios below loq were detected after 48 hours post dosing.

Taken together, plasmakinetic data of ^{14}C -4,4'-sulphonyldiphenol show fast absorption of the test substance after oral administration leading to a dose dependent increase in maximum plasma concentrations with first T_{Max} -values of generally 1 h post dosing. The observation of a second c_{Max} -value at later T_{Max} (at 4 hours post dosing) for both dose levels and genders indicate a potential enterohepatic recirculation of the test substance and/or its metabolites. For the high dose, the mean maximum plasma concentration in female animals one hour after administration was almost twice as high as the mean plasma concentration of male animals at the corresponding time point. Thereafter, the plasma concentrations of the high dose were comparable for male and female animals. For the low dose group, mean plasma concentrations were comparable for male and female animals. Internal doses (indicated as $\text{AUC}_{0 \rightarrow \infty}$) were slightly lower for males compared to females for both dose groups tested. The maximum plasma concentrations are more or less linear over dose for male animals and supralinear over dose for female animals. The internal doses (indicated as $\text{AUC}_{0 \rightarrow \infty}$) are generally slightly higher for females compared to males. As can be seen from the AUC versus dose ratio relationship, the internal dose (indicated by the AUC) increases slightly over-proportional to the actual nominal administered dose: For male animals, the 10.1-fold increase of external dose (from the actual nominal low dose of 30.2 to the actual nominal high dose of 305.5 mg/kg bw.) is correlated to a 13.6-fold increase of the internal dose (from 74 to 1005 $\mu\text{g Eq} \times \text{h} / \text{g}$), for female animals, the 10.1-fold increase of external dose (from the actual nominal low dose of 30.3 to the actual nominal high dose of 304.7 mg/kg bw.) lead to a 13.5-fold increase of the internal dose (from 80 to 1083 $\mu\text{g Eq} \times \text{h} / \text{g}$).

These data indicate a potential saturation of kinetics at higher doses, which may be caused by a potential active transport of the test substance and/or its metabolites.

4.3.2. Balance/excretion

Mean values of excreted and residual radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol to male and female rats at target dose levels of 300 and 30 mg/kg bw and after 15 daily oral administrations of DHDPS (14 x unlabeled at 30 mg/kg bw; 1 x radio-labeled at 30 mg/kg bw at day 15) to male and female rats are presented in table 1. The respective cumulative excretion based on mean group data is shown in figures 1 - 3. The corresponding single animal data are included in tables 8 – 13. Radioactive residues in organs and tissues after balance experiments (after 168 h), expressed as $\mu\text{g Eq/g}$ are outlined in tables 35; 44 and 45.

- Dose level: 300 mg/kg bw
(experiment 3, tables 1, 8 - 9, 35, figure 1)

Mean total recoveries of radioactivity were found to be 95.14 and 98.58 % of dose in male and female rats, respectively. Within 48 hours after single oral administration of 300 mg/kg bw to male and female rats 41.30 and 34.00 % of the administered radioactivity were found in urine, respectively. Total excretion of radioactivity via urine after 168 hours was 48.05 and 39.02 % of dose for males and females, respectively. These data indicate that urinary excretion occurred predominantly within the two days after test substance administration.

During the first 48 hours after administration, 38.74 % and 50.13 % of the administered radioactivity were excreted via feces by males and females, respectively. After 168 hours the total amount of radioactivity excreted via feces was found to be 44.20 and 55.71 % of dose for males and females, respectively. These excretion data from urine and feces indicate that major excretion of absorbed ^{14}C -4,4'-sulphonyldiphenol occurs within 48 hours after dosing.

Together with cage wash, the total amount of excreted radioactivity was found to be 94.81 % of the administered radioactivity in males and 97.33 % of the administered radioactivity in females reflecting more or less complete excretion of orally dosed ^{14}C -4,4'-sulphonyldiphenol for male and female rats. 168 hours post-dosing, small amounts of radioactive residues of ^{14}C -4,4'-sulphonyldiphenol were found in skin (0.02 and 0.05 % of dose), carcass (0.19 and 1.16 % of dose), gut and stomach content (0.01 and 0.01 % of dose) and gut content (0.10 and 0.04 % of dose) for male and female animals. Highest total radioactive residues (in $\mu\text{g Eq/g}$) 168 h post dosing (except GI tract) were found in thyroid and carcass for male animals and in carcass for female animals and lowest in plasma (both sexes).

- Dose level: 30 mg/kg bw
(experiment 4, tables 1, 10 – 11, 44, figure 2)

Mean total recoveries of radioactivity were found to be 105.33 and 97.17 % of dose in male and female rats, respectively. As < 0.1% of the administered dose were detected as CO_2 in exhaled air, it could be concluded that exhalation is not a relevant excretion pathway for ^{14}C -4,4'-sulphonyldiphenol and/or its metabolites. Accordingly, balance experiments within the present study were performed in open metabolism cages.

Within 48 hours after single oral administration of 30 mg/kg bw to male and female rats 56.94 and 47.09 % of the administered radioactivity were found in urine, respectively. Total excretion of radioactivity via urine after 168 hours was 60.13 and 51.45 % of dose for males and

females, respectively. These data indicate that urinary excretion occurred predominantly within two days after test substance administration.

During the first 48 hours after administration, 41.75 % and 39.40 % of the administered radioactivity were excreted via feces by males and females, respectively. After 168 hours the total amount of radioactivity excreted via feces was found to be 43.00 and 40.85 % of dose for males and females, respectively. These excretion data from urine and feces indicate that major excretion of absorbed ^{14}C -4,4'-sulphonyldiphenol occurs within 48 hours after dosing.

Together with cage wash, the total amount of excreted radioactivity was found to be 104.33 % of the administered radioactivity in males and 96.06 % of the administered radioactivity in females reflecting more or less complete excretion of orally dosed ^{14}C -4,4'-sulphonyldiphenol for male and female rats. 168 hours post-dosing, small amounts of radioactive residues of ^{14}C -4,4'-sulphonyldiphenol were found in carcass (0.93 and 0.98 % of dose), skin (0.01 % of dose for both sexes) stomach content (0.02 % of dose for both sexes), gut content (0.05 and 0.09 % of dose for male and female animals, respectively) and gut (0.01 % of dose in female animals). Highest total radioactive residues (in μg Eq/g) 168 h post dosing (except GI tract) were found in carcass for both sexes, for all other tissues the residues ranged between 0.0 and 0.1 μg Eq/g.

- Dose level: 14 + 1, 30 mg/kg bw
(experiment 5, tables 1, 12 – 13, 45, figure 3)

Mean total recoveries of radioactivity were found to be 96.21 and 99.69 % of dose in male and female rats, respectively. Within 48 hours after single oral administration of 30 mg/kg bw to male and female rats 46.56 and 46.88 % of the administered radioactivity were found in urine, respectively. Total excretion of radioactivity via urine after 168 hours was 51.09 and 51.82 % of dose for males and females, respectively. These data indicate that urinary excretion occurred predominantly within two days after test substance administration.

During the first 48 hours after administration, 40.16 % and 42.59 % of the administered radioactivity were excreted via feces by males and females, respectively. After 168 hours the total amount of radioactivity excreted via feces was found to be 42.33 and 43.99 % of dose for males and females, respectively. These excretion data from urine and feces indicate that major excretion of absorbed ^{14}C -4,4'-sulphonyldiphenol occurs within 48 hours after dosing.

Together with cage wash, the total amount of excreted radioactivity was found to be 95.53 % of the administered radioactivity in males and 98.10 % of the administered radioactivity in females reflecting more or less complete excretion of orally dosed ^{14}C -4,4'-sulphonyldiphenol for male and female rats. 168 hours post-dosing, small amounts of radioactive residues of ^{14}C -4,4'-sulphonyldiphenol were found in carcass (0.52 and 1.47 % of dose), stomach content (0.01 % of dose only detected in male animals), gut content (0.12 and 0.08 % of dose for male and female animals) and gut (0.01 % of dose for both sexes). Highest total radioactive residues (in μg Eq/g) 168 h post dosing (except GI tract) were found in carcass for both sexes and for all other tissues the residues ranged between 0.0 and 0.07 μg Eq/g.

Overall, the balance data demonstrate that excretion of ^{14}C -4,4'-sulphonyldiphenol dosed orally by gavage to Wistar rats at a single low and high dose as well as multiple low dose (14 + 1) was fast via urine and feces. Thereby, urinary excretion was slightly higher than fecal excretion for male animals of all dose groups and female animals of the low dose group, single

and multiple dosing, whereas for female animals of the high dose group, excretion via urine was about 17 % lower than fecal excretion. Excretion was almost complete and occurred to a major extent within two days after oral dosing. Generally, it can be concluded, that based on the current data, excretion of ^{14}C -4,4'-sulphonyldiphenol in the low dose is independent from frequency of treatment and gender.

4.3.3. Excretion via bile

The mean biliary excretion of radioactivity after a single oral administration of ^{14}C -4,4'-sulphonyldiphenol to rats at target dose levels of 300 and 30 mg/kg bw is presented in tables 4 and 5. The corresponding single animal data are included in tables 19 – 26, bile flow of single animals is presented in tables 27 - 30.

It should be mentioned that calculated means for bile excretion in the tables (data of bile excretion and mass balance) result in minor deviations based on mathematical routines and the number of digits applied (especially when means of single excretion data over collection periods are compared versus means of single animal data). These differences are assessed to be minor and without impact on the overall data assessment of the experiments.

Bile excretion experiments were performed after bile catheterization as balance experiments and bile, urine and feces were collected in defined time intervals up to 72 hours from rats that were dosed with a single oral dose of ^{14}C -4,4'-sulphonyldiphenol at target dose levels of 300 mg/kg bw and 30 mg/kg bw. After the experiments, animals were sacrificed under isoflurane anesthesia, the GI-tract was removed, and the remaining activity was measured in the content of the stomach, the gut as well as in stomach and gut. Based on the data of excreted radioactivity via bile and urine as well as on the remaining radioactive residue in carcass, the fraction absorbed of dosed ^{14}C -4,4'-sulphonyldiphenol was calculated.

- Dose level: 300 mg/kg bw
(Tables 4 and 5; 19 - 20; 23 – 24, 27 - 28)

Mean total recoveries of radioactivity were found to be 93.83 and 97.55 % of dose in male and female rats, respectively. Within 72 hours after administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw, excretion via bile was found to be 43.81 and 45.65 % of the administered radioactivity in males and females, respectively. Total excretion of radioactivity via urine until 72 hours post dosing was 47.52 and 48.91 % of dose for males and females, respectively. During the experimental period of 72 hours, the total amount of radioactivity excreted via feces was found to be 1.02 and 1.03 % of dose for male and for female animals, respectively. The total amount of radioactivity in the GI tract was 0.09 % of dose in males and 0.35 % of dose in females.

Based on the amounts of radioactivity excreted via bile and urine, as well as the radioactive residues found in cage wash and carcass, oral absorption of ^{14}C -4,4'-sulphonyldiphenol in rats was calculated to be 92.72 and 96.16 % of the administered dose for males and females at a dose level of 300 mg/kg bw, respectively.

- Dose level: 30 mg/kg bw
(Tables 4 and 5; 21 - 22; 25 – 26, 29 - 30)

Mean total recoveries of radioactivity were found to be 96.74 and 89.82 % of dose in male and female rats, respectively. Within 72 hours after administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw, excretion via bile was found to be 56.39 and 38.21 % of the administered radioactivity in males and females, respectively. Total excretion of radioactivity via urine until 72 hours post dosing was 37.72 and 46.37 % of dose for males and females, respectively. During the experimental period of 72 hours, the total amount of radioactivity excreted via feces was found to be 1.28 and 3.03 % of dose for male and for female animals, respectively. The total amount of radioactivity in the GI tract was 0.06 % of dose in males and 0.11 % of dose in females.

Based on the amounts of radioactivity excreted via bile and urine, as well as the radioactive residues found in cage wash and carcass, oral absorption of ^{14}C -4,4'-sulphonyldiphenol in rats was calculated to be 95.40 and 86.68 % of the administered dose for males and females at a dose level of 30 mg/kg bw, respectively.

Taken together, the current bile excretion experiments demonstrate that excretion of ^{14}C -4,4'-sulphonyldiphenol dosed orally by gavage to Wistar rats with single doses of 300 and 30 mg/kg bw was fast and occurred mainly via urine and bile for both dose levels. Compared to the balance experiments, mean urinary excretions were generally lower in bile excretion experiments, except for females of the high dose experiment, demonstrating reabsorption of the test substance into the systemic circulation under physiological conditions. This finding correlates to indications for potential enterohepatic recirculation obtained in plasmakinetik experiments. Absorptions of ^{14}C -4,4'-sulphonyldiphenol were high and accounted to about 93 to 96 % of dose for male animals of both dose groups and to 87 to 95 % of dose for female animals of both dose groups.

4.3.4. Tissue distribution

Mean results of the distribution of radioactivity into organs and tissues investigated at defined time points after a single oral administration of ^{14}C -4,4'-sulphonyldiphenol to male and female rats at target dose levels of 300 and 30 mg/kg bw are presented in tables 6 - 7. The corresponding single animal data are included in tables 31 - 49.

The observation time points for sampling the organ/tissue samples within the tissue distribution experiments are based on results of plasmakinetik (see 4.3.1.) and should refer to time points following maximum plasma concentrations MPC, second maximum plasma concentration based on potential enterohepatic recirculation, 1/2 MPC and 1/4 MPC.

- Dose level: 300 mg/kg bw
(Tables 6; 31 – 39)

Male animals were sacrificed 1 h, 4 h, 36 h and 46 h after administration of the test substance. Female animals were sacrificed 1 h, 4 h, 37 h and 50 h after administration of the test substance. The detected mean plasma levels at these sacrifice time points were 57.39, 26.54, 8.54 and 5.23 as well as 65.22, 26.00, 10.31 and 4.29 $\mu\text{g Eq/g}$ for male and female animals,

respectively. When plasma concentrations of the tissue distribution experiments are compared to results of plasmakinetics (see 4.3.1.), mean plasma levels of female animals at the 1-hour sampling time point showed high experimental variability ($104.93 \pm 29.22 \mu\text{g Eq/g}$ in plasma kinetic experiment, $65.22 \pm 19.55 \mu\text{g Eq/g}$ in tissue distribution experiment). This variability is based on the fact, that especially in females, mean plasma levels decline very fast, especially within the first two hours post dosing; Therefore, individual maximum plasma levels of single animals cannot be outlined in detail by two collection time points of blood samples in this sampling period. Apart from the plasma levels of female animals one hour after administration, there is a general accordance of the measured data between the the experiments.

At all observation time points after oral administration of ^{14}C -4,4'-sulphonyldiphenol to male and female rats, highest tissue concentrations (means) were found in the GI tract/GI tract contents. With the exception of the GI-tract (including its content), highest residues (means) in male rats 1 h after administration were found in kidney, liver, plasma, carcass, lung and skin, resulting in 100.61, 67.88, 57.39, 49.42, 33.22 and $30.64 \mu\text{g Eq/g}$. For male animals, lowest mean radioactive residues at this time point were measured in adipose tissue, brain and bone with concentrations of 3.49, 4.30 and $4.81 \mu\text{g Eq/g}$. With the exception of the GI-tract (including its content), highest residues (means) in female rats 1 h post doing were found in brain, plasma liver, thyroid, pancreas, lung, skin and carcass, resulting in 78.51, 65.22, 64.40, 44.63, 43.33, 40.89, 40.83 and $39.87 \mu\text{g Eq/g}$. For female animals, lowest mean radioactive residues at this time point were measured in adipose tissue, bone and kidney, corresponding to 5.46, 5.74 and $6.61 \mu\text{g Eq/g}$. It should be mentioned here, that the relatively high radioactive residue in brain of female animals of the high dose level tested is consistent between the different observation time points but is in contrast to the findings in male animals and in the female animals of the low dose group. In male and female animals, radioactive residue concentrations generally declined in organs and tissues parallel to the radioactive residues in plasma with the exception of mean residues in carcass samples in which the concentrations declined until the 4-hour sampling time point and increased thereafter to the 37- and 38-hour time point and dropped at the last sampling time point to a value which was still above the 4-hour sampling time point. This time dependency was observed generally for both sexes.

- Low dose
(Tables 7; 40 – 49)

Male animals were sacrificed 1 h, 4 h, 18 h and 25 h after administration of ^{14}C - 4,4'- sulphonyldiphenol and female animals were sacrificed 1 h, 4 h, 17 h and 22 h after administration of the test substance. The detected mean plasma levels at these sacrifice time points were 10.50, 3.00, 1.24 and 0.76 as well as 6.38, 4.35, 1.88 and $1.10 \mu\text{g Eq/g}$ for male and female animals, respectively. Comparing the results of plasma concentrations of radioactivity to the plasmakinetik experiments (see 4.3.1.) the measured data are in general accordance between these experiments.

At 1 hour after oral administration of ^{14}C -4,4'-sulphonyldiphenol to male and female rats, highest tissue concentrations (means) were found in the GI tract/Gi-tract contents. With the exception of the GI-tract (including its content), highest residues (means) in male rats were found in liver and kidney, resulting in 19.25 and $16.17 \mu\text{g Eq/g}$. For male animals, lowest mean

radioactive residues at this time point were measured in brain, adipose tissue and bone with values between 0.42 and 0.79 µg Eq/g.

With the exception of the GI-tract (including its content), highest residues (means) in female rats 1 hour post oral dosing of ¹⁴C-4,4'-sulphonyldiphenol were found in liver, kidney and thyroid resulting in 8.76, 7.12 and 5.39 µg Eq/g. For female animals, lowest mean radioactive residues at this observation time point were measured in brain, bone, adipose tissue and muscle with values between 0.18 and 0.57 µg Eq/g.

In male and female animals, radioactive residue concentrations generally declined in organs and tissues parallel to the radioactive residues in plasma. There were slight increases in the concentrations in carcass samples of male animals and in liver samples of female animals at the 4-hour observation time point. Concentrations in both tissues decreased to the last observation time points.

Taken together, tissue distribution experiments demonstrated that for both sexes and in both genders, radioactive residue concentrations generally declined in organs and tissues from the 1 h time point on and parallel to the radioactive residues in plasma. In contrast to this general trend, radioactive residues in carcass showed delayed clearance, especially in the high dose group tested. Whereas a general sublinear correlation between the radioactive residues in organs and tissues and the administered dose was found, the radioactive residues of carcass samples were overproportional to dose. This overproportional ratio is more pronounced at later sampling time points and is in line with the observation of an overproportional increase of internal dose versus external dose as described in plasmakinetics.

5. CONCLUSION

Taken together, ¹⁴C-4,4'-sulphonyldiphenol was rapidly absorbed from the gastrointestinal tract. Based on the bile excretion experiments, oral absorption was calculated to be about 93 and 96 % of the administered dose at a dose level of 300 mg/kg bw for male and female rats, respectively. At a dose level of 30 mg/kg bw about 95% of the administered dose was absorbed for males and 87% of the administered dose were measured as absorbed for females. The excretion of radioactivity occurred mainly within two days after dosing, generally via urine and bile in bile excretion experiments and with a generally, slightly higher excretion in urine than in feces in balance experiments. Plasma kinetics confirmed high oral absorption and demonstrated potential enterohepatic recirculation, fast excretion and a slight supralinear correlation of the internal exposure to the oral dose. In tissue distribution experiments, residues of ¹⁴C-4,4'-sulphonyldiphenol and/or its metabolites in organs and tissues showed generally sublinear correlation between radioactive residues in organs and tissues and administered oral doses. However, supralinear correlation between radioactive residues in carcass and the external dose was observed in these experiments that is in relation to the findings of plasmakinetics.

6. LIST OF ABBREVIATIONS

The following list contains abbreviations and definitions generally used in reports for this study type.

This report will not necessarily use all expressions listed below.

ACN	acetonitrile
a.i.	active ingredient
AAALAC	Association for Assessment and Accreditation of Laboratory Animal Care
AUC _{0-->168}	area under the curve
AUC _{0->∞}	area under the curve from 0 to infinity
bw	body weight
Bq	Becquerel
C _{Max}	maximum plasma concentration
CPM	counts per minute
DPM	disintegrations per minute
Eq, eq	equivalents
GV-SOLAS	Gesellschaft für Versuchstierkunde/Society of Laboratory Animal Science
HCOOH	formic acid
HPLC	high performance liquid chromatography
LSC	liquid scintillation counter
MBq	mega-becquerel
M	molar
n.d.	not determined
n.s.	no sample
PK	pharmacokinetics
OECD	Organisation for Economic Co-operation and Development
SD	standard deviation
T _{1/2}	half life
TFA	trifluoro-acetic acid
T _{Max}	time at which the maximum plasma concentration occurs
TRR	total radioactive residue
US EPA	United States Environmental Protection Agency
VWD	variable wavelength detector

7. TABLES

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Table 1: Mean excretion and retention of radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at target dose levels of 300 and 30 mg/kg bw and after 14 daily oral administrations of DHDPS and one oral administration of ^{14}C -4,4'-sulphonyldiphenol on day 15 (30 mg/kg bw) to male and female rats

Results expressed in % of dose administered

Balance/Excretion	300 mg/kg bw		30 mg/kg bw		30 mg/kg bw (14+1)	
	male	female	male	female	male	female
Animal weight [g]	296.3	221.5	340.7	225.4	338.4	236.1
Spec. activity [MBq/g]	51.2	51.2	508.0	508.0	508.0	508.0
Dose admin. [mg/kg bw]	311.0	315.9	30.4	30.8	30.5	31.3
Radioact. dose [MBq/animal]	4.70	3.57	5.27	3.53	5.25	3.77
Urine 0-6	7.69	11.39	15.63	13.32	8.45	14.18
Urine 6-12	8.87	4.93	20.01	15.18	10.39	9.12
Urine 12-24	10.33	7.90	13.60	12.56	20.53	17.34
Urine 24-48	14.41	9.78	7.69	6.03	7.18	6.24
Urine 48-72	3.75	2.85	1.71	1.84	2.00	2.42
Urine 72-96	1.41	0.81	0.47	0.81	0.88	0.89
Urine 96-120	0.67	0.54	0.50	0.67	0.80	0.79
Urine 120-144	0.50	0.54	0.27	0.59	0.49	0.45
Urine 144-168	0.41	0.27	0.25	0.45	0.37	0.39
Subtotal Urine	48.05	39.02	60.13	51.45	51.09	51.82
Feces 0-24	21.39	26.55	32.17	33.59	27.90	29.58
Feces 24-48	17.35	23.58	9.58	5.81	12.26	13.01
Feces 48-72	4.31	4.17	0.85	0.82	0.95	0.66
Feces 72-96	0.80	0.97	0.22	0.29	0.36	0.30
Feces 96-120	0.16	0.22	0.09	0.16	0.22	0.21
Feces 129-144	0.10	0.12	0.05	0.10	0.17	0.13
Feces 144-168	0.08	0.10	0.05	0.08	0.47	0.10
Subtotal Feces	44.20	55.71	43.00	40.85	42.33	43.99
Cage wash	2.56	2.60	1.20	3.76	2.11	2.28
Blood cells	0.00	0.00	0.00	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Lung	0.00	0.00	0.00	0.00	0.00	0.00
Heart	0.00	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00	0.00
Kidney	0.00	0.00	0.00	0.00	0.00	0.00
Adrenals	0.00	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00	0.00
Uterus	---	0.00	---	0.00	---	0.00
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00	0.00
Stomach cont.	0.01	0.01	0.02	0.02	0.01	0.00
Stomach	0.00	0.00	0.00	0.00	0.00	0.00
Gut cont.	0.10	0.04	0.05	0.09	0.12	0.08
Gut	0.01	0.01	0.00	0.01	0.01	0.01
Liver	0.00	0.00	0.00	0.00	0.00	0.00
Skin	0.02	0.05	0.01	0.01	0.01	0.02
Carcass	0.19	1.16	0.93	0.98	0.52	1.47
Total	95.14	98.58	105.33	97.17	96.21	99.69

Table 2: Mean plasma concentrations of radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at target dose levels of 300 and 30 mg/kg bw to male and female rats

Results expressed in $\mu\text{g Eq/g}$ plasma

Time [h]	300 mg/kg bw		30 mg/kg bw	
	Males	Females	Males	Females
1	58.16	104.93	8.66	6.59
2	23.39	22.90	3.28	1.93
4	27.48	26.47	3.81	4.55
8	24.36	24.63	2.55	3.42
24	21.66	18.98	0.99	0.95
48	5.41	7.18	0.13	0.15
72	0.85	1.98	< loq	0.01
96	< loq	< loq	< loq	< loq
120	< loq	< loq	< loq	< loq
144	< loq	< loq	< loq	< loq
168	< loq	< loq	< loq	< loq

Table 3: Pharmacokinetic parameters of radioactivity in plasma after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at target dose levels of 300 and 30 mg/kg bw to male and female rats

Sex	target dose [mg/kg bw]	Mean actual nominal dose [mg/kg bw]	C _{MAX} [$\mu\text{g Eq/g}$]	T _{MAX} [h]	Terminal half life [h]	AUC _{0-->168} [$\mu\text{g Eq x h/g}$]	AUC _{0-->∞} [$\mu\text{g Eq x h/g}$]
male	300	305.5	58.16; 27.48	1; 4	10.3	1003	1005
male	30	30.2	8.66; 3.81	1; 4	9.2	73	74
actual dose ratio high dose to low dose:10.1 AUC _{0-->∞} ratio high dose to low dose: 13.6							
female	300	304.7	104.93; 26.47	1; 4	14.7	1064	1083
female	30	30.3	6.59; 4.55	1; 4	8.9	80	80

actual dose ratio high dose to low dose:10.1
AUC_{0-->∞} ratio high dose to low dose: 13.5

Table 4: Excretion and retention of radioactivity via urine, feces and bile after single oral administration of ^{14}C -4,4'-sulphonyldiphenol to male and female rats at target dose levels of 300 and 30 mg/kg bw

Results expressed as % of the radioactivity administered

	300 mg/kg bw		30 mg/kg bw	
	Males	Females	Males	Females
Animal weight [g]	287.5	237.5	312.0	209.8
Spec. activity [MBq/g]	45.7	44.5	408.8	406
Dose admin. [mg/kg bw]	310.7	301.9	32.61	31.18
Radioact. dose [MBq/animal]	4.08	3.19	4.16	2.65
Urine 0-24	42.71	42.65	36.96	45.56
Urine 24-48	4.53	5.95	0.57	0.59
Urine 48-72	0.28	0.31	0.19	0.27
Subtotal Urine	47.52	48.91	37.72	46.37
Feces 0-24	0.60	0.43	0.65	2.51
Feces 24-48	0.27	0.48	0.55	0.31
Feces 48-72	0.15	0.12	0.10	0.26
Subtotal Feces	1.02	1.03	1.28	3.03
Bile 0-24h	40.66	44.85	56.20	38.02
Bile 24-48h	3.10	0.71	0.16	0.19
Bile 48-72h	0.06	0.09	0.03	0.06
Subtotal Bile	43.81	45.65	56.39	38.21
Cage wash	1.00	1.07	0.71	1.30
Stomach cont.	0.04	0.29	0.01	0.01
Stomach	0.01	0.02	0.00	0.02
Gut cont.	0.04	0.04	0.04	0.07
Gut	0.00	0.00	0.00	0.01
Carcass	0.39	0.54	0.58	0.80
Total	93.83	97.55	96.74	89.82
fraction absorbed	92.72	96.16	95.40	86.68

Table 5: Excretion pattern of radioactivity via bile of male and female rats after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at target dose levels of 300 and 30 mg/kg bw

Results expressed as % of the radioactivity administered

Time interval [h]	300 mg/kg bw		30 mg/kg bw	
	Males	Females	Males	Females
0-3	20.91	21.45	37.32	25.99
3-6	9.30	10.38	10.31	8.70
6-9	4.08	5.31	4.08	2.23
9-12	2.11	5.08	2.18	0.76
12-15	1.45	2.29	1.14	0.31
15-18	1.88	1.96	0.90	0.14
18-21	1.25	1.12	0.24	0.09
21-24	0.79	0.82	0.07	0.09
24-27	1.13	0.57	0.06	0.08
27-30	1.19	0.22	0.03	0.04
30-33	0.50	0.18	0.01	0.03
33-36	0.14	0.08	0.02	0.02
36-39	0.09	0.05	0.02	0.01
39-42	0.04	0.04	0.02	0.01
42-45	0.03	0.02	0.02	0.01
45-48	0.01	0.02	0.01	0.01
48-51	0.01	0.02	0.01	0.02
51-54	0.01	0.03	0.01	0.03
54-57	0.01	0.01	0.01	0.03
57-60	0.01	0.01	0.01	0.00
60-63	0.01	0.01	0.01	0.00
63-66	0.01	0.01	0.01	0.00
66-69	0.01	0.01	0.00	0.00
69-72	0.01	0.01	0.00	0.00
Total	43.81	45.65	56.39	38.21

Table 6: Mean tissue concentrations of radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw to male and female rats

Single animal data and group mean values. Results are expressed in $\mu\text{g Eq/g}$

Time after administration	male animals				female animals			
	1 h	4 h	36 h	46 h	1 h	4 h	37 h	50 h
Blood cells	10.00	4.73	2.80	1.44	16.86	5.20	2.84	1.93
Plasma	57.39	26.54	8.54	5.23	65.22	26.00	10.31	4.29
Lung	33.22	11.34	3.51	2.18	40.89	11.47	4.32	1.74
Heart	17.38	7.51	2.14	1.08	17.97	6.03	2.15	1.12
Spleen	11.62	5.72	2.30	1.44	17.13	3.01	0.81	0.46
Kidney	100.61	48.32	14.77	8.87	6.61	2.02	0.70	0.36
Adrenal glands	22.20	10.76	4.35	1.77	29.94	9.02	3.45	1.55
Testes/Ovaries	11.12	5.85	1.62	1.09	33.64	14.78	3.93	2.01
Uterus	---	---	---	---	28.53	10.51	3.77	1.52
Muscle	11.21	3.18	0.92	0.63	18.16	3.09	0.93	0.47
Brain	4.30	1.22	0.49	0.37	78.51	27.22	9.32	5.00
Adipose tissue	3.49	1.41	0.74	0.77	5.46	3.22	0.86	0.55
Bone	4.81	2.20	0.66	0.45	5.74	2.37	0.89	0.39
Bone marrow	14.12	7.58	2.74	1.83	16.63	6.10	3.73	2.51
Thyroid	25.55	11.51	4.37	3.34	44.63	17.98	7.20	5.28
Pancreas	25.11	16.01	9.81	4.23	43.33	16.26	3.24	2.04
Stomach content	7607.60	7583.13	1202.81	16.38	6217.84	8113.56	41.54	36.09
Stomach	1418.18	604.60	155.30	5.05	1224.41	715.93	7.32	3.19
Gut content	2109.62	3716.80	872.45	447.83	1399.90	2854.16	1095.54	536.71
Gut	407.99	554.84	146.20	88.21	566.76	744.24	250.08	93.19
Liver	67.88	48.07	19.94	8.61	64.40	41.08	18.14	7.09
Skin	30.64	10.12	3.47	2.20	40.83	9.35	4.50	1.78
Carcass	49.42	24.93	39.59	33.10	39.87	21.21	49.89	33.01

Table 7: Mean tissue concentrations of radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to male and female rats

Single animal data and group mean values. Results are expressed in $\mu\text{g Eq/g}$

Time after administration	male animals				female animals			
	1	4	18	25	1 h	4 h	17 h	22 h
Blood cells	1.29	0.26	0.12	0.08	0.78	0.41	0.27	0.12
Plasma	10.50	3.00	1.24	0.76	6.38	4.35	1.88	1.10
Lung	4.39	1.14	0.47	0.30	3.29	1.77	0.68	0.38
Heart	2.85	0.65	0.26	0.16	1.30	0.96	0.42	0.22
Spleen	1.26	0.40	0.16	0.10	0.78	0.49	0.21	0.12
Kidney	16.17	5.49	2.19	1.35	7.12	4.01	1.79	1.13
Adrenal glands	3.12	0.90	0.39	0.23	1.92	1.66	0.50	0.35
Testes/Ovaries	1.67	0.47	0.21	0.14	3.21	1.64	0.72	0.40
Uterus	---	---	---	---	2.09	1.40	0.54	0.33
Muscle	1.05	0.26	0.13	0.07	0.57	0.36	0.15	0.09
Brain	0.42	0.09	0.04	0.02	0.18	0.11	0.05	0.04
Adipose tissue	0.53	0.14	0.07	0.04	0.45	0.22	0.08	0.05
Bone	0.79	0.23	0.08	0.06	0.28	0.19	0.05	0.04
Bone marrow	1.98	0.56	0.25	0.23	1.09	0.97	0.69	0.47
Thyroid	3.59	1.70	0.61	0.46	5.39	2.91	0.86	0.67
Pancreas	3.42	0.75	0.33	0.22	1.81	1.72	0.43	0.25
Stomach content	620.47	267.98	3.93	36.52	974.46	288.63	2.19	4.35
Stomach	63.97	47.31	1.34	1.26	132.97	50.64	1.85	1.17
Gut content	476.09	544.84	160.30	119.15	286.02	621.81	253.87	138.22
Gut	56.85	58.59	19.06	14.93	113.67	83.01	26.59	13.18
Liver	19.25	8.67	2.92	1.66	8.76	9.26	3.23	1.98
Skin	4.21	1.07	0.56	0.29	2.41	1.42	0.64	0.40
Carcass	3.71	3.85	1.62	1.29	2.12	2.05	2.20	1.50

Table 8: Excretion and retention of radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol to male rats at a target dose level of 300 mg/kg bw

Single animal data and group mean values. Results expressed as % of the radioactivity administered

Animal No.	1	2	3	4	Mean	SD
Animal weight [g]	299.1	277.5	302.5	306.2	296.3	12.9
Spec. activity [MBq/g]	---	---	---	---	51.2	---
Dose admin. [mg/kg bw]	307.9	311.6	310.2	314.3	311.0	2.7
Radioact. dose [MBq/animal]	4.70	4.41	4.79	4.91	4.70	0.21
Urine 0-6h	7.88	6.68	11.04	5.18	7.69	2.49
Urine 6-12h	5.74	5.16	10.81	13.78	8.87	4.14
Urine 12-24h	6.64	10.44	11.46	12.78	10.33	2.64
Urine 24-48h	9.10	14.61	18.76	15.17	14.41	3.99
Urine 48-72h	2.25	5.42	3.98	3.34	3.75	1.32
Urine 72-96h	1.15	1.50	1.02	1.97	1.41	0.42
Urine 96-120h	0.48	0.58	0.61	1.00	0.67	0.23
Urine 120-144h	0.41	0.38	0.43	0.79	0.50	0.19
Urine 144-168h	0.48	0.41	0.21	0.55	0.41	0.15
Subtotal Urine	34.13	45.18	58.32	54.57	48.05	10.80
Feces 0-24h	33.69	19.26	11.94	20.66	21.39	9.05
Feces 24-48h	18.25	21.01	16.40	13.74	17.35	3.06
Feces 48-72h	1.63	8.01	5.05	2.56	4.31	2.85
Feces 72-96h	0.46	1.37	0.85	0.53	0.80	0.41
Feces 96-120h	0.07	0.20	0.21	0.17	0.16	0.06
Feces 120-144h	0.07	0.07	0.11	0.13	0.10	0.03
Feces 144-168h	0.05	0.07	0.11	0.09	0.08	0.02
Subtotal Feces	54.22	49.99	34.67	37.90	44.20	9.39
Cage wash	1.72	2.17	2.52	3.84	2.56	0.92
Blood cells	0.00	0.00	0.00	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Lung	0.00	0.00	0.00	0.00	0.00	0.00
Heart	0.00	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00	0.00
Kidney	0.00	0.00	0.00	0.00	0.00	0.00
Adrenals	0.00	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00	0.00
Uterus	---	---	---	---	---	---
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00	0.00
Stomach cont.	0.01	0.00	0.00	0.01	0.01	0.01
Stomach	0.00	0.00	0.00	0.00	0.00	0.00
Gut cont.	0.06	0.13	0.11	0.09	0.10	0.03
Gut	0.00	0.01	0.01	0.01	0.01	0.00
Liver	0.00	0.00	0.00	0.00	0.00	0.00
Skin	0.02	0.01	0.01	0.02	0.02	0.01
Carcass	0.23	0.10	0.22	0.21	0.19	0.06
Total	90.41	97.60	95.87	96.66	95.14	3.23

Table 9: Excretion and retention of radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol to female rats at a target dose level of 300 mg/kg bw

Single animal data and group mean values. Results expressed as % of the radioactivity

Animal No.	5	6	7	8	Mean	SD
Animal weight [g]	228.3	209.8	215.4	232.4	221.5	10.6
Spec. activity [MBq/g]	---	---	---	---	51.2	---
Dose admin. [mg/kg bw]	312.7	314.0	320.8	316.3	315.9	3.6
Radioact. dose [MBq/animal]	3.64	3.36	3.52	3.75	3.57	0.17
Urine 0-6	13.39	9.79	10.54	11.85	11.39	1.58
Urine 6-12	4.77	5.72	3.17	6.07	4.93	1.30
Urine 12-24	6.51	8.03	7.47	9.59	7.90	1.29
Urine 24-48	8.38	10.15	8.47	12.12	9.78	1.76
Urine 48-72	2.48	1.65	1.53	5.75	2.85	1.98
Urine 72-96	0.59	0.48	0.76	1.41	0.81	0.42
Urine 96-120	0.66	0.58	0.60	0.32	0.54	0.15
Urine 120-144	0.73	0.53	0.73	0.17	0.54	0.26
Urine 144-168	0.48	0.19	0.29	0.14	0.27	0.15
Subtotal Urine	37.99	37.11	33.55	47.43	39.02	5.93
Feces 0-24h	38.53	19.49	35.60	12.59	26.55	12.52
Feces 24-48h	13.68	30.77	22.95	26.92	23.58	7.33
Feces 48-72h	4.01	2.98	2.67	7.01	4.17	1.98
Feces 72-96h	0.58	0.47	0.28	2.55	0.97	1.06
Feces 96-120h	0.09	0.17	0.29	0.33	0.22	0.11
Feces 120-144h	0.09	0.15	0.21	0.04	0.12	0.07
Feces 144-168h	0.05	0.17	0.13	0.03	0.10	0.07
Subtotal Feces	57.03	54.19	62.13	49.47	55.71	5.30
Cage wash	4.18	2.41	2.36	1.45	2.60	1.15
Blood cells	0.00	0.00	0.00	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Lung	0.00	0.00	0.00	0.00	0.00	0.00
Heart	0.00	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00	0.00
Kidney	0.00	0.00	0.00	0.00	0.00	0.00
Adrenals	0.00	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00	0.00
Uterus	0.00	0.00	0.00	0.00	0.00	0.00
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00	0.00
Stomach cont.	0.00	0.02	0.01	0.01	0.01	0.01
Stomach	0.00	0.00	0.00	0.00	0.00	0.00
Gut cont.	0.04	0.04	0.04	0.03	0.04	0.01
Gut	0.00	0.01	0.01	0.00	0.01	0.00
Liver	0.00	0.00	0.00	0.00	0.00	0.00
Skin	0.01	0.07	0.06	0.04	0.05	0.02
Carcass	0.99	1.57	1.47	0.60	1.16	0.45
Total	100.26	95.42	99.63	99.03	98.58	2.17

Table 10: Excretion and retention of radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol to male rats at a target dose level of 30 mg/kg bw

Single animal data and group mean values. Results expressed as % of the radioactivity administered

Animal No.	9	10	11	12	Mean ¹	SD ¹	Mean ²	SD ²
Animal weight [g]	356.1	334.8	345.7	331.3	340.7	13.4	342.0	11.2
Spec. activity [MBq/g]	---	---	---	---	508.0	---	508.0	---
Dose admin. [mg/kg bw]	30.6	30.3	30.4	30.3	30.4	0.2	30.4	0.1
Radioact. dose [MBq/animal]	5.54	5.16	5.35	5.10	5.27	0.24	5.29	0.20
Urine 0-6h	12.54	25.34	16.06	9.03	15.63	8.58	15.74	7.01
Urine 6-12h	26.10	20.99	10.21	12.94	20.01	6.63	17.56	7.30
Urine 12-24h	8.51	16.02	7.69	16.28	13.60	4.41	12.12	4.66
Urine 24-48h	6.55	4.46	7.23	12.08	7.69	3.94	7.58	3.22
Urine 48-72h	0.90	0.86	1.40	3.37	1.71	1.44	1.63	1.18
Urine 72-96h	0.29	0.29	0.46	0.82	0.47	0.31	0.46	0.25
Urine 96-120h	0.18	0.31	0.31	1.00	0.50	0.44	0.45	0.37
Urine 120-144h	0.12	0.18	0.54	0.50	0.27	0.20	0.34	0.22
Urine 144-168h	0.11	0.17	0.36	0.46	0.25	0.19	0.28	0.16
Subtotal Urine	55.31	68.60	44.25	56.47	60.13	7.36	56.16	9.96
Feces 0-24h	39.01	27.53	30.01	29.96	32.17	6.05	31.63	5.06
Feces 24-48h	11.40	5.56	6.81	11.79	9.58	3.49	8.89	3.17
Feces 48-72h	0.61	0.52	0.57	1.42	0.85	0.50	0.78	0.43
Feces 72-96h	0.09	0.07	0.14	0.50	0.22	0.25	0.20	0.21
Feces 96-120h	0.06	0.02	0.15	0.17	0.09	0.08	0.10	0.07
Feces 120-144h	0.05	0.02	0.06	0.08	0.05	0.03	0.05	0.03
Feces 144-168h	0.04	0.01	0.07	0.09	0.05	0.04	0.05	0.04
Subtotal Feces	51.26	33.72	37.81	44.03	43.00	8.81	41.70	7.65
Cage wash	0.21	0.27	3.04	3.12	1.20	1.66	1.66	1.64
Blood cells	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Lung	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Heart	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Kidney	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Adrenals	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Uterus	---	---	---	---	---	---	---	---
Muscle	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Stomach cont.	0.02	0.01	0.00	0.03	0.02	0.01	0.01	0.01
Stomach	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Gut cont.	0.02	0.02	0.05	0.10	0.05	0.05	0.05	0.04
Gut	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Liver	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Skin	0.01	0.01	0.02	0.01	0.01	0.00	0.01	0.01
Carcass	0.89	0.70	1.57	1.20	0.93	0.25	1.09	0.38
Total	107.71	103.32	86.74	104.96	105.33	2.22	100.68	9.47

¹ animal 11 was not included into statistics due to insufficient recovery

² mean calculated for all four animals, as pooled for metabolism investigations (AP study ID 858428)

Table 11: Excretion and retention of radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol to female rats at a target dose level of 30 mg/kg bw

Single animal data and group mean values. Results expressed as % of the radioactivity administered

Animal No.	13	14	15	16	Mean	SD
Animal weight [g]	213.8	242.3	229.7	215.9	225.4	13.3
Spec. activity [MBq/g]	---	---	---	---	508.0	---
Dose admin. [mg/kg bw]	30.4	31.2	31.4	30.2	30.8	0.6
Radioact. dose [MBq/animal]	3.30	3.85	3.67	3.32	3.53	0.27
Urine 0-6	16.02	12.38	8.39	16.51	13.32	3.77
Urine 6-12	22.31	12.67	11.30	14.46	15.18	4.92
Urine 0-24	24.96	10.98	5.29	9.01	12.56	8.60
Urine 24-48	3.79	5.20	5.36	9.76	6.03	2.59
Urine 48-72	1.82	1.09	3.23	1.23	1.84	0.98
Urine 72-96	0.70	0.53	1.35	0.65	0.81	0.37
Urine 96-120	0.57	0.40	0.73	0.98	0.67	0.25
Urine 120-144	0.22	0.18	0.98	0.97	0.59	0.45
Urine 144-168	0.37	0.23	0.98	0.24	0.45	0.36
Subtotal Urine	70.75	43.64	37.61	53.79	51.45	14.50
Feces 0-24h	24.95	37.31	42.35	29.73	33.59	7.75
Feces 24-48h	4.32	7.36	5.57	5.99	5.81	1.25
Feces 48-72h	0.43	0.93	0.89	1.02	0.82	0.26
Feces 72-96h	0.38	0.19	0.41	0.18	0.29	0.12
Feces 96-120h	0.20	0.11	0.17	0.16	0.16	0.04
Feces 120-144h	0.10	0.10	0.08	0.14	0.10	0.03
Feces 144-168h	0.04	0.08	0.11	0.10	0.08	0.03
Subtotal Feces	30.44	46.07	49.58	37.32	40.85	8.65
Cage wash	4.43	2.64	5.25	2.72	3.76	1.29
Blood cells	0.00	0.00	0.00	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Lung	0.00	0.00	0.00	0.00	0.00	0.00
Heart	0.00	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00	0.00
Kidney	0.00	0.00	0.00	0.00	0.00	0.00
Adrenals	0.00	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00	0.00
Uterus	0.00	0.00	0.00	0.00	0.00	0.00
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00	0.00
Stomach cont.	0.01	0.01	0.03	0.02	0.02	0.01
Stomach	0.00	0.00	0.00	0.00	0.00	0.00
Gut cont.	0.12	0.11	0.09	0.04	0.09	0.04
Gut	0.01	0.00	0.01	0.01	0.01	0.00
Liver	0.00	0.00	0.00	0.00	0.00	0.00
Skin	0.00	0.02	0.01	0.01	0.01	0.01
Carcass	0.52	0.52	1.12	1.75	0.98	0.59
Total	106.29	93.02	93.72	95.65	97.17	6.18

Table 12: Excretion and retention of radioactivity after 14 daily oral administrations of DHDPS and one oral administration of ^{14}C -4,4'-sulphonyldiphenol on day 15 (30 mg/kg bw) to male rats

Single animal data and group mean values. Results expressed as % of the radioactivity administered

Animal No.	17	18	19	20	Mean ¹	SD ¹
Animal weight [g]	352.8	331.5	340.2	322.1	338.4	15.4
Spec. activity [MBq/g]	---	---	---	---	508.0	---
Dose admin. [mg/kg bw]	30.7	30.5	30.4	30.5	30.5	0.2
Radioact. dose [MBq/animal]	5.51	5.15	5.25	5.00	5.25	0.26
Urine 0-6h	5.69	18.39	14.90	4.75	8.45	5.60
Urine 6-12h	5.92	11.05	9.32	15.94	10.39	5.10
Urine 12-24h	28.58	13.24	16.39	16.62	20.53	6.97
Urine 24-48h	7.51	4.58	7.09	6.95	7.18	0.29
Urine 48-72h	1.58	1.59	2.64	1.77	2.00	0.57
Urine 72-96h	0.66	0.77	0.95	1.03	0.88	0.19
Urine 96-120h	0.56	0.70	0.65	1.19	0.80	0.34
Urine 120-144h	0.37	0.53	0.47	0.63	0.49	0.13
Urine 144-168h	0.27	0.92	0.50	0.33	0.37	0.12
Subtotal Urine	51.15	51.77	52.91	49.21	51.09	1.85
Feces 0-24h	26.42	17.32	29.56	27.72	27.90	1.58
Feces 24-48h	15.59	4.26	9.67	11.52	12.26	3.03
Feces 48-72h	0.95	0.49	0.84	1.06	0.95	0.11
Feces 72-96h	0.34	0.23	0.44	0.31	0.36	0.07
Feces 96-120h	0.17	0.15	0.26	0.22	0.22	0.05
Feces 120-144h	0.16	0.11	0.19	0.15	0.17	0.02
Feces 144-168h	0.10	0.10	0.10	1.21	0.47	0.64
Subtotal Feces	43.73	22.65	41.06	42.19	42.33	1.34
Cage wash	1.96	1.21	2.52	1.86	2.11	0.35
Blood cells	0.00	0.00	0.00	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Lung	0.00	0.00	0.00	0.00	0.00	0.00
Heart	0.00	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00	0.00
Kidney	0.00	0.00	0.00	0.00	0.00	0.00
Adrenals	0.00	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00	0.00
Uterus	---	---	---	---	---	---
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00	0.00
Stomach cont.	0.01	0.03	0.03	0.00	0.01	0.01
Stomach	0.00	0.00	0.00	0.00	0.00	0.00
Gut cont.	0.08	0.12	0.19	0.09	0.12	0.06
Gut	0.01	0.01	0.01	0.01	0.01	0.00
Liver	0.00	0.00	0.00	0.00	0.00	0.00
Skin	0.01	0.01	0.01	0.01	0.01	0.00
Carcass	0.71	0.98	0.46	0.39	0.52	0.17
Total	97.65	76.78	97.20	93.77	96.21	2.12

¹ animal 18 was not included into statistics due to insufficient recovery

Table 13: Excretion and retention of radioactivity after 14 daily oral administrations of DHDPS and one oral administration of ^{14}C -4,4'-sulphonyldiphenol on day 15 (30 mg/kg bw) to female rats

Single animal data and group mean values. Results expressed as % of the radioactivity administered

Animal No.	21	22	23	24	Mean	SD
Animal weight [g]	223.8	238.9	242.8	239.0	236.1	8.4
Spec. activity [MBq/g]	---	---	---	---	508.0	---
Dose admin. [mg/kg bw]	31.0	30.9	31.1	32.4	31.3	0.7
Radioact. dose [MBq/animal]	3.53	3.75	3.85	3.94	3.77	0.17
Urine 0-6	12.99	23.49	12.02	8.22	14.18	6.54
Urine 6-12	9.02	7.75	13.98	5.73	9.12	3.51
Urine 12-24	3.90	17.06	27.51	20.91	17.34	9.95
Urine 24-48	8.67	5.08	5.35	5.85	6.24	1.65
Urine 48-72	3.32	1.32	3.00	2.03	2.42	0.92
Urine 72-96	0.68	0.75	1.02	1.12	0.89	0.21
Urine 96-120	0.67	0.60	0.89	1.01	0.79	0.19
Urine 120-144	0.92	0.18	0.38	0.31	0.45	0.33
Urine 144-168	0.33	0.23	0.62	0.39	0.39	0.17
Subtotal Urine	40.51	56.45	64.76	45.57	51.82	10.89
Feces 0-24h	31.35	21.80	27.23	37.95	29.58	6.81
Feces 24-48h	16.88	13.11	9.75	12.29	13.01	2.95
Feces 48-72h	1.19	0.34	0.60	0.50	0.66	0.37
Feces 72-96h	0.32	0.17	0.41	0.31	0.30	0.10
Feces 96-120h	0.26	0.11	0.18	0.28	0.21	0.08
Feces 120-144h	0.20	0.08	0.10	0.14	0.13	0.05
Feces 144-168h	0.19	0.03	0.07	0.10	0.10	0.07
Subtotal Feces	50.41	35.63	38.35	51.57	43.99	8.17
Cage wash	2.02	1.18	3.99	1.96	2.28	1.20
Blood cells	0.00	0.00	0.00	0.00	0.00	0.00
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Lung	0.00	0.00	0.00	0.00	0.00	0.00
Heart	0.00	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00	0.00
Kidney	0.00	0.00	0.00	0.00	0.00	0.00
Adrenals	0.00	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00	0.00
Uterus	0.00	0.00	0.00	0.00	0.00	0.00
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00	0.00
Stomach cont.	0.01	0.01	0.00	0.00	0.00	0.00
Stomach	0.00	0.00	0.00	0.00	0.00	0.00
Gut cont.	0.06	0.07	0.11	0.09	0.08	0.02
Gut	0.01	0.00	0.01	0.01	0.01	0.00
Liver	0.00	0.00	0.00	0.00	0.00	0.00
Skin	0.01	0.05	0.01	0.01	0.02	0.02
Carcass	1.22	1.46	1.63	1.57	1.47	0.18
Total	94.24	94.84	108.86	100.79	99.69	6.80

Table 14: Concentrations of plasma and blood cells of radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol to male rats at a target dose level of 300 mg/kg bw

Single animal data and group mean values. Results are expressed in $\mu\text{g Eq/g}$

Animal No.	39	40	41	42	Mean	SD
Body weight [g]	331.9	323.2	324.3	306.4	321.5	10.8
Spec. act. [MBq/g]	---	---	---	---	33.45	---
Dose [mg/kg bw]	303.7	309.4	301.5	307.5	305.5	3.6
Radioact. dose [MBq/animal]	3.37	3.35	3.27	3.15	3.29	0.10
Time [h]						
Plasma						
1	63.06	39.39	63.20	66.97	58.16	12.64
2	18.04	21.38	23.92	30.22	23.39	5.15
4	24.16	22.05	36.28	27.43	27.48	6.27
8	27.53	18.55	24.06	27.30	24.36	4.18
24	17.02	25.36	27.31	16.96	21.66	5.45
48	7.93	5.74	2.36	5.60	5.41	2.29
72	1.65	0.95	< loq	0.80	0.85	0.68
96	< loq	< loq	< loq	< loq	< loq	n.d.
120	< loq	< loq	< loq	< loq	< loq	n.d.
144	< loq	< loq	< loq	< loq	< loq	n.d.
168	< loq	< loq	< loq	< loq	< loq	n.d.
Blood cells						
1	18.92	8.19	9.72	12.96	12.45	4.75
2	2.54	2.64	3.24	4.00	3.10	0.67
4	4.61	2.72	10.68	5.01	5.76	3.43
8	3.61	5.17	5.25	3.87	4.48	0.86
24	7.94	6.26	2.44	3.18	4.96	2.59
48	1.04	1.68	< loq	2.19	1.23	0.94
72	< loq	< loq	< loq	< loq	< loq	n.d.
96	< loq	< loq	< loq	< loq	< loq	n.d.
120	< loq	< loq	< loq	< loq	< loq	n.d.
144	< loq	< loq	< loq	< loq	< loq	n.d.
168	< loq	< loq	< loq	< loq	< loq	n.d.

for statistics, values < loq are set to 0

Table 15: Concentrations of plasma and blood cells of radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol to female rats at a target dose level of 300 mg/kg bw

Single animal data and group mean values. Results are expressed in $\mu\text{g Eq/g}$

Animal No.	43	44	45	46	Mean	SD
Body weight [g]	245.6	241.4	250.1	233.4	242.6	7.1
Spec. act. [MBq/g]	---	---	---	---	33.45	---
Dose [mg/kg bw]	304.0	316.3	306.4	292.3	304.7	9.9
Radioact. dose [MBq/animal]	2.50	2.55	2.56	2.28	2.47	0.13
Time [h]						
Plasma						
1	121.51	84.74	76.13	137.32	104.93	29.22
2	18.80	31.34	21.84	19.64	22.90	5.77
4	31.31	28.83	24.35	21.40	26.47	4.44
8	23.71	30.48	24.95	19.37	24.63	4.58
24	13.73	22.05	23.17	16.97	18.98	4.42
48	3.30	7.80	9.55	8.06	7.18	2.70
72	2.38	4.15	1.38	< loq	1.98	1.75
96	< loq	< loq	< loq	< loq	< loq	n.d.
120	< loq	< loq	< loq	< loq	< loq	n.d.
144	< loq	< loq	< loq	< loq	< loq	n.d.
168	< loq	< loq	< loq	< loq	< loq	n.d.
Blood cells						
1	19.57	11.00	19.89	31.60	20.52	8.46
2	3.48	4.79	4.70	4.95	4.48	0.68
4	8.72	8.97	4.87	3.84	6.60	2.63
8	4.79	5.30	3.81	4.07	4.49	0.68
24	2.26	2.87	4.82	2.58	3.13	1.15
48	1.29	1.70	2.13	1.82	1.73	0.35
72	0.76	1.00	1.22	1.08	1.01	0.19
96	< loq	< loq	< loq	< loq	< loq	n.d.
120	< loq	< loq	< loq	< loq	< loq	n.d.
144	< loq	< loq	< loq	< loq	< loq	n.d.
168	< loq	< loq	< loq	< loq	< loq	n.d.

for statistics, values < loq are set to 0

Table 16: Concentrations of plasma and blood cells of radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol to male rats at a target dose level of 30 mg/kg bw

Single animal data and group mean values. Results are expressed in $\mu\text{g Eq/g}$

Animal No.	47	48	49	50	Mean	SD
Body weight [g]	331.7	325.6	312.4	308.9	319.7	10.8
Spec. act. [MBq/g]	---	---	---	---	319.5	---
Dose [mg/kg bw]	29.9	30.4	30.1	30.3	30.2	0.2
Radioact. dose [MBq/animal]	3.17	3.17	3.01	3.00	3.09	0.10
Time [h]						
Plasma						
1	7.50	9.38	9.12	8.61	8.66	0.83
2	2.87	3.97	4.14	2.13	3.28	0.95
4	3.99	5.06	2.30	3.88	3.81	1.14
8	2.87	2.91	1.77	2.64	2.55	0.53
24	1.46	0.71	0.80	0.98	0.99	0.33
48	0.16	0.09	0.13	0.13	0.13	0.03
72	< loq	< loq	< loq	< loq	< loq	n.d.
96	< loq	< loq	< loq	< loq	< loq	n.d.
120	< loq	< loq	< loq	< loq	< loq	n.d.
144	< loq	< loq	< loq	< loq	< loq	n.d.
168	< loq	< loq	< loq	< loq	< loq	n.d.
Blood cells						
1	1.70	1.86	1.65	1.33	1.63	0.22
2	0.56	0.75	0.69	0.54	0.64	0.10
4	0.54	0.75	0.35	0.62	0.56	0.17
8	0.42	0.46	0.32	0.31	0.38	0.07
24	< loq	0.15	0.16	0.30	0.15	0.12
48	< loq	< loq	< loq	< loq	< loq	n.d.
72	< loq	< loq	< loq	< loq	< loq	n.d.
96	< loq	< loq	< loq	< loq	< loq	n.d.
120	< loq	< loq	< loq	< loq	< loq	n.d.
144	0.26	< loq	0.20	< loq	0.11	0.13
168	< loq	< loq	< loq	< loq	< loq	n.d.

for statistics, values < loq are set to 0

Table 17: Concentrations of plasma and blood cells of radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol to female rats at a target dose level of 30 mg/kg bw

Single animal data and group mean values. Results are expressed in $\mu\text{g Eq/g}$

Animal No.	51	52	53	54	Mean	SD
Body weight [g]	232.2	239.9	209.5	243.3	231.2	15.2
Spec. act. [MBq/g]	---	---	---	---	319.5	---
Dose [mg/kg bw]	30.3	29.9	30.5	30.6	30.3	0.3
Radioact. dose [MBq/animal]	2.25	2.29	2.05	2.38	2.24	0.14
Time [h]						
Plasma						
1	7.79	6.21	8.55	3.82	6.59	2.09
2	2.42	1.73	2.44	1.13	1.93	0.62
4	5.47	4.52	4.57	3.64	4.55	0.75
8	3.31	3.51	4.79	2.07	3.42	1.11
24	0.64	0.60	0.99	1.56	0.95	0.45
48	0.08	0.09	0.19	0.23	0.15	0.07
72	< loq	< loq	< loq	0.04	0.01	0.02
96	< loq	< loq	< loq	< loq	< loq	n.d.
120	< loq	< loq	< loq	< loq	< loq	n.d.
144	< loq	< loq	< loq	< loq	< loq	n.d.
168	< loq	< loq	< loq	< loq	< loq	n.d.
Blood cells						
1	1.23	0.69	2.36	0.50	1.19	0.84
2	0.29	0.37	0.40	0.28	0.33	0.06
4	0.67	0.84	1.28	0.54	0.83	0.32
8	0.47	0.56	0.84	0.41	0.57	0.19
24	0.18	0.16	0.19	0.19	0.18	0.01
48	< loq	< loq	< loq	< loq	< loq	n.d.
72	< loq	< loq	< loq	0.12	0.03	0.06
96	0.28	< loq	0.09	< loq	0.09	0.13
120	0.11	< loq	< loq	0.22	0.08	0.11
144	0.15	< loq	0.28	0.15	0.15	0.12
168	< loq	0.15	0.23	0.15	0.13	0.09

for statistics, values < loq are set to 0

Table 18: Ratio of blood cells/plasma concentrations of radioactivity after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at target dose levels of 300 and 30 mg/kg bw to male and female rats, respectively

300 mg/kg bw

Time [h]	male	female	mean
1	0.21	0.20	0.20
2	0.13	0.20	0.16
4	0.21	0.25	0.23
8	0.18	0.18	0.18
24	0.23	0.17	0.20
48	0.23	0.24	0.24
72	< loq	0.51	n.d.
96	< loq	< loq	< loq
120	< loq	< loq	< loq
144	< loq	< loq	< loq
168	< loq	< loq	< loq
Mean	0.11	0.16	0.15

for statistics, values < loq are set to 0

30 mg/kg bw

Time [h]	male	female	mean
1	0.19	0.18	0.18
2	0.19	0.17	0.18
4	0.15	0.18	0.17
8	0.15	0.17	0.16
24	0.15	0.19	0.17
48	< loq	< loq	< loq
72	< loq	3.00	n.d.
96	< loq	< loq	< loq
120	< loq	< loq	< loq
144	< loq	< loq	< loq
168	< loq	< loq	< loq
Mean	0.08	0.35	0.09

for statistics, values < loq are set to 0

Table 19: Excretion pattern of radioactivity via bile after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw to male rats

Single animal data and group mean values. Results expressed in % of the radioactivity administered

Animal No.	27	28	29	30	31	32	Mean	SD
Animal weight [g]	266.6	278.9	245.4	306.4	306.5	321.1	287.5	28.7
Spec. activity [MBq/g]	---	---	---	---	---	---	45.7	---
Dose admin. [mg/kg bw]	310.3	308.6	320.1	313.8	304.2	307.2	310.7	5.6
Radioact. dose [MBq/animal]	3.78	3.93	3.59	4.39	4.26	4.50	4.08	0.36
Urine 0-24	22.11	22.04	32.07	52.77	38.19	89.08	42.71	25.44
Urine 24-48	0.44	1.03	17.52	0.66	6.99	0.55	4.53	6.85
Urine 48-72	0.08	0.10	0.44	0.35	0.54	0.18	0.28	0.19
Subtotal Urine	22.63	23.16	50.03	53.79	45.72	89.81	47.52	24.70
Feces 0-24	0.49	0.00	0.35	1.09	0.97	0.71	0.60	0.41
Feces 24-48	0.10	0.07	0.77	0.23	0.37	0.07	0.27	0.27
Feces 48-72	0.03	0.24	0.31	0.06	0.08	0.15	0.15	0.11
Subtotal Feces	0.62	0.31	1.44	1.38	1.42	0.93	1.02	0.47
Bile 0-24h	69.66	62.86	41.88	36.20	26.20	7.12	40.66	23.19
Bile 24-48h	0.35	5.23	1.21	0.32	11.49	0.00	3.10	4.55
Bile 48-72h	0.07	0.10	0.06	0.00	0.10	0.01	0.06	0.04
Subtotal Bile	70.08	68.20	43.15	36.52	37.79	7.14	43.81	23.32
Cage wash	0.25	0.50	1.20	0.91	2.58	0.56	1.00	0.84
Stomach cont.	0.02	0.01	0.06	0.04	0.10	0.02	0.04	0.03
Stomach	0.00	0.01	0.00	0.00	0.02	0.00	0.01	0.01
Gut cont.	0.04	0.06	0.03	0.02	0.07	0.01	0.04	0.02
Gut	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Carcass	0.04	0.32	0.60	0.54	0.41	0.41	0.39	0.20
Total	93.70	92.57	96.50	93.20	88.11	98.88	93.83	3.67
fraction absorbed	93.01	92.18	94.98	91.75	86.49	97.92	92.72	3.80

Table 20: Excretion pattern of radioactivity via bile after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw to female rats

Single animal data and group mean values. Results expressed in % of the radioactivity administered

Animal No.	55	56	57	58	59	60	Mean	SD
Animal weight [g]	236.0	218.8	233.7	268.5	225.6	242.2	237.5	17.3
Spec. activity [MBq/g]	---	---	---	---	---	---	44.50	---
Dose admin. [mg/kg bw]	311.3	306.8	309.0	309.9	294.1	280.2	301.9	12.3
Radioact. dose [MBq/animal]	3.27	2.99	3.21	3.70	2.95	3.02	3.19	0.28
Urine 0-24	25.74	22.56	30.96	34.27	65.56	76.82	42.65	22.76
Urine 24-48	0.64	0.92	0.36	30.67	1.51	1.61	5.95	12.12
Urine 48-72	0.10	0.09	0.16	0.60	0.36	0.52	0.31	0.22
Subtotal Urine	26.47	23.56	31.49	65.55	67.43	78.95	48.91	24.38
Feces 0-24	0.46	0.11	0.39	0.63	0.49	0.53	0.43	0.18
Feces 24-48	0.30	0.48	0.49	0.81	0.77	0.00	0.48	0.30
Feces 48-72	0.04	0.07	0.31	0.02	0.12	0.17	0.12	0.11
Subtotal Feces	0.80	0.65	1.19	1.46	1.38	0.70	1.03	0.36
Bile 0-24h	67.27	73.16	63.94	14.88	30.32	19.51	44.85	26.16
Bile 24-48h	2.40	1.56	0.31	0.01	0.00	0.00	0.71	1.02
Bile 48-72h	0.25	0.08	0.07	0.13	0.00	0.00	0.09	0.09
Subtotal Bile	69.92	74.80	64.32	15.01	30.32	19.51	45.65	27.00
Cage wash	1.09	0.19	0.41	1.98	2.16	0.60	1.07	0.83
Stomach cont.	1.62	0.01	0.01	0.02	0.04	0.03	0.29	0.65
Stomach	0.09	0.00	0.00	0.00	0.00	0.00	0.02	0.04
Gut cont.	0.07	0.02	0.03	0.05	0.06	0.03	0.04	0.02
Gut	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Carcass	0.17	0.07	0.31	1.08	0.57	1.01	0.54	0.43
Total	100.25	99.32	97.77	85.14	101.96	100.83	97.55	6.24
fraction absorbed	97.67	98.63	96.53	83.61	100.48	100.07	96.16	6.32

Table 21: Excretion pattern of radioactivity via bile after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to male rats

Single animal data and group mean values. Results expressed in % of the radioactivity administered

Animal No.	33	34	35	36	37	38	Mean	SD
Animal weight [g]	308.9	293.9	306.7	308.3	337.2	316.9	312.0	14.4
Spec. activity [MBq/g]	---	---	---	---	---	---	408.80	---
Dose admin. [mg/kg bw]	33.3	33.6	32.8	31.8	31.9	32.3	32.6	0.7
Radioact. dose [MBq/animal]	4.20	4.04	4.12	4.02	4.40	4.18	4.16	0.14
Urine 0-24	20.30	43.77	20.99	22.25	31.58	82.87	36.96	24.21
Urine 24-48	0.26	1.33	0.42	0.10	0.40	0.91	0.57	0.46
Urine 48-72	0.06	0.31	0.21	0.09	0.17	0.29	0.19	0.10
Subtotal Urine	20.62	45.41	21.61	22.45	32.15	84.07	37.72	24.59
Feces 0-24	0.88	0.07	0.77	0.55	1.60	0.03	0.65	0.58
Feces 24-48	1.07	0.61	0.44	0.19	0.29	0.70	0.55	0.32
Feces 48-72	0.06	0.05	0.14	n.s.	0.06	0.17	0.10	0.05
Subtotal Feces	2.01	0.73	1.35	0.74	1.95	0.89	1.28	0.59
Bile 0-24h	69.55	50.10	72.47	68.70	64.45	11.93	56.20	23.08
Bile 24-48h	0.21	0.08	0.21	0.22	0.20	0.02	0.16	0.08
Bile 48-72h	0.06	0.01	0.00	0.02	0.08	0.01	0.03	0.03
Subtotal Bile	69.82	50.20	72.69	68.94	64.73	11.96	56.39	23.17
Cage wash	0.75	0.74	0.40	0.26	1.13	1.00	0.71	0.34
Stomach cont.	0.04	0.01	0.02	0.01	0.00	0.00	0.01	0.02
Stomach	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Gut cont.	0.02	0.06	0.05	0.09	0.02	0.03	0.04	0.03
Gut	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Carcass	0.33	0.43	0.73	0.87	0.39	0.76	0.58	0.23
Total	93.59	97.57	96.84	93.35	100.37	98.72	96.74	2.80
fraction absorbed	91.52	96.77	95.43	92.51	98.40	97.79	95.40	2.83

animal 38 was dosed 20 minutes later, therefore time intervals are postponed by 20 minutes

Table 22: Excretion pattern of radioactivity via bile after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to female rats

Single animal data and group mean values. Results expressed in % of the radioactivity administered

Animal No.	61	62	63	64	65	66	Mean	SD
Animal weight [g]	189.5	205.2	226.4	222.5	217.0	205.5	209.8	14.9
Spec. activity [MBq/g]	---	---	---	---	---	---	405.8	---
Dose admin. [mg/kg bw]	31.6	31.3	30.1	31.5	29.9	31.4	31.2	0.6
Radioact. dose [MBq/animal]	2.43	2.61	2.76	2.84	2.63	2.62	2.65	0.16
Urine 0-24	76.81	15.89	46.66	27.79	85.02	60.67	45.56	24.51
Urine 24-48	0.76	0.48	0.70	0.11	1.33	0.92	0.59	0.31
Urine 48-72	0.58	0.15	n.s.	0.09	0.64	0.25	0.27	0.22
Subtotal Urine	78.15	16.52	47.36	27.98	86.98	61.85	46.37	24.90
Feces 0-24	1.24	6.29	1.77	1.68	0.89	1.59	2.51	2.12
Feces 24-48	0.21	0.71	0.13	0.27	0.47	0.23	0.31	0.23
Feces 48-72	0.30	0.61	n.s.	0.03	0.13	0.11	0.26	0.26
Subtotal Feces	1.75	7.60	1.91	1.98	1.49	1.92	3.03	2.56
Bile 0-24h	14.30	53.39	37.07	59.60	0.07	25.73	38.02	18.82
Bile 24-48h	0.26	0.17	0.20	0.13	0.41	n.s.	0.19	0.05
Bile 48-72h	0.13	0.02	n.s.	0.03	0.09	n.s.	0.06	0.06
Subtotal Bile	14.69	53.58	37.27	59.76	0.57	25.73	38.21	18.78
Cage wash	1.67	0.51	3.35	0.36	1.56	0.60	1.30	1.26
Stomach cont.	0.02	0.01	0.00	0.01	0.02	0.01	0.01	0.01
Stomach	0.00	0.00	0.09	0.00	0.00	0.00	0.02	0.04
Gut cont.	0.12	0.07	0.05	0.04	0.14	0.08	0.07	0.03
Gut	0.01	0.00	0.02	0.00	0.00	0.00	0.01	0.01
Carcass	0.84	1.06	0.68	0.67	0.51	0.76	0.80	0.16
Total	97.24	79.35	90.74	90.80	91.28	90.95	89.82	6.48
fraction absorbed	95.35	71.66	88.66	88.77	89.62	88.94	86.68	8.86

animal 65 not included into statistics due to low bile flow between 0-9 h

animal 63 died about 2 days after administration, therefore no urine, feces and bile samples were collected 48 – 72 h

Table 23: Excretion of radioactivity via bile after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a dose target level of 300 mg/kg bw to male rats

Single animal data and group mean values. Results expressed in % of the radioactivity administered

Animal No.	27	28	29	30	31	32	Mean	SD
Animal weight [g]	266.6	278.9	245.4	306.4	306.5	321.1	287.5	28.7
Specific activity [MBq/g]	---	---	---	---	---	---	45.70	---
Dose admin. [mg/kg bw]	310.3	308.6	320.1	313.8	304.2	307.2	310.7	5.6
Radioact. Dose [MBq/animal]	3.78	3.93	3.59	4.39	4.26	4.50	4.08	0.36
Time interval [h]								
0-3	37.92	24.89	20.85	21.48	14.99	5.34	20.91	10.80
3-6	16.99	10.45	15.59	9.82	1.79	1.18	9.30	6.67
6-9	8.25	6.73	3.81	3.42	1.78	0.50	4.08	2.93
9-12	4.44	4.47	0.66	0.92	n.s.	0.06	2.11	2.16
12-15	0.90	4.63	n.s.	0.13	1.57	0.02	1.45	1.89
15-18	0.42	4.64	n.s.	0.17	4.15	0.02	1.88	2.31
18-21	0.48	4.48	n.s.	0.14	1.12	0.00	1.25	1.86
21-24	0.27	2.57	0.96	0.12	0.81	0.00	0.79	0.95
24-27	0.14	3.12	0.00	0.12	3.40	0.00	1.13	1.65
27-30	0.06	1.41	0.07	0.08	5.49	0.00	1.19	2.18
30-33	0.03	0.41	0.93	0.05	1.57	0.00	0.50	0.63
33-36	0.01	0.16	0.04	0.03	0.58	0.00	0.14	0.22
36-39	0.02	0.12	0.11	0.02	0.24	0.00	0.09	0.09
39-42	0.04	n.s.	0.00	0.02	0.12	0.00	0.04	0.05
42-45	0.03	n.s.	0.03	n.s.	0.08	0.00	0.03	0.03
45-48	0.01	0.01	0.02	0.00	0.01	0.00	0.01	0.01
48-51	0.01	0.03	0.01	n.s.	0.01	0.00	0.01	0.01
51-54	0.01	0.01	0.00	0.00	0.04	0.00	0.01	0.01
54-57	0.00	0.01	0.01	n.s.	0.02	0.00	0.01	0.01
57-60	0.00	0.01	0.01	n.s.	0.01	0.00	0.01	0.01
60-63	0.00	0.01	0.01	n.s.	0.01	0.00	0.01	0.00
63-66	0.00	0.01	0.01	n.s.	0.00	0.00	0.01	0.00
66-69	0.01	0.01	0.01	n.s.	n.s.	0.00	0.01	0.00
69-72	0.03	0.01	0.01	0.00	0.00	0.00	0.01	0.01
Total	70.08	68.20	43.15	36.52	37.79	7.14	43.81	23.32

Table 24: Excretion of radioactivity via bile after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw to female rats

Single animal data and group mean values. Results expressed in % of the radioactivity administered

Animal No.	55	56	57	58	59	60	Mean	SD
Animal weight [g]	236.0	218.8	233.7	268.5	225.6	242.2	237.5	17.3
Specific activity [MBq/g]	---	---	---	---	---	---	44.5	---
Dose admin. [mg/kg bw]	311.3	306.8	309.0	309.9	294.1	280.2	301.9	12.3
Radioact. Dose [MBq/animal]	3.27	2.99	3.21	3.70	2.95	3.02	3.19	0.28
Time interval [h]								
0-3	20.56	30.64	33.11	13.89	18.14	12.37	21.45	8.62
3-6	16.78	13.49	16.65	0.58	9.06	5.69	10.38	6.47
6-9	10.32	6.52	5.76	n.s.	2.83	1.13	5.31	3.55
9-12	7.21	6.26	6.62	n.s.	n.s.	0.23	5.08	3.26
12-15	6.08	3.82	1.07	0.38	n.s.	0.08	2.29	2.59
15-18	4.16	5.26	0.36	0.02	n.s.	0.00	1.96	2.55
18-21	1.84	4.34	0.24	0.00	0.29	0.00	1.12	1.72
21-24	0.33	2.83	0.13	0.00	n.s.	n.s.	0.82	1.34
24-27	0.62	1.00	0.08	n.s.	n.s.	n.s.	0.57	0.46
27-30	0.58	0.25	0.04	n.s.	n.s.	0.00	0.22	0.27
30-33	0.53	0.14	0.06	n.s.	n.s.	0.00	0.18	0.24
33-36	0.23	0.07	0.04	n.s.	n.s.	0.00	0.08	0.10
36-39	0.17	0.04	0.02	0.00	n.s.	0.00	0.05	0.07
39-42	0.13	0.03	0.04	0.00	n.s.	0.00	0.04	0.05
42-45	0.09	0.01	0.02	0.00	n.s.	0.00	0.02	0.04
45-48	0.06	0.02	0.01	0.00	n.s.	n.s.	0.02	0.03
48-51	0.05	0.01	0.02	0.01	n.s.	0.00	0.02	0.02
51-54	0.12	0.01	0.01	0.01	n.s.	0.00	0.03	0.05
54-57	0.04	0.01	0.01	0.02	n.s.	0.00	0.01	0.01
57-60	0.01	0.01	0.01	0.02	n.s.	0.00	0.01	0.01
60-63	0.01	0.01	0.01	0.02	n.s.	0.00	0.01	0.01
63-66	0.01	0.01	0.01	0.02	n.s.	0.00	0.01	0.01
66-69	0.00	0.01	0.00	0.02	n.s.	n.s.	0.01	0.01
69-72	0.01	0.01	0.00	0.01	n.s.	0.00	0.01	0.01
Total	69.92	74.80	64.32	15.01	30.32	19.51	45.65	27.00

Table 25: Excretion of radioactivity via bile after single oral administration of ¹⁴C-4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to male rats

Single animal data and group mean values. Results expressed in % of the radioactivity administered

Animal No.	33	34	35	36	37	38	Mean	SD
Animal weight [g]	308.9	293.9	306.7	308.3	337.2	316.9	312.0	14.4
Specific activity [MBq/g]	---	---	---	---	---	---	408.8	---
Dose admin. [mg/kg bw]	33.3	33.6	32.8	31.8	31.9	32.3	32.6	0.7
Radioact. Dose [MBq/animal]	4.2	4.0	4.1	4.0	4.4	4.2	4.16	0.14
Time interval [h]								
0-3 (0-2.40)	57.75	43.22	28.98	40.42	51.11	2.45	37.32	19.69
3-6 (2.40-5.40)	7.31	5.67	15.23	15.65	12.14	5.85	10.31	4.62
6-9 (5.40-8.40)	2.85	1.18	9.57	6.80	1.11	2.98	4.08	3.39
9-12 (8.40-11.40)	0.98	0.02	7.14	4.26	0.08	0.56	2.18	2.90
12-15 (11.40-14.40)	0.38	0.00	5.39	0.96	0.00	0.08	1.14	2.12
15-18 (14.40-17.40)	0.16	0.00	4.89	0.35	0.00	0.02	0.90	1.96
18-21 (17.40-20.40)	0.07	0.00	0.98	0.17	0.00	n.s.	0.24	0.42
21-24 (20.40-23.40)	0.05	0.00	0.30	0.09	0.00	0.00	0.07	0.11
24-27 (23.40-26.40)	0.04	n.s.	0.12	0.05	0.01	n.s.	0.06	0.05
27-30 (26.40-29.40)	0.04	0.00	0.08	0.05	0.02	0.00	0.03	0.03
30-33 (29.40-32.40)	0.03	0.00	0.00	0.03	0.02	0.00	0.01	0.01
33-36 (32.40-35.40)	0.02	0.00	n.s.	0.02	0.03	0.00	0.02	0.01
36-39 (35.40-38.40)	0.03	0.02	n.s.	0.02	0.03	0.00	0.02	0.01
39-42 (38.40-41.40)	0.02	0.02	n.s.	0.02	0.05	0.00	0.02	0.02
42-45 (41.40-44.40)	0.02	0.02	n.s.	0.01	0.03	0.00	0.02	0.01
45-48 (44.40-47.40)	0.01	0.02	0.01	0.01	0.02	0.00	0.01	0.01
48-51 (47.40-50.40)	0.01	0.01	n.s.	0.01	0.02	0.00	0.01	0.01
51-54 (50.40-53.40)	0.01	0.00	n.s.	0.01	0.01	0.00	0.01	0.00
54-57 (53.40-56.40)	0.01	n.s.	n.s.	n.s.	0.01	0.00	0.01	0.00
57-60 (56.40-59.40)	0.01	n.s.	n.s.	n.s.	0.01	n.s.	0.01	0.00
60-63 (59.40-62.40)	0.01	n.s.	0.00	n.s.	0.01	n.s.	0.01	0.00
63-66 (62.40-65.40)	0.01	n.s.	n.s.	n.s.	0.01	n.s.	0.01	0.00
66-69 (65.40-68.40)	0.01	0.00	n.s.	n.s.	0.01	n.s.	0.00	0.00
69-72 (68.40-71.40)	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00
Total	69.82	50.20	72.69	68.94	64.73	11.96	56.39	23.17

animal 38 was dosed 20 minutes later, therefore time intervals (in brackets) are postponed by 20 minutes

Table 26: Excretion of radioactivity via bile after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to female rats

Single animal data and group mean values. Results expressed in % of the radioactivity administered

Animal No.	61	62	63	64	65	66	Mean	SD
Animal weight [g]	189.5	205.2	226.4	222.5	217.0	205.5	209.8	14.9
Specific activity [MBq/g]	---	---	---	---	---	---	405.8	---
Dose admin. [mg/kg bw]	31.6	31.3	30.1	31.5	29.9	31.4	31.2	0.6
Radioact. Dose [MBq/animal]	2.4	2.6	2.8	2.8	2.6	2.6	2.65	0.16
Time interval [h]								
0-3	6.60	41.47	14.29	48.66	0.00	18.91	25.99	18.14
3-6	6.06	10.09	14.18	7.69	0.00	5.48	8.70	3.55
6-9	1.54	1.16	5.52	1.82	0.00	1.11	2.23	1.86
9-12	n.s.	0.27	1.83	0.72	0.03	0.20	0.76	0.75
12-15	n.s.	0.15	0.65	0.41	0.00	0.02	0.31	0.28
15-18	n.s.	0.08	0.28	0.19	0.00	0.00	0.14	0.12
18-21	n.s.	0.06	0.20	0.08	0.00	0.00	0.09	0.08
21-24	0.11	0.09	0.13	0.04	0.03	n.s.	0.09	0.04
24-27	0.09	0.11	0.08	0.03	0.09	n.s.	0.08	0.03
27-30	0.04	0.05	0.05	0.02	0.07	n.s.	0.04	0.02
30-33	0.05	n.s.	0.03	0.02	0.05	n.s.	0.03	0.02
33-36	0.03	n.s.	0.02	0.02	0.05	n.s.	0.02	0.01
36-39	0.01	n.s.	0.01	0.01	0.04	n.s.	0.01	0.00
39-42	0.01	n.s.	0.00	0.01	0.03	n.s.	0.01	0.01
42-45	0.00	0.01	0.00	0.01	0.04	n.s.	0.01	0.01
45-48	0.02	0.00	0.00	0.01	0.04	n.s.	0.01	0.01
48-51	0.02	n.s.	n.s.	0.01	0.04	n.s.	0.02	0.01
51-54	0.04	n.s.	n.s.	0.01	0.04	n.s.	0.03	0.02
54-57	0.06	n.s.	n.s.	0.01	0.01	n.s.	0.03	0.03
57-60	0.00	0.00	n.s.	n.s.	n.s.	n.s.	0.00	0.00
60-63	n.s.	0.00	n.s.	n.s.	n.s.	n.s.	0.00	n.d.
63-66	0.00	0.00	n.s.	0.00	n.s.	n.s.	0.00	0.00
66-69	0.00	0.00	n.s.	n.s.	n.s.	n.s.	0.00	0.00
69-72	0.00	0.00	n.s.	0.00	0.00	n.s.	0.00	0.00
Total	14.69	53.58	37.27	59.76	0.57	25.73	38.21	18.78

animal 65 not included into statistics due to low bile flow between 0-9 h

Table 27: Bile flow of male rats after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw

Single animal data and group mean values. Results expressed in g

Animal No.	27	28	29	30	31	32	MEAN	SD
Animal weight [g]	266.6	278.9	245.4	306.4	306.5	321.1	287.5	28.7
Specific activity [MBq/g]	---	---	---	---	---	---	45.7	---
Dose admin. [mg/kg bw]	310.3	308.6	320.1	313.8	304.2	307.2	310.7	5.6
Radioact. Dose [MBq/animal]	3.78	3.93	3.59	4.39	4.26	4.50	4.08	0.36
Time interval [h]								
0-3	7.44	6.93	3.78	10.12	2.94	2.89	5.68	2.94
3-6	4.47	3.75	3.26	6.54	0.32	0.58	3.15	2.37
6-9	3.97	3.81	1.03	5.50	1.80	0.49	2.76	1.96
9-12	3.61	3.15	0.17	4.56	n.s.	0.14	2.33	2.04
12-15	3.04	3.18	n.s.	4.71	2.28	0.01	2.64	1.72
15-18	2.81	3.44	n.s.	4.12	4.38	0.05	2.96	1.74
18-21	2.49	3.00	n.s.	4.01	1.49	0.20	2.24	1.46
21-24	2.66	2.66	0.28	3.27	1.85	0.41	1.86	1.25
24-27	2.22	2.46	0.95	3.52	3.71	0.64	2.25	1.27
27-30	2.07	2.02	2.67	3.74	3.85	0.63	2.50	1.21
30-33	1.81	1.83	3.59	3.79	2.00	0.44	2.24	1.26
33-36	1.53	1.81	0.07	3.92	1.85	0.73	1.65	1.31
36-39	2.44	2.11	0.87	3.69	3.28	0.32	2.12	1.32
39-42	2.98	n.s.	2.35	1.68	3.35	1.74	2.42	0.74
42-45	2.58	n.s.	4.16	n.s.	2.74	2.86	3.08	0.73
45-48	2.14	1.11	2.22	0.10	0.32	0.88	1.13	0.89
48-51	2.31	2.04	0.47	n.s.	0.54	2.75	1.62	1.05
51-54	1.68	2.13	2.11	0.01	2.37	2.15	1.74	0.87
54-57	1.33	2.63	3.81	n.s.	2.20	2.67	2.53	0.90
57-60	1.85	2.87	4.19	n.s.	2.20	2.38	2.70	0.91
60-63	2.77	2.89	3.92	n.s.	1.94	3.81	3.07	0.82
63-66	2.84	2.51	3.40	n.s.	0.08	3.90	2.55	1.48
66-69	2.84	2.68	3.35	n.s.	n.s.	2.70	2.89	0.31
69-72	3.81	3.12	3.83	1.37	0.67	2.65	2.58	1.30
Total	67.67	62.14	50.47	64.65	46.17	36.01	54.52	12.35

Table 28: Bile flow of female rats after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw

Single animal data and group mean values. Results expressed in g

Animal No.	55	56	57	58	59	60	Mean	SD
Animal weight [g]	236.0	218.8	233.7	268.5	225.6	242.2	237.5	17.3
Specific activity [MBq/g]	---	---	---	---	---	---	44.5	---
Dose admin. [mg/kg bw]	311.3	306.8	309.0	309.9	294.1	280.2	301.9	12.3
Radioact. Dose [MBq/animal]	3.3	3.0	3.2	3.7	3.0	3.0	3.19	0.28
Time interval [h]								
0-3	5.32	6.94	5.79	3.27	3.76	3.06	4.69	1.56
3-6	4.56	4.33	5.27	0.10	2.92	2.09	3.21	1.91
6-9	3.72	3.60	3.62	n.s.	1.61	0.96	2.70	1.32
9-12	3.23	3.69	3.49	n.s.	n.s.	0.20	2.65	1.65
12-15	3.22	3.50	2.98	0.13	n.s.	0.39	2.04	1.64
15-18	3.51	3.67	3.10	0.22	n.s.	0.08	2.12	1.81
18-21	3.15	3.52	2.92	0.43	0.26	0.60	1.81	1.53
21-24	1.09	3.27	3.09	0.33	n.s.	n.s.	1.95	1.46
24-27	2.37	2.92	3.06	n.s.	n.s.	n.s.	2.78	0.37
27-30	2.76	2.65	3.11	n.s.	n.s.	0.03	2.14	1.42
30-33	2.60	2.65	3.50	n.s.	n.s.	0.28	2.26	1.38
33-36	2.27	2.83	3.56	n.s.	n.s.	0.04	2.17	1.52
36-39	2.04	2.89	3.49	0.39	n.s.	0.07	1.78	1.50
39-42	1.98	2.92	3.73	1.14	n.s.	0.42	2.04	1.33
42-45	1.65	2.91	3.36	1.82	n.s.	0.08	1.96	1.27
45-48	1.35	2.76	2.81	2.59	n.s.	0.00	1.90	1.22
48-51	1.27	2.72	3.41	2.42	n.s.	0.06	1.97	1.32
51-54	1.09	2.61	3.71	2.92	n.s.	0.08	2.08	1.47
54-57	0.85	2.69	3.78	3.24	n.s.	0.24	2.16	1.54
57-60	0.54	2.56	3.19	4.17	n.s.	0.49	2.19	1.63
60-63	0.37	2.81	3.72	3.98	n.s.	0.62	2.30	1.71
63-66	0.25	2.44	2.63	3.51	n.s.	1.04	1.97	1.31
66-69	0.03	2.37	0.83	3.06	n.s.	n.s.	1.57	1.39
69-72	0.87	2.28	1.15	3.59	n.s.	0.26	1.63	1.32
Total	50.08	75.50	79.31	37.31	8.55	11.07	43.64	30.53

Table 29: Bile flow of male rats after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw

Single animal data and group mean values. Results expressed in g

Animal No.	33	34	35	36	37	38	Mean	SD
Animal weight [g]	308.9	293.9	306.7	308.3	337.2	316.9	312.0	14.4
Specific activity [MBq/g]	---	---	---	---	---	---	408.8	---
Dose admin. [mg/kg bw]	33.3	33.6	32.8	31.8	31.9	32.3	32.6	0.7
Radioact. Dose [MBq/animal]	4.20	4.04	4.12	4.02	4.40	4.18	4.16	0.14
Time interval [h]								
0-3 (0-2.40)	4.91	5.94	3.52	6.07	2.99	4.01	4.57	1.28
3-6 (2.40-5.40)	2.90	2.56	2.73	3.18	1.29	2.96	2.60	0.68
6-9 (5.40-8.40)	3.13	1.95	3.07	2.82	1.07	2.12	2.36	0.80
9-12 (8.40-11.40)	3.24	1.46	3.43	3.40	0.82	2.09	2.40	1.12
12-15 (11.40-14.40)	3.20	0.91	3.47	3.40	0.65	1.86	2.25	1.28
15-18 (14.40-17.40)	2.95	1.46	3.79	3.04	1.10	0.95	2.21	1.19
18-21 (17.40-20.40)	2.81	1.23	3.17	2.53	1.24	n.s.	2.20	0.91
21-24 (20.40-23.40)	2.27	0.37	2.48	1.93	2.96	0.18	1.70	1.16
24-27 (23.40-26.40)	2.73	n.s.	2.15	1.72	3.84	n.s.	2.61	0.92
27-30 (26.40-29.40)	2.81	0.08	1.73	1.67	3.75	2.16	2.03	1.23
30-33 (29.40-32.40)	3.31	1.00	0.13	2.45	4.19	1.76	2.14	1.49
33-36 (32.40-35.40)	3.12	5.09	n.s.	0.90	4.78	1.48	3.07	1.89
36-39 (35.40-38.40)	3.09	5.17	n.s.	1.37	4.60	0.08	2.86	2.14
39-42 (38.40-41.40)	2.93	5.33	n.s.	1.23	4.33	2.09	3.18	1.65
42-45 (41.40-44.40)	2.60	5.58	n.s.	1.39	3.50	1.81	2.97	1.66
45-48 (44.40-47.40)	1.97	5.25	0.26	0.79	3.29	1.52	2.18	1.83
48-51 (47.40-50.40)	1.80	5.08	n.s.	0.45	3.20	1.38	2.38	1.80
51-54 (50.40-53.40)	1.89	0.05	n.s.	0.71	2.88	0.96	1.30	1.10
54-57 (53.40-56.40)	2.62	n.s.	n.s.	n.s.	3.52	0.24	2.13	1.70
57-60 (56.40-59.40)	3.12	n.s.	n.s.	n.s.	3.69	n.s.	3.41	0.41
60-63 (59.40-62.40)	3.23	n.s.	0.20	n.s.	3.61	n.s.	2.35	1.87
63-66 (62.40-65.40)	2.85	n.s.	n.s.	n.s.	3.42	n.s.	3.14	0.40
66-69 (65.40-68.40)	2.48	0.07	n.s.	n.s.	3.37	n.s.	1.97	1.71
69-72 (68.40-71.40)	2.61	3.07	1.83	0.26	2.91	1.20	1.98	1.10
Total	68.56	51.65	31.97	39.29	71.03	28.85	48.56	18.24

animal 38 was dosed 20 minutes later, therefore time intervals (in brackets) are postponed by 20 minutes

Table 30: Bile flow of female rats after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw

Single animal data and group mean values. Results expressed in g

Animal No.	61	62	63	64	65	66	Mean	SD
Animal weight [g]	189.5	205.2	226.4	222.5	217.0	205.5	209.8	14.9
Specific activity [MBq/g]	---	---	---	---	---	---	405.8	---
Dose admin. [mg/kg bw]	31.6	31.3	30.1	31.5	29.9	31.4	31.2	0.6
Radioact. Dose [MBq/animal]	2.43	2.61	2.76	2.84	2.63	2.62	2.65	0.16
Time interval [h]								
0-3	4.65	5.59	4.22	4.48	0.59	2.47	4.28	1.14
3-6	3.63	3.94	2.14	2.24	0.00	0.69	2.53	1.31
6-9	2.77	3.52	2.05	2.36	0.21	0.32	2.21	1.19
9-12	n.s.	3.62	1.86	2.49	0.90	0.20	2.04	1.43
12-15	n.s.	3.61	1.64	2.70	1.01	0.09	2.01	1.51
15-18	n.s.	3.49	1.60	2.82	0.53	0.11	2.00	1.49
18-21	n.s.	3.09	1.57	2.60	0.63	0.08	1.83	1.33
21-24	1.78	2.72	1.50	2.14	3.65	n.s.	2.04	0.53
24-27	2.41	2.79	1.53	2.18	3.53	n.s.	2.23	0.53
27-30	1.07	2.92	1.53	1.61	3.10	n.s.	1.78	0.79
30-33	2.15	n.s.	1.60	2.53	3.39	n.s.	2.09	0.47
33-36	2.16	n.s.	1.36	2.88	3.39	n.s.	2.14	0.76
36-39	0.69	n.s.	0.88	3.14	3.51	n.s.	1.57	1.36
39-42	0.74	n.s.	0.37	3.03	3.30	n.s.	1.38	1.44
42-45	0.53	0.31	0.03	2.58	3.36	n.s.	0.86	1.16
45-48	1.94	1.50	0.48	2.31	2.86	n.s.	1.56	0.79
48-51	1.73	n.s.	n.s.	2.24	2.72	n.s.	1.99	0.36
51-54	1.70	n.s.	n.s.	2.26	2.52	n.s.	1.98	0.39
54-57	1.64	n.s.	n.s.	2.08	0.64	n.s.	1.86	0.31
57-60	0.14	2.86	n.s.	n.s.	n.s.	n.s.	1.50	1.92
60-63	n.s.	4.53	n.s.	n.s.	n.s.	n.s.	4.53	n.d.
63-66	0.09	4.22	n.s.	0.05	n.s.	n.s.	1.45	2.40
66-69	0.04	4.00	n.s.	n.s.	n.s.	n.s.	2.02	2.80
69-72	0.22	3.01	n.s.	0.53	0.47	n.s.	1.25	1.53
Total	30.08	55.73	24.36	49.24	40.31	3.95	32.67	20.66

animal 65 not included into statistics due to low bile flow between 0-9 h

Table 31: Tissue concentrations of radioactivity 1 h after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw to male and female rats

Single animal data and group mean values. Results expressed in μg Eq/g

Male animal No.	67	68	69	Mean	SD
Body weight [g]	317.1	351.2	338.5	335.6	17.2
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	298.6	302.2	303.8	301.5	2.7
Radioact. Dose [MBq/animal]	1.13	1.27	1.23	1.21	0.07
Blood cells	10.40	6.63	12.98	10.00	3.20
Plasma	61.01	48.38	62.79	57.39	7.86
Lung	25.26	18.77	55.63	33.22	19.68
Heart	19.01	12.91	20.22	17.38	3.92
Spleen	10.18	9.42	15.25	11.62	3.17
Kidney	121.96	83.78	96.09	100.61	19.49
Adrenal glands	20.92	17.32	28.36	22.20	5.63
Testes/Ovaries	10.42	8.26	14.68	11.12	3.27
Uterus	---	---	---	---	---
Muscle	11.06	7.56	15.00	11.21	3.72
Brain	3.90	2.48	6.53	4.30	2.06
Adipose tissue	3.25	3.15	4.06	3.49	0.50
Bone	4.47	4.33	5.63	4.81	0.71
Bone marrow	15.52	10.10	16.75	14.12	3.54
Thyroid	20.77	22.73	33.15	25.55	6.66
Pancreas	23.66	17.30	34.37	25.11	8.63
Stomach content	6507.01	9332.09	6983.69	7607.60	1512.36
Stomach	971.92	1535.52	1747.11	1418.18	400.69
Gut content	1977.95	2278.61	2072.32	2109.62	153.76
Gut	452.96	386.17	384.85	407.99	38.95
Liver	72.49	55.72	75.44	67.88	10.64
Skin	33.55	22.61	35.76	30.64	7.04
Carcass	20.90	45.96	81.39	49.42	30.39

Female animal No.	79	80	81	Mean	SD
Body weight [g]	228.9	240.6	241.3	236.9	7.0
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	310.2	309.0	315.0	311.4	3.2
Radioact. Dose [MBq/animal]	0.85	0.89	0.91	0.88	0.03
Blood cells	15.36	20.33	14.89	16.86	3.01
Plasma	45.06	84.10	66.51	65.22	19.55
Lung	25.84	61.78	35.06	40.89	18.67
Heart	12.76	22.90	18.24	17.97	5.07
Spleen	15.30	20.27	15.82	17.13	2.73
Kidney	4.10	10.04	5.68	6.61	3.08
Adrenal glands	20.48	37.34	32.00	29.94	8.62
Testes/Ovaries	19.29	38.77	27.51	28.53	9.78
Uterus	25.27	41.19	34.45	33.64	7.99
Muscle	13.92	22.24	18.33	18.16	4.17
Brain	49.79	96.73	89.02	78.51	25.17
Adipose tissue	4.71	5.85	5.81	5.46	0.65
Bone	4.95	6.81	5.47	5.74	0.96
Bone marrow	11.39	21.40	17.10	16.63	5.02
Thyroid	27.97	72.38	33.53	44.63	24.20
Pancreas	22.53	76.74	30.73	43.33	29.22
Stomach content	5747.86	7132.68	5772.97	6217.84	792.38
Stomach	943.98	1317.61	1411.64	1224.41	247.37
Gut content	1469.55	1426.63	1303.54	1399.90	86.17
Gut	588.80	538.02	573.46	566.76	26.04
Liver	48.68	63.99	80.53	64.40	15.93
Skin	31.53	53.10	37.86	40.83	11.09
Carcass	44.08	25.21	50.30	39.87	13.07

Table 32: Tissue concentrations of radioactivity 4 h after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw to male and female rats

Single animal data and group mean values. Results expressed in μg Eq/g

Male animal No.	70	71	72	Mean	SD
Body weight [g]	339.0	341.3	323.4	334.6	9.7
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	305.3	312.3	308.0	308.5	3.5
Radioact. Dose [MBq/animal]	1.24	1.27	1.19	1.23	0.04
Blood cells	4.10	6.17	3.93	4.73	1.25
Plasma	22.95	32.31	24.34	26.54	5.05
Lung	9.42	13.03	11.56	11.34	1.81
Heart	6.05	10.47	6.02	7.51	2.56
Spleen	4.09	5.48	7.59	5.72	1.76
Kidney	41.80	55.17	47.98	48.32	6.69
Adrenal glands	8.00	13.64	10.64	10.76	2.82
Testes/Ovaries	4.74	8.08	4.72	5.85	1.93
Uterus	---	---	---	---	---
Muscle	2.38	4.56	2.60	3.18	1.20
Brain	1.18	1.42	1.05	1.22	0.19
Adipose tissue	0.81	1.81	1.61	1.41	0.53
Bone	1.67	2.69	2.24	2.20	0.51
Bone marrow	6.31	10.24	6.19	7.58	2.31
Thyroid	8.44	13.89	12.19	11.51	2.79
Pancreas	12.10	11.39	24.52	16.01	7.38
Stomach content	5443.82	9112.41	8193.16	7583.13	1908.86
Stomach	424.71	598.15	790.94	604.60	183.20
Gut content	3795.88	3546.62	3807.92	3716.80	147.51
Gut	483.16	489.53	691.81	554.84	118.66
Liver	44.62	50.36	49.22	48.07	3.04
Skin	8.39	12.68	9.28	10.12	2.26
Carcass	12.77	33.18	28.85	24.93	10.75

Female animal No.	82	83	84	Mean	SD
Body weight [g]	259.3	230.7	239.1	243.0	14.7
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	295.5	307.9	308.0	303.8	7.2
Radioact. Dose [MBq/animal]	0.92	0.85	0.88	0.88	0.03
Blood cells	5.12	4.45	6.03	5.20	0.80
Plasma	27.86	19.87	30.26	26.00	5.44
Lung	11.77	9.06	13.57	11.47	2.27
Heart	6.36	4.61	7.12	6.03	1.29
Spleen	2.09	2.86	4.08	3.01	1.00
Kidney	1.70	2.10	2.24	2.02	0.28
Adrenal glands	9.02	7.76	10.27	9.02	1.25
Testes/Ovaries	9.54	8.15	13.83	10.51	2.96
Uterus	14.52	8.05	21.75	14.78	6.85
Muscle	3.27	3.55	2.46	3.09	0.56
Brain	32.31	19.13	30.23	27.22	7.09
Adipose tissue	3.59	2.64	3.42	3.22	0.51
Bone	2.23	1.70	3.19	2.37	0.76
Bone marrow	5.86	5.02	7.41	6.10	1.21
Thyroid	14.18	22.34	17.42	17.98	4.11
Pancreas	8.93	16.19	23.66	16.26	7.36
Stomach content	10118.45	8299.21	5923.02	8113.56	2103.87
Stomach	861.62	601.03	685.15	715.93	132.99
Gut content	2214.25	3192.67	3155.56	2854.16	554.49
Gut	690.91	779.05	762.77	744.24	46.90
Liver	36.17	40.62	46.47	41.08	5.16
Skin	11.15	6.73	10.18	9.35	2.33
Carcass	21.33	21.24	21.07	21.21	0.13

Table 33: Tissue concentrations of radioactivity 36 h and 37 h after single oral administration of ¹⁴C-4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw to male and female rats, respectively

Single animal data and group mean values. Results expressed in µg Eq/g

Male animal No.	73	74	75	Mean	SD
Body weight [g]	327.9	317.9	318.8	321.5	5.5
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	313.3	314.4	312.8	313.5	0.8
Radioact. Dose [MBq/animal]	1.23	1.20	1.19	1.21	0.02
Blood cells	1.72	5.66	1.01	2.80	2.51
Plasma	8.72	14.47	2.43	8.54	6.02
Lung	3.81	5.56	1.16	3.51	2.21
Heart	1.86	4.00	0.56	2.14	1.74
Spleen	1.73	4.24	0.93	2.30	1.73
Kidney	14.73	24.71	4.88	14.77	9.92
Adrenal glands	2.45	9.71	0.90	4.35	4.70
Testes/Ovaries	1.60	2.52	0.75	1.62	0.88
Uterus	---	---	---	---	---
Muscle	0.90	1.42	0.45	0.92	0.49
Brain	0.48	0.63	0.38	0.49	0.13
Adipose tissue	0.64	1.04	0.53	0.74	0.26
Bone	0.64	1.07	0.26	0.66	0.41
Bone marrow	3.00	3.95	1.26	2.74	1.37
Thyroid	3.59	6.74	2.78	4.37	2.09
Pancreas	2.71	25.97	0.75	9.81	14.03
Stomach content	1031.27	2569.82	7.33	1202.81	1289.83
Stomach	224.37	238.55	2.97	155.30	132.11
Gut content	790.41	1609.61	217.34	872.45	699.75
Gut	138.46	260.46	39.66	146.20	110.60
Liver	22.44	30.81	6.58	19.94	12.31
Skin	3.42	5.48	1.51	3.47	1.99
Carcass	37.25	40.97	40.55	39.59	2.04

Female animal No.	85	86	87	Mean	SD
Body weight [g]	246.7	243.7	237.4	242.6	4.7
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	316.1	321.4	323.0	320.1	3.6
Radioact. Dose [MBq/animal]	0.93	0.94	0.92	0.93	0.01
Blood cells	2.84	2.51	3.17	2.84	0.33
Plasma	8.09	11.27	11.57	10.31	1.93
Lung	3.35	4.39	5.21	4.32	0.93
Heart	1.83	2.23	2.39	2.15	0.29
Spleen	0.86	0.84	0.74	0.81	0.06
Kidney	0.59	0.64	0.87	0.70	0.15
Adrenal glands	2.89	3.34	4.13	3.45	0.63
Testes/Ovaries	3.18	4.02	4.10	3.77	0.51
Uterus	3.25	4.38	4.14	3.93	0.60
Muscle	0.75	1.01	1.02	0.93	0.15
Brain	7.57	11.45	8.94	9.32	1.97
Adipose tissue	0.68	1.09	0.82	0.86	0.21
Bone	0.83	0.77	1.07	0.89	0.16
Bone marrow	2.56	5.03	3.61	3.73	1.24
Thyroid	9.56	5.10	6.94	7.20	2.24
Pancreas	4.21	2.31	3.18	3.24	0.95
Stomach content	33.62	32.13	58.87	41.54	15.02
Stomach	9.23	5.80	6.94	7.32	1.75
Gut content	988.69	1045.54	1252.39	1095.54	138.78
Gut	154.65	263.49	332.11	250.08	89.49
Liver	15.00	20.80	18.63	18.14	2.93
Skin	4.39	5.21	3.89	4.50	0.67
Carcass	37.79	48.42	63.45	49.89	12.89

Table 34: Tissue concentrations of radioactivity 46 h and 50 h after single oral administration of ¹⁴C-4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw to male and female rats, respectively

Single animal data and group mean values. Results expressed in µg Eq/g

Male animal No.	76	77	78	Mean	SD
Body weight [g]	323.5	331.2	323.6	326.1	4.4
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	325.0	321.6	324.5	323.7	1.9
Radioact. Dose [MBq/animal]	1.26	1.27	1.26	1.26	0.01
Blood cells	0.98	2.11	1.24	1.44	0.59
Plasma	3.52	7.97	4.18	5.23	2.40
Lung	1.57	3.26	1.72	2.18	0.93
Heart	0.82	1.63	0.79	1.08	0.47
Spleen	0.71	2.87	0.74	1.44	1.24
Kidney	6.62	10.51	9.47	8.87	2.02
Adrenal glands	1.38	2.60	1.34	1.77	0.72
Testes/Ovaries	0.90	1.35	1.01	1.09	0.24
Uterus	---	---	---	---	---
Muscle	0.55	0.86	0.47	0.63	0.20
Brain	0.31	0.48	0.32	0.37	0.10
Adipose tissue	0.66	0.69	0.97	0.77	0.17
Bone	0.31	0.66	0.37	0.45	0.19
Bone marrow	1.62	2.33	1.55	1.83	0.43
Thyroid	2.44	4.81	2.78	3.34	1.29
Pancreas	1.05	10.31	1.35	4.23	5.26
Stomach content	23.63	9.80	15.70	16.38	6.94
Stomach	6.80	5.15	3.20	5.05	1.80
Gut content	172.56	539.05	631.89	447.83	242.87
Gut	49.65	121.79	93.19	88.21	36.33
Liver	6.00	12.80	7.04	8.61	3.66
Skin	1.67	3.01	1.93	2.20	0.71
Carcass	40.72	30.31	28.27	33.10	6.67

Female animal No.	88	89	90	Mean	SD
Body weight [g]	237.4	259.5	240.8	245.9	11.9
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	325.1	319.7	317.6	320.8	3.9
Radioact. Dose [MBq/animal]	0.92	0.99	0.91	0.94	0.04
Blood cells	1.30	2.89	1.60	1.93	0.84
Plasma	4.49	5.48	2.91	4.29	1.30
Lung	1.70	2.22	1.30	1.74	0.46
Heart	1.13	1.57	0.65	1.12	0.46
Spleen	0.43	0.44	0.50	0.46	0.04
Kidney	0.39	0.40	0.29	0.36	0.06
Adrenal glands	1.41	2.02	1.22	1.55	0.41
Testes/Ovaries	1.39	2.06	1.10	1.52	0.49
Uterus	1.54	3.04	1.46	2.01	0.89
Muscle	0.54	0.52	0.34	0.47	0.11
Brain	3.24	8.80	2.97	5.00	3.29
Adipose tissue	0.58	0.64	0.44	0.55	0.10
Bone	0.42	0.44	0.29	0.39	0.08
Bone marrow	1.97	3.22	2.34	2.51	0.64
Thyroid	2.75	3.62	9.47	5.28	3.65
Pancreas	1.14	3.52	1.46	2.04	1.29
Stomach content	5.44	62.68	40.15	36.09	28.84
Stomach	2.07	4.73	2.77	3.19	1.38
Gut content	516.39	545.59	548.15	536.71	17.65
Gut	107.61	76.86	95.10	93.19	15.46
Liver	7.32	8.03	5.93	7.09	1.07
Skin	1.86	2.33	1.14	1.78	0.59
Carcass	19.72	39.51	39.80	33.01	11.51

Table 35: Tissue concentrations of radioactivity 168 h after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw to male and female rats

Samples generated in experiment 3 (balance high dose). Results expressed in $\mu\text{g Eq/g}$

Male animal No.	1	2	3	4	Mean	SD
Blood cells	0.03	0.02	0.04	0.06	0.04	0.02
Plasma	0.01	0.04	0.02	0.04	0.03	0.01
Lung	0.07	0.08	0.06	0.08	0.07	0.01
Heart	0.06	0.06	0.06	0.13	0.08	0.03
Spleen	0.08	0.11	0.09	0.26	0.13	0.09
Kidney	0.24	0.37	0.45	0.40	0.36	0.09
Adrenals	0.17	0.10	0.10	0.10	0.12	0.03
Testes/Ovaries	0.03	0.03	0.03	0.03	0.03	0.00
Uterus	---	---	---	---	---	---
Muscle	0.04	0.04	0.04	0.05	0.04	0.01
Brain	0.04	0.03	0.03	0.02	0.03	0.00
Adipose Tissue	0.07	0.06	0.07	0.08	0.07	0.01
Bone	0.05	0.05	0.07	0.06	0.06	0.01
Bone marrow	0.15	0.24	0.16	0.19	0.18	0.04
Thyroid	1.01	0.38	0.20	0.29	0.47	0.37
Pancreas	0.06	0.09	0.09	0.09	0.08	0.01
Stomach cont.	3.12	0.92	0.85	8.86	3.44	3.77
Stomach	0.06	0.07	0.16	0.16	0.11	0.05
Gut cont.	3.90	7.73	7.59	6.14	6.34	1.78
Gut	0.67	1.57	1.22	1.71	1.29	0.46
Liver	0.11	0.19	0.21	0.37	0.22	0.11
Skin	0.52	0.15	0.28	0.44	0.35	0.17
Carcass	1.09	0.54	1.06	1.10	0.95	0.27

Female animal No.	5	6	7	8	Mean	SD
Blood cells	0.08	0.04	0.08	0.04	0.06	0.03
Plasma	0.01	0.02	0.02	0.00	0.02	0.01
Lung	0.07	0.07	0.07	0.09	0.08	0.01
Heart	0.18	0.07	0.06	0.06	0.09	0.06
Spleen	0.09	0.14	0.14	0.07	0.11	0.03
Kidney	0.30	0.27	0.27	0.19	0.26	0.05
Adrenals	0.14	0.10	0.06	0.09	0.10	0.04
Testes/Ovaries	0.05	0.05	0.05	0.05	0.05	0.00
Uterus	0.03	0.09	0.06	0.05	0.06	0.02
Muscle	0.03	0.03	0.04	0.03	0.03	0.01
Brain	0.03	0.04	0.04	0.08	0.05	0.03
Adipose Tissue	0.06	0.07	0.06	0.07	0.07	0.01
Bone	0.05	0.04	0.03	0.01	0.03	0.02
Bone marrow	0.24	0.28	0.32	0.29	0.28	0.03
Thyroid	0.25	0.31	0.15	0.88	0.40	0.33
Pancreas	0.09	0.17	0.09	0.11	0.11	0.04
Stomach cont.	1.88	11.60	4.06	1.11	4.66	4.79
Stomach	0.25	0.20	0.19	0.06	0.17	0.08
Gut cont.	2.25	2.63	3.13	1.35	2.34	0.75
Gut	0.52	1.10	0.89	0.35	0.71	0.34
Liver	0.12	0.27	0.16	0.08	0.16	0.08
Skin	0.30	1.49	1.25	0.87	0.98	0.52
Carcass	4.91	8.37	7.59	3.12	6.00	2.42

Table 36: Tissue concentrations of radioactivity 1 h after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw to male and female rats

Single animal data and group mean values. Results expressed in % of dose

Male animal No.	67	68	69	Mean	SD
Body weight [g]	317.1	351.2	338.5	335.6	17.2
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	298.6	302.2	303.8	301.5	2.7
Radioact. Dose [MBq/animal]	1.13	1.27	1.23	1.21	0.07
Blood cells	0.04	0.03	0.06	0.04	0.01
Plasma	0.23	0.20	0.26	0.23	0.03
Lung	0.03	0.02	0.08	0.05	0.03
Heart	0.02	0.01	0.02	0.02	0.00
Spleen	0.01	0.01	0.01	0.01	0.00
Kidney	0.25	0.17	0.24	0.22	0.04
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.03	0.03	0.05	0.04	0.01
Uterus	---	---	---	---	---
Muscle	0.01	0.02	0.02	0.02	0.00
Brain	0.01	0.00	0.01	0.01	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.02	0.01	0.04	0.02	0.01
Stomach content	55.02	54.20	54.49	54.57	0.42
Stomach	1.45	2.37	2.18	2.00	0.49
Gut content	32.28	29.74	39.24	33.76	4.92
Gut	3.23	2.44	2.42	2.70	0.46
Liver	0.77	0.62	0.80	0.73	0.10
Skin	1.70	1.22	1.74	1.56	0.29
Carcass	4.32	9.17	16.26	9.92	6.00

Female animal No.	79	80	81	Mean	SD
Body weight [g]	228.9	240.6	241.3	236.9	7.0
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	310.2	309.0	315.0	311.4	3.2
Radioact. Dose [MBq/animal]	0.85	0.89	0.91	0.88	0.03
Blood cells	0.07	0.08	0.05	0.07	0.02
Plasma	0.19	0.39	0.26	0.28	0.10
Lung	0.04	0.14	0.05	0.08	0.05
Heart	0.01	0.02	0.02	0.02	0.00
Spleen	0.01	0.01	0.01	0.01	0.00
Kidney	0.01	0.02	0.01	0.01	0.01
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.01	0.00	0.00	0.00
Uterus	0.01	0.03	0.02	0.02	0.01
Muscle	0.04	0.02	0.06	0.04	0.02
Brain	0.14	0.23	0.24	0.21	0.06
Adipose tissue	0.01	0.01	0.01	0.01	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.02	0.11	0.02	0.05	0.05
Stomach content	58.74	47.51	56.56	54.27	0.04
Stomach	1.48	46.95	2.01	16.81	26.10
Gut content	25.60	27.05	24.71	25.78	1.18
Gut	4.03	3.72	3.44	3.73	0.29
Liver	0.51	0.64	0.84	0.66	0.17
Skin	1.43	2.26	1.72	1.80	0.42
Carcass	8.53	5.01	9.47	7.67	2.35

Table 37: Tissue concentrations of radioactivity 4 h after single oral administration of ¹⁴C-4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw to male and female rats

Single animal data and group mean values. Results expressed in µg % of dose

Male animal No.	70	71	72	Mean	SD
Body weight [g]	339.0	341.3	323.4	334.6	9.7
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	305.3	312.3	308.0	308.5	3.5
Radioact. Dose [MBq/animal]	1.24	1.27	1.19	1.23	0.04
Blood cells	0.01	0.02	0.01	0.02	0.00
Plasma	0.08	0.10	0.09	0.09	0.01
Lung	0.01	0.02	0.02	0.02	0.00
Heart	0.01	0.01	0.01	0.01	0.00
Spleen	0.00	0.00	0.00	0.00	0.00
Kidney	0.09	0.10	0.11	0.10	0.01
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.01	0.02	0.02	0.02	0.01
Uterus	---	---	---	---	---
Muscle	0.00	0.01	0.00	0.01	0.00
Brain	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.01	0.01	0.02	0.01	0.01
Stomach content	25.36	36.50	31.83	31.23	5.59
Stomach	0.64	0.85	1.19	0.89	0.27
Gut content	57.83	44.53	53.49	51.95	6.78
Gut	2.98	2.99	4.18	3.38	0.69
Liver	0.46	0.48	0.53	0.49	0.04
Skin	0.46	0.73	0.46	0.55	0.15
Carcass	2.52	6.27	5.76	4.85	2.04

Female animal No.	82	83	84	Mean	SD
Body weight [g]	259.3	230.7	239.1	243.0	14.7
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	295.5	307.9	308.0	303.8	7.2
Radioact. Dose [MBq/animal]	0.92	0.85	0.88	0.88	0.03
Blood cells	0.02	0.02	0.02	0.02	0.00
Plasma	0.11	0.08	0.12	0.10	0.02
Lung	0.02	0.02	0.02	0.02	0.00
Heart	0.01	0.01	0.01	0.01	0.00
Spleen	0.00	0.00	0.00	0.00	0.00
Kidney	0.00	0.00	0.00	0.00	0.00
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00
Uterus	0.01	0.01	0.01	0.01	0.00
Muscle	0.01	0.01	0.01	0.01	0.00
Brain	0.08	0.05	0.08	0.07	0.02
Adipose tissue	0.01	0.00	0.01	0.01	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.01	0.02	0.03	0.02	0.01
Stomach content	30.43	21.36	22.47	24.75	2.53
Stomach	1.43	1.03	0.99	1.15	0.24
Gut content	43.07	49.13	54.77	48.99	5.85
Gut	5.13	5.61	4.23	4.99	0.70
Liver	0.43	0.46	0.48	0.46	0.03
Skin	0.49	0.31	0.45	0.42	0.10
Carcass	4.13	4.08	4.16	4.12	0.04

Table 38: Tissue concentrations of radioactivity 36 and 37 h after single oral administration of ¹⁴C-4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw to male and female rats, respectively

Single animal data and group mean values. Results expressed in µg % of dose

Male animal No.	73	74	75	Mean	SD
Body weight [g]	327.9	317.9	318.8	321.5	5.5
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	313.3	314.4	312.8	313.5	0.8
Radioact. Dose [MBq/animal]	1.23	1.20	1.19	1.21	0.02
Blood cells	0.01	0.02	0.00	0.01	0.01
Plasma	0.01	0.04	0.01	0.02	0.02
Lung	0.01	0.01	0.00	0.01	0.00
Heart	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00
Kidney	0.03	0.05	0.01	0.03	0.02
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.01	0.01	0.00	0.01	0.00
Uterus	---	---	---	---	---
Muscle	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.02	0.00	0.01	0.01
Stomach content	4.66	8.14	0.03	4.28	4.07
Stomach	0.43	0.33	0.00	0.26	0.22
Gut content	9.94	27.87	3.95	13.92	12.45
Gut	1.32	1.69	0.23	1.08	0.76
Liver	0.23	0.29	0.07	0.20	0.11
Skin	0.14	0.29	0.08	0.17	0.11
Carcass	6.75	7.65	7.86	7.42	0.59

Female animal No.	85	86	87	Mean	SD
Body weight [g]	246.7	243.7	237.4	242.6	4.7
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	316.1	321.4	323.0	320.1	3.6
Radioact. Dose [MBq/animal]	0.93	0.94	0.92	0.93	0.01
Blood cells	0.01	0.01	0.01	0.01	0.00
Plasma	0.04	0.04	0.04	0.04	0.00
Lung	0.01	0.01	0.01	0.01	0.00
Heart	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00
Kidney	0.00	0.00	0.00	0.00	0.00
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00
Uterus	0.00	0.00	0.01	0.00	0.00
Muscle	0.00	0.00	0.00	0.00	0.00
Brain	0.02	0.03	0.02	0.02	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00
Stomach content	0.06	0.01	0.03	0.03	0.02
Stomach	0.01	0.01	0.01	0.01	0.00
Gut content	15.14	15.31	17.43	15.96	1.28
Gut	1.05	2.94	3.76	2.58	1.39
Liver	0.14	0.20	0.19	0.18	0.04
Skin	0.20	0.22	0.19	0.20	0.01
Carcass	7.20	8.49	11.70	9.13	2.32

Table 39: Tissue concentrations of radioactivity 46 and 50 h after single oral administration of ¹⁴C-4,4'-sulphonyldiphenol at a target dose level of 300 mg/kg bw to male and female rats, respectively

Single animal data and group mean values. Results expressed in µg % of dose

Male animal No.	76	77	78	Mean	SD
Body weight [g]	323.5	331.2	323.6	326.1	4.4
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	325.0	321.6	324.5	323.7	1.9
Radioact. Dose [MBq/animal]	1.26	1.27	1.26	1.26	0.01
Blood cells	0.00	0.01	0.00	0.00	0.00
Plasma	0.01	0.03	0.02	0.02	0.01
Lung	0.00	0.00	0.00	0.00	0.00
Heart	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00
Kidney	0.01	0.02	0.02	0.02	0.00
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00
Uterus	---	---	---	---	---
Muscle	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.01	0.00	0.00	0.01
Stomach content	0.10	0.04	0.05	0.07	0.03
Stomach	0.01	0.01	0.00	0.01	0.00
Gut content	2.19	9.61	10.58	7.46	4.59
Gut	0.44	0.62	0.50	0.52	0.09
Liver	0.06	0.12	0.07	0.08	0.03
Skin	0.07	0.14	0.09	0.10	0.04
Carcass	7.44	5.69	5.21	6.11	1.18

Female animal No.	88	89	90	Mean	SD
Body weight [g]	237.4	259.5	240.8	245.9	11.9
Specific activity [dpm/mg]	---	---	---	720000	--
Dose admin. [mg/kg bw]	325.1	319.7	317.6	320.8	3.9
Radioact. Dose [MBq/animal]	0.92	0.99	0.91	0.94	0.04
Blood cells	0.00	0.01	0.01	0.01	0.00
Plasma	0.02	0.02	0.01	0.01	0.00
Lung	0.00	0.00	0.00	0.00	0.00
Heart	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00
Kidney	0.00	0.00	0.00	0.00	0.00
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00
Uterus	0.00	0.00	0.00	0.00	0.00
Muscle	0.00	0.00	0.00	0.00	0.00
Brain	0.01	0.02	0.01	0.01	0.01
Adipose tissue	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.01	0.00	0.00	0.00
Stomach content	0.01	0.06	0.05	0.04	0.03
Stomach	0.00	0.01	0.01	0.01	0.00
Gut content	7.62	8.33	7.52	7.82	0.44
Gut	1.16	0.62	1.00	0.93	0.28
Liver	0.07	0.08	0.06	0.07	0.01
Skin	0.07	0.10	0.05	0.07	0.02
Carcass	3.48	7.39	7.53	6.13	2.30

Table 40: Tissue concentrations of radioactivity 1 h after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to male and female rats

Single animal data and group mean values. Results expressed in μg Eq/g

Male animal No.	91	92	93	Mean	SD
Body weight [g]	292.9	300.0	292.8	295.2	4.1
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	32.6	31.8	32.9	32.5	0.6
Radioact. Dose [MBq/animal]	2.19	2.19	2.21	2.20	0.01
Blood cells	2.66	0.64	0.57	1.29	1.19
Plasma	15.31	8.46	7.73	10.50	4.18
Lung	7.14	3.09	2.94	4.39	2.38
Heart	5.19	1.95	1.41	2.85	2.05
Spleen	1.94	1.02	0.83	1.26	0.59
Kidney	23.93	12.87	11.71	16.17	6.75
Adrenal glands	5.23	2.45	1.68	3.12	1.87
Testes/Ovaries	2.25	1.45	1.31	1.67	0.51
Uterus	---	---	---	---	---
Muscle	1.70	0.82	0.62	1.05	0.58
Brain	0.66	0.29	0.32	0.42	0.21
Adipose tissue	0.94	0.37	0.29	0.53	0.35
Bone	1.08	0.72	0.58	0.79	0.26
Bone marrow	3.05	1.82	1.06	1.98	1.00
Thyroid	5.35	2.79	2.61	3.59	1.53
Pancreas	6.79	2.07	1.40	3.42	2.94
Stomach content	558.15	755.59	547.68	620.47	117.13
Stomach	53.40	85.39	53.14	63.97	18.54
Gut content	475.08	471.74	481.47	476.09	4.94
Gut	62.57	45.77	62.21	56.85	9.60
Liver	28.20	15.74	13.81	19.25	7.81
Skin	5.93	3.54	3.15	4.21	1.51
Carcass	5.38	3.22	2.53	3.71	1.49

Female animal No.	103	104	105	Mean	SD
Body weight [g]	240.5	231.1	239.6	237.1	5.2
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	33.5	32.5	33.5	33.2	0.5
Radioact. Dose [MBq/animal]	1.85	1.73	1.84	1.80	0.07
Blood cells	1.25	0.35	0.75	0.78	0.45
Plasma	8.46	2.93	7.76	6.38	3.01
Lung	3.46	2.93	3.48	3.29	0.31
Heart	1.71	0.58	1.61	1.30	0.62
Spleen	0.89	0.61	0.83	0.78	0.15
Kidney	8.78	3.08	9.52	7.12	3.53
Adrenal glands	2.21	1.96	1.58	1.92	0.32
Testes/Ovaries	3.86	1.68	4.08	3.21	1.33
Uterus	2.66	1.08	2.54	2.09	0.88
Muscle	0.69	0.30	0.74	0.57	0.24
Brain	0.23	0.08	0.21	0.18	0.08
Adipose tissue	0.43	0.24	0.69	0.45	0.23
Bone	0.29	0.27	0.29	0.28	0.02
Bone marrow	1.42	0.67	1.18	1.09	0.38
Thyroid	8.67	2.09	5.40	5.39	3.29
Pancreas	3.05	0.69	1.69	1.81	1.19
Stomach content	1404.24	1061.98	457.17	974.46	479.57
Stomach	94.04	214.46	90.42	132.97	70.59
Gut content	348.32	127.68	382.06	286.02	138.16
Gut	84.73	22.81	233.48	113.67	108.28
Liver	10.06	5.56	10.67	8.76	2.79
Skin	3.30	1.14	2.78	2.41	1.13
Carcass	3.61	1.29	1.46	2.12	1.29

Table 41: Tissue concentrations of radioactivity 4 h after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to male and female rats

Single animal data and group mean values. Results expressed in $\mu\text{g Eq/g}$

Male animal No.	94	95	96	Mean	SD
Body weight [g]	310.5	300.5	325.2	312.1	12.4
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	32.4	31.0	32.9	32.1	1.0
Radioact. Dose [MBq/animal]	2.31	2.14	2.46	2.30	0.16
Blood cells	0.30	0.32	0.17	0.26	0.08
Plasma	3.74	3.27	2.00	3.00	0.90
Lung	1.43	1.24	0.77	1.14	0.34
Heart	0.74	0.71	0.50	0.65	0.13
Spleen	0.49	0.47	0.24	0.40	0.14
Kidney	7.43	5.92	3.11	5.49	2.20
Adrenal glands	1.05	0.99	0.66	0.90	0.21
Testes/Ovaries	0.53	0.57	0.33	0.47	0.13
Uterus	---	---	---	---	---
Muscle	0.33	0.28	0.17	0.26	0.09
Brain	0.10	0.11	0.06	0.09	0.02
Adipose tissue	0.15	0.15	0.13	0.14	0.01
Bone	0.36	0.21	0.12	0.23	0.12
Bone marrow	0.74	0.58	0.36	0.56	0.19
Thyroid	1.70	1.23	2.18	1.70	0.48
Pancreas	0.99	0.79	0.48	0.75	0.26
Stomach content	306.51	275.31	222.13	267.98	42.66
Stomach	46.08	62.44	33.42	47.31	14.55
Gut content	445.56	555.45	633.51	544.84	94.43
Gut	47.60	70.57	57.62	58.59	11.52
Liver	11.30	8.69	6.01	8.67	2.64
Skin	1.11	1.08	1.03	1.07	0.04
Carcass	1.01	5.81	4.73	3.85	2.52

Female animal No.	106	107	108	Mean	SD
Body weight [g]	220.1	231.8	233.1	228.3	7.2
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	33.5	32.2	33.0	32.9	0.7
Radioact. Dose [MBq/animal]	1.69	1.71	1.77	1.72	0.04
Blood cells	0.48	0.38	0.38	0.41	0.06
Plasma	4.53	4.08	4.43	4.35	0.24
Lung	2.02	1.59	1.68	1.77	0.23
Heart	0.95	0.93	1.00	0.96	0.04
Spleen	0.50	0.44	0.52	0.49	0.04
Kidney	3.35	3.75	4.94	4.01	0.83
Adrenal glands	1.14	2.51	1.33	1.66	0.74
Testes/Ovaries	1.53	1.60	1.79	1.64	0.14
Uterus	1.11	1.64	1.45	1.40	0.27
Muscle	0.36	0.36	0.37	0.36	0.01
Brain	0.10	0.11	0.11	0.11	0.01
Adipose tissue	0.26	0.19	0.21	0.22	0.04
Bone	0.29	0.10	0.19	0.19	0.09
Bone marrow	0.96	0.87	1.09	0.97	0.11
Thyroid	3.43	2.48	2.81	2.91	0.49
Pancreas	0.92	3.29	0.95	1.72	1.36
Stomach content	412.01	308.49	145.40	288.63	134.41
Stomach	71.75	41.61	38.56	50.64	18.35
Gut content	538.10	540.82	786.51	621.81	142.64
Gut	81.34	60.60	107.09	83.01	23.29
Liver	9.45	8.38	9.94	9.26	0.80
Skin	1.36	1.31	1.58	1.42	0.14
Carcass	1.26	1.97	2.91	2.05	0.83

Table 42: Tissue concentrations of radioactivity 18 h and 17 h after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to male and female rats, respectively

Single animal data and group mean values. Results expressed in $\mu\text{g Eq/g}$

Male animal No.	97	98	99	Mean	SD
Body weight [g]	313.0	303.2	295.4	303.9	8.8
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	32.9	34.3	30.8	32.6	1.7
Radioact. Dose [MBq/animal]	2.36	2.38	2.09	2.28	0.16
Blood cells	0.12	0.13	0.11	0.12	0.01
Plasma	1.25	1.46	1.02	1.24	0.22
Lung	0.48	0.52	0.40	0.47	0.06
Heart	0.22	0.32	0.24	0.26	0.05
Spleen	0.16	0.20	0.12	0.16	0.04
Kidney	2.16	2.33	2.10	2.19	0.12
Adrenal glands	0.41	0.37	0.38	0.39	0.02
Testes/Ovaries	0.19	0.24	0.19	0.21	0.03
Uterus	---	---	---	---	---
Muscle	0.11	0.14	0.15	0.13	0.02
Brain	0.04	0.05	0.03	0.04	0.01
Adipose tissue	0.07	0.07	0.06	0.07	0.01
Bone	0.07	0.12	0.06	0.08	0.03
Bone marrow	0.26	0.34	0.16	0.25	0.09
Thyroid	0.64	0.77	0.41	0.61	0.18
Pancreas	0.27	0.51	0.22	0.33	0.15
Stomach content	4.29	5.59	1.90	3.93	1.87
Stomach	1.47	1.47	1.09	1.34	0.22
Gut content	182.05	191.51	107.33	160.30	46.11
Gut	20.34	22.28	14.57	19.06	4.01
Liver	2.77	2.59	3.40	2.92	0.42
Skin	0.57	0.60	0.52	0.56	0.04
Carcass	2.34	0.99	1.52	1.62	0.68
Female animal No.	109	110	111	Mean	SD
Body weight [g]	254.2	254.3	258.9	255.8	2.7
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	32.1	32.8	32.5	32.4	0.4
Radioact. Dose [MBq/animal]	1.87	1.91	1.93	1.90	0.03
Blood cells	0.42	0.21	0.17	0.27	0.13
Plasma	2.44	1.57	1.64	1.88	0.48
Lung	0.83	0.58	0.62	0.68	0.13
Heart	0.55	0.39	0.33	0.42	0.11
Spleen	0.25	0.17	0.21	0.21	0.04
Kidney	1.99	1.57	1.80	1.79	0.21
Adrenal glands	0.57	0.44	0.50	0.50	0.07
Testes/Ovaries	0.96	0.50	0.70	0.72	0.23
Uterus	0.65	0.49	0.47	0.54	0.10
Muscle	0.18	0.11	0.15	0.15	0.04
Brain	0.06	0.05	0.04	0.05	0.01
Adipose tissue	0.10	0.06	0.08	0.08	0.02
Bone	0.06	0.04	0.04	0.05	0.01
Bone marrow	0.75	0.61	0.70	0.69	0.07
Thyroid	0.92	0.78	0.86	0.86	0.07
Pancreas	0.38	0.39	0.51	0.43	0.07
Stomach content	2.15	1.35	3.07	2.19	0.86
Stomach	2.02	1.27	2.26	1.85	0.52
Gut content	192.83	162.28	406.51	253.87	133.07
Gut	27.71	25.41	26.65	26.59	1.15
Liver	3.14	2.81	3.74	3.23	0.47
Skin	0.76	0.54	0.63	0.64	0.11
Carcass	4.52	1.14	0.94	2.20	2.01

Table 43: Tissue concentrations of radioactivity 25 h and 22 h after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to male and female rats, respectively

Single animal data and group mean values. Results expressed in $\mu\text{g Eq/g}$

Male animal No.	100	101	102	Mean	SD
Body weight [g]	290.0	301.8	289.1	293.6	7.1
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	33.0	33.2	32.3	32.8	0.5
Radioact. Dose [MBq/animal]	2.19	2.30	2.14	2.21	0.08
Blood cells	0.13	0.06	0.06	0.08	0.04
Plasma	1.12	0.59	0.58	0.76	0.31
Lung	0.42	0.23	0.24	0.30	0.11
Heart	0.21	0.15	0.12	0.16	0.05
Spleen	0.13	0.09	0.08	0.10	0.03
Kidney	1.80	1.23	1.03	1.35	0.40
Adrenal glands	0.35	0.18	0.16	0.23	0.11
Testes/Ovaries	0.20	0.12	0.11	0.14	0.05
Uterus	---	---	---	---	---
Muscle	---	0.07	0.06	0.06	0.01
Brain	0.03	0.03	0.02	0.02	0.00
Adipose tissue	0.07	0.02	0.03	0.04	0.03
Bone	0.09	0.03	0.05	0.06	0.03
Bone marrow	0.28	0.19	0.22	0.23	0.05
Thyroid	0.79	0.31	0.29	0.46	0.28
Pancreas	0.21	0.32	0.13	0.22	0.10
Stomach content	6.08	99.36	4.13	36.52	54.43
Stomach	2.06	0.96	0.77	1.26	0.70
Gut content	128.25	117.61	111.59	119.15	8.44
Gut	21.12	11.83	11.83	14.93	5.36
Liver	2.17	1.35	1.44	1.66	0.45
Skin	0.40	0.24	0.23	0.29	0.09
Carcass	1.10	1.09	1.70	1.29	0.35
Female animal No.	112	113	114	Mean	SD
Body weight [g]	251.8	261.0	257.4	256.7	4.6
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	32.8	32.8	32.9	32.8	0.1
Radioact. Dose [MBq/animal]	1.90	1.96	1.94	1.93	0.04
Blood cells	0.15	0.09	0.11	0.12	0.03
Plasma	1.40	0.87	1.02	1.10	0.28
Lung	0.46	0.35	0.33	0.38	0.07
Heart	0.24	0.21	0.20	0.22	0.02
Spleen	0.14	0.12	0.11	0.12	0.02
Kidney	1.22	1.07	1.10	1.13	0.08
Adrenal glands	0.30	0.50	0.25	0.35	0.13
Testes/Ovaries	0.51	0.35	0.34	0.40	0.10
Uterus	0.42	0.29	0.28	0.33	0.08
Muscle	0.09	0.07	0.09	0.09	0.01
Brain	0.04	0.04	0.03	0.04	0.01
Adipose tissue	0.06	0.03	0.05	0.05	0.01
Bone	0.04	0.03	0.06	0.04	0.02
Bone marrow	0.47	0.53	0.43	0.47	0.05
Thyroid	0.73	0.62	0.67	0.67	0.06
Pancreas	0.22	0.37	0.18	0.25	0.10
Stomach content	5.68	4.22	3.16	4.35	1.26
Stomach	1.45	1.43	0.63	1.17	0.47
Gut content	243.36	39.53	131.77	138.22	102.07
Gut	21.12	3.99	14.44	13.18	8.63
Liver	2.14	2.02	1.77	1.98	0.19
Skin	0.47	0.34	0.38	0.40	0.07
Carcass	0.93	1.77	1.80	1.50	0.50

Table 44: Tissue concentrations of radioactivity 168 h after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to male and female rats (in $\mu\text{g eq/g}$)

Samples generated in experiment 4 (balance low dose). Results expressed in $\mu\text{g Eq/g}$

Male animal No.	9	10	11	12	Mean	SD
Blood cells	0.01	0.01	0.01	0.01	0.01	0.00
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Lung	0.01	0.01	0.01	0.03	0.02	0.01
Heart	0.01	0.01	0.01	0.01	0.01	0.00
Spleen	0.01	0.01	0.01	0.01	0.01	0.00
Kidney	0.03	0.02	0.05	0.03	0.02	0.01
Adrenals	0.02	0.02	0.01	0.01	0.02	0.01
Testes/Ovaries	0.00	0.01	0.00	0.00	0.00	0.00
Uterus	---	---	---	---	---	---
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose Tissue	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.01	0.01	0.00	0.01	0.01	0.00
Bone marrow	0.02	0.03	0.02	0.02	0.02	0.01
Thyroid	0.10	0.02	0.06	0.15	0.09	0.07
Pancreas	0.01	0.00	0.00	0.01	0.01	0.00
Stomach cont.	0.18	0.17	0.46	0.51	0.29	0.19
Stomach	0.01	0.01	0.02	0.01	0.01	0.00
Gut cont.	0.22	0.16	0.41	0.72	0.37	0.31
Gut	0.04	0.02	0.05	0.06	0.04	0.02
Liver	0.01	0.01	0.02	0.02	0.01	0.00
Skin	0.01	0.01	0.03	0.01	0.01	0.00
Carcass	0.47	0.38	0.79	0.56	0.47	0.09

animal 11 was not included into statistics due to insufficient recovery

Female animal No.	13	14	15	16	Mean	SD
Blood cells	0.01	0.02	0.01	0.01	0.01	0.00
Plasma	0.00	0.00	0.01	0.00	0.00	0.00
Lung	0.01	0.01	0.01	0.01	0.01	0.00
Heart	0.01	0.01	0.02	0.01	0.01	0.00
Spleen	0.01	0.01	0.01	0.01	0.01	0.00
Kidney	0.03	0.04	0.02	0.03	0.03	0.01
Adrenals	0.01	0.01	0.01	0.01	0.01	0.00
Testes/Ovaries	0.01	0.00	0.01	0.00	0.01	0.00
Uterus	0.01	0.00	0.01	0.00	0.00	0.00
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.01	0.01	0.00	0.01	0.01	0.00
Adipose Tissue	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.01	0.01	0.00	0.00	0.00	0.00
Bone marrow	0.03	0.03	0.02	0.00	0.02	0.01
Thyroid	0.18	0.03	0.13	0.05	0.10	0.07
Pancreas	0.01	0.01	0.01	0.01	0.01	0.00
Stomach cont.	0.17	0.41	1.81	0.60	0.75	0.73
Stomach	0.01	0.01	0.03	0.01	0.01	0.01
Gut cont.	0.67	0.84	0.60	0.33	0.61	0.21
Gut	0.08	0.07	0.10	0.07	0.08	0.01
Liver	0.02	0.02	0.02	0.01	0.02	0.00
Skin	0.01	0.04	0.02	0.01	0.02	0.01
Carcass	0.27	0.29	0.58	0.92	0.51	0.31

Table 45: Tissue concentrations of radioactivity 168 h after 14 daily oral administrations of DHDPS and one oral administration of ^{14}C -4,4'-sulphonyldiphenol on day 15 (30 mg/kg bw) to male and female rats

Samples generated in experiment 5 (14+1 dose group). Results expressed in $\mu\text{g Eq/g}$

Male animal No.	17	18	19	20	Mean	SD
Blood cells	0.01	0.01	0.01	0.01	0.01	0.00
Plasma	0.00	0.01	0.01	0.01	0.01	0.00
Lung	0.01	0.01	0.01	0.01	0.01	0.00
Heart	0.01	0.01	0.01	0.01	0.01	0.00
Spleen	0.01	0.01	0.01	0.01	0.01	0.00
Kidney	0.02	0.03	0.03	0.04	0.03	0.01
Adrenals	0.02	0.01	0.01	0.01	0.01	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00	0.00
Uterus	---	---	---	---	---	---
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose Tissue	0.00	0.00	0.00	0.00	0.00	0.00
Bone	0.02	0.02	0.01	0.02	0.01	0.00
Bone marrow	0.02	0.02	0.02	0.03	0.02	0.01
Thyroid	0.06	0.04	0.02	0.05	0.04	0.02
Pancreas	0.01	0.01	0.01	0.01	0.01	0.00
Stomach cont.	0.70	1.71	0.97	0.17	0.61	0.40
Stomach	0.01	0.01	0.02	0.03	0.02	0.01
Gut cont.	0.67	1.03	1.35	0.75	0.93	0.37
Gut	0.09	0.16	0.15	0.13	0.12	0.03
Liver	0.01	0.02	0.02	0.02	0.02	0.01
Skin	0.01	0.03	0.02	0.02	0.02	0.00
Carcass	0.35	0.47	0.23	0.20	0.26	0.08

Female animal No.	21	22	23	24	Mean	SD
Blood cells	0.01	0.01	0.01	0.00	0.01	0.00
Plasma	0.00	0.00	0.00	0.00	0.00	0.00
Lung	0.01	0.00	0.01	0.01	0.01	0.00
Heart	0.01	0.01	0.01	0.01	0.01	0.00
Spleen	0.01	0.01	0.01	0.01	0.01	0.00
Kidney	0.04	0.04	0.02	0.02	0.03	0.01
Adrenals	0.01	0.01	0.01	0.01	0.01	0.00
Testes/Ovaries	0.01	0.01	0.01	0.01	0.01	0.00
Uterus	0.00	0.00	0.01	0.01	0.01	0.00
Muscle	0.00	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00	0.00
Adipose Tissue	0.01	0.01	0.00	0.01	0.01	0.00
Bone	0.02	0.02	0.01	0.00	0.01	0.01
Bone marrow	0.03	0.04	0.02	0.02	0.03	0.01
Thyroid	0.12	0.08	0.05	0.02	0.07	0.04
Pancreas	0.01	0.01	0.01	0.01	0.01	0.00
Stomach cont.	0.14	0.23	9.38	0.10	2.46	4.62
Stomach	0.02	0.01	0.01	0.01	0.01	0.00
Gut cont.	0.57	0.39	0.59	0.70	0.56	0.13
Gut	0.13	0.06	0.11	0.16	0.11	0.04
Liver	0.03	0.02	0.02	0.01	0.02	0.01
Skin	0.02	0.11	0.03	0.02	0.04	0.04
Carcass	0.63	0.72	0.86	0.83	0.76	0.11

animal 18 was not included into statistics due to insufficient recovery

Table 46: Tissue concentrations of radioactivity 1 h after single oral administration of ^{14}C -4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to male and female rats

Single animal data and group mean values. Results expressed in % of dose

Male animal No.	91	92	93	Mean	SD
Body weight [g]	292.9	300.0	292.8	295.2	4.1
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	32.6	31.8	32.9	32.5	0.6
Radioact. Dose [MBq/animal]	2.19	2.19	2.21	2.20	0.01
Blood cells	0.08	0.02	0.02	0.04	0.04
Plasma	0.44	0.26	0.28	0.33	0.10
Lung	0.12	0.04	0.04	0.07	0.05
Heart	0.06	0.02	0.01	0.03	0.03
Spleen	0.01	0.01	0.01	0.01	0.00
Kidney	0.53	0.28	0.23	0.35	0.16
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.07	0.05	0.04	0.05	0.01
Uterus	---	---	---	---	---
Muscle	0.02	0.01	0.01	0.01	0.01
Brain	0.01	0.01	0.01	0.01	0.00
Adipose tissue	0.01	0.00	0.00	0.00	0.00
Bone	0.00	0.01	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.05	0.01	0.01	0.02	0.02
Stomach content	17.88	21.72	28.31	22.64	5.28
Stomach	0.71	1.45	0.70	0.95	0.43
Gut content	55.68	55.81	57.51	56.34	1.02
Gut	3.22	3.27	2.76	3.08	0.28
Liver	2.82	1.86	1.37	2.02	0.74
Skin	2.71	1.92	1.34	1.99	0.68
Carcass	10.23	5.82	4.71	6.92	2.92
Female animal No.	103	104	105	Mean	SD
Body weight [g]	240.5	231.1	239.6	237.1	5.2
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	33.5	32.5	33.5	33.2	0.5
Radioact. Dose [MBq/animal]	1.85	1.73	1.84	1.80	0.07
Blood cells	0.03	0.01	0.02	0.02	0.01
Plasma	0.26	0.12	0.24	0.21	0.08
Lung	0.07	0.04	0.10	0.07	0.03
Heart	0.01	0.01	0.01	0.01	0.01
Spleen	0.01	0.00	0.00	0.00	0.00
Kidney	0.17	0.06	0.19	0.14	0.07
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00
Uterus	0.02	0.01	0.02	0.02	0.01
Muscle	0.01	0.01	0.01	0.01	0.00
Brain	0.01	0.00	0.01	0.00	0.00
Adipose tissue	0.00	0.00	0.01	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.03	0.00	0.01	0.02	0.01
Stomach content	31.53	55.42	18.57	35.17	0.04
Stomach	1.40	3.29	1.59	2.10	1.04
Gut content	48.05	17.35	48.45	37.95	17.84
Gut	5.32	1.58	17.92	8.27	8.56
Liver	1.05	0.60	1.12	0.92	0.28
Skin	1.36	0.45	1.21	1.00	0.49
Carcass	6.59	2.33	2.62	3.85	2.38

Table 47: Tissue concentrations of radioactivity 4 h after single oral administration of ¹⁴C-4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to male and female rats

Single animal data and group mean values. Results expressed in % of dose

Male animal No.	94	95	96	Mean	SD
Body weight [g]	310.5	300.5	325.2	312.1	12.4
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	32.4	31.0	32.9	32.1	1.0
Radioact. Dose [MBq/animal]	2.31	2.14	2.46	2.30	0.16
Blood cells	0.01	0.01	0.01	0.01	0.00
Plasma	0.14	0.15	0.08	0.12	0.04
Lung	0.02	0.02	0.01	0.02	0.00
Heart	0.01	0.01	0.00	0.01	0.00
Spleen	0.00	0.00	0.00	0.00	0.00
Kidney	0.15	0.14	0.07	0.12	0.04
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.02	0.02	0.01	0.02	0.01
Uterus	---	---	---	---	---
Muscle	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00
Stomach content	14.12	8.80	3.28	8.73	5.42
Stomach	0.62	0.90	0.50	0.67	0.21
Gut content	53.98	65.35	81.47	66.93	13.81
Gut	3.49	4.81	4.15	4.15	0.66
Liver	1.25	0.94	0.64	0.94	0.30
Skin	0.55	0.53	0.52	0.53	0.01
Carcass	1.80	11.48	8.61	7.30	4.98

Female animal No.	106	107	108	Mean	SD
Body weight [g]	220.1	231.8	233.1	228.3	7.2
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	33.5	32.2	33.0	32.9	0.7
Radioact. Dose [MBq/animal]	1.69	1.71	1.77	1.72	0.04
Blood cells	0.02	0.01	0.01	0.01	0.00
Plasma	0.19	0.19	0.17	0.18	0.01
Lung	0.04	0.03	0.03	0.03	0.00
Heart	0.01	0.01	0.01	0.01	0.00
Spleen	0.00	0.00	0.00	0.00	0.00
Kidney	0.07	0.08	0.11	0.09	0.02
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00
Uterus	0.01	0.01	0.01	0.01	0.00
Muscle	0.01	0.01	0.01	0.01	0.00
Brain	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.04	0.00	0.02	0.02
Stomach content	7.78	11.18	5.05	8.00	2.53
Stomach	1.22	0.66	0.66	0.85	0.32
Gut content	57.95	68.41	64.19	63.52	5.26
Gut	5.92	5.30	8.47	6.56	1.68
Liver	1.00	0.87	0.97	0.95	0.07
Skin	0.56	0.55	0.65	0.59	0.06
Carcass	2.21	3.76	5.45	3.81	1.62

Table 48: Tissue concentrations of radioactivity 18 h and 17 h after single oral administration of ¹⁴C-4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to male and female rats, respectively

Single animal data and group mean values. Results expressed in % of dose

Male animal No.	97	98	99	Mean	SD
Body weight [g]	313.0	303.2	295.4	303.9	8.8
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	32.9	34.3	30.8	32.6	1.7
Radioact. Dose [MBq/animal]	2.36	2.38	2.09	2.28	0.16
Blood cells	0.00	0.00	0.00	0.00	0.00
Plasma	0.05	0.04	0.04	0.04	0.00
Lung	0.01	0.01	0.01	0.01	0.00
Heart	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00
Kidney	0.04	0.04	0.04	0.04	0.00
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.01	0.01	0.01	0.01	0.00
Uterus	---	---	---	---	---
Muscle	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00
Stomach content	0.05	0.09	0.04	0.01	0.03
Stomach	0.02	0.02	0.02	0.01	0.00
Gut content	24.25	22.29	14.50	1.11	5.16
Gut	1.29	1.54	1.02	0.12	0.26
Liver	0.29	0.25	0.39	0.24	0.07
Skin	0.30	0.24	0.26	0.24	0.03
Carcass	4.37	1.81	2.94	1.13	1.28

Female animal No.	109	110	111	Mean	SD
Body weight [g]	254.2	254.3	258.9	255.8	2.7
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	32.1	32.8	32.5	32.4	0.4
Radioact. Dose [MBq/animal]	1.87	1.91	1.93	1.90	0.03
Blood cells	0.01	0.01	0.01	0.01	0.00
Plasma	0.08	0.06	0.06	0.07	0.01
Lung	0.02	0.01	0.01	0.01	0.00
Heart	0.01	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00
Kidney	0.04	0.03	0.03	0.04	0.01
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.00	0.00	0.00	0.00	0.00
Uterus	0.01	0.00	0.01	0.01	0.00
Muscle	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00
Stomach content	0.07	0.05	0.08	0.06	0.02
Stomach	0.03	0.02	0.04	0.03	0.01
Gut content	26.53	19.40	50.03	31.99	16.03
Gut	2.30	1.83	1.91	2.01	0.25
Liver	0.34	0.25	0.38	0.32	0.07
Skin	0.34	0.24	0.28	0.28	0.05
Carcass	8.91	2.15	1.75	4.27	4.03

Table 49: Tissue concentrations of radioactivity 25 h and 22 h after single oral administration of ¹⁴C-4,4'-sulphonyldiphenol at a target dose level of 30 mg/kg bw to male and female rats, respectively

Single animal data and group mean values. Results expressed in % of dose

Male animal No.	100	101	102	Mean	SD
Body weight [g]	290.0	301.8	289.1	293.6	7.1
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	33.0	33.2	32.3	32.8	0.5
Radioact. Dose [MBq/animal]	2.19	2.30	2.14	2.21	0.08
Blood cells	0.00	0.00	0.00	0.00	0.00
Plasma	0.04	0.02	0.02	0.03	0.01
Lung	0.01	0.00	0.01	0.00	0.00
Heart	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00
Kidney	0.04	0.02	0.02	0.03	0.01
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.01	0.00	0.00	0.00	0.00
Uterus	---	---	---	---	---
Muscle	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00
Stomach content	0.09	1.16	0.02	0.42	0.64
Stomach	0.03	0.01	0.01	0.02	0.01
Gut content	12.79	13.10	11.64	12.51	0.77
Gut	1.24	0.83	0.73	0.94	0.27
Liver	0.21	0.14	0.15	0.17	0.04
Skin	0.20	0.11	0.11	0.14	0.05
Carcass	2.10	1.98	3.08	2.39	0.60

Female animal No.	112	113	114	Mean	SD
Body weight [g]	251.8	261.0	257.4	256.7	4.6
Specific activity [dpm/mg]	---	---	---	13758000	--
Dose admin. [mg/kg bw]	32.8	32.8	32.9	32.8	0.1
Radioact. Dose [MBq/animal]	1.90	1.96	1.94	1.93	0.04
Blood cells	0.00	0.00	0.00	0.00	0.00
Plasma	0.05	0.03	0.04	0.04	0.01
Lung	0.01	0.01	0.00	0.01	0.00
Heart	0.00	0.00	0.00	0.00	0.00
Spleen	0.00	0.00	0.00	0.00	0.00
Kidney	0.03	0.02	0.02	0.02	0.00
Adrenal glands	0.00	0.00	0.00	0.00	0.00
Testes/Ovaries	0.01	0.00	0.00	0.00	0.00
Uterus	0.00	0.00	0.00	0.00	0.00
Muscle	0.00	0.00	0.00	0.00	0.00
Brain	0.00	0.00	0.00	0.00	0.00
Adipose tissue	0.00	0.00	0.00	0.00	0.00
Bone	0.00	0.00	0.00	0.00	0.00
Bone marrow	0.00	0.00	0.00	0.00	0.00
Thyroid	0.00	0.00	0.00	0.00	0.00
Pancreas	0.00	0.00	0.00	0.00	0.00
Stomach content	0.08	0.08	0.04	0.07	0.02
Stomach	0.02	0.02	0.01	0.02	0.01
Gut content	36.62	5.00	15.64	19.09	16.09
Gut	1.15	0.32	0.98	0.82	0.44
Liver	0.22	0.20	0.18	0.20	0.02
Skin	0.18	0.16	0.16	0.17	0.01
Carcass	1.79	3.29	3.42	2.83	0.91