

(b) (4)

FINAL REPORT

Test Facility Study No. 185350
Sponsor Reference No. ALC-NC-0552

**A Tissue Distribution Study of a [³H]-Labelled Lipid Nanoparticle-mRNA
Formulation Containing ALC-0315 and ALC-0159 Following
Intramuscular Administration in Wistar Han Rats**

TEST FACILITY:

(b) (4)

SPONSOR:

Acuitas Therapeutics Inc.
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1 COMPLIANCE STATEMENT

Study Title: A Tissue Distribution Study of a [³H]-Labelled Lipid Nanoparticle-mRNA Formulation Containing ALC-0315 and ALC-0159 Following Intramuscular Administration in Wistar Han Rats

GLP regulations are not applicable to studies of this nature therefore no claim of GLP compliance is made. Nevertheless, as Study Director, I confirm that this study was conducted in a GLP compliant facility and that the practices and procedures adopted during its conduct were consistent with the OECD Principles of Good Laboratory Practice as incorporated into the United Kingdom Statutory Instrument for GLP.

The study was conducted according to the procedures herein described and this report represents a true and accurate record of the results obtained.

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(b) (4)
Study Director

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2 QUALITY ASSURANCE STATEMENT

Study Title: A Tissue Distribution Study of a [³H]-Labelled Lipid Nanoparticle-mRNA Formulation Containing ALC-0315 and ALC-0159 Following Intramuscular Administration in Wistar Han Rats

This study has not been subjected to any study specific Quality Assurance procedures.

3 RESPONSIBLE PERSONNEL

Study Director: (b) (4)

Sponsor Representative: (b) (6)

Test Facility Management: (b) (4)

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4 SUMMARY

The test item, 08-A01-C01, is an aqueous dispersion of lipid nanoparticles (LNP), comprised of a proprietary mixture of lipid components (including ALC-0315, ALC-0159, distearoylphosphatidylcholine, and cholesterol) and mRNA. The mRNA encodes a model protein (luciferase) and is not pharmacologically active. The test item contains trace amounts of radiolabelled [Cholesteryl-1,2-³H(N)]-Cholesteryl Hexadecyl Ether (³H)-CHE), a non-exchangeable, non-metabolisable lipid marker used to monitor the disposition of the lipid nanoparticles (containing encapsulated mRNA). Once intracellular, the [³H]-CHE does not recirculate and therefore allows assessment of distribution of the particles.

The objectives of this study were to:

1. Characterise the disposition of 08-A01-C01 containing a radiolabelled lipid marker in male and female Wistar Han rats following a single intramuscular administration.
2. Determine the concentration and content of radioactivity in blood, plasma and tissues of rats (expressed as µg lipid eq/mL (or per g for tissue), and % administered (injected dose)/tissue, where appropriate).

Wistar Han rats (21 male and 21 female) each received a single intramuscular dose of [³H]-08-A01-C01 at a target mRNA total dose of 50 µg/animal (1.29 mg/animal total lipid dose). The content and concentration of total radioactivity in blood, plasma and tissues were determined at pre-defined time points following administration.

Whole blood and tissue samples were collected at 0.25, 1, 2, 4, 8, 24 and 48 hours post-dose (three animals/sex/timepoint) and plasma was subsequently separated from blood by centrifugation. The concentration of total radioactivity was measured by liquid scintillation counting (LSC).

Following intramuscular administration of [³H]-08-A01-C01 to male and female Wistar Han rats at a target dose level of 50 µg/animal (1.29 mg/animal total lipid dose), the greatest mean concentration was found remaining in the injection site at each time point in both sexes. Outside the injection site, low levels of radioactivity were detected in most tissues, with the greatest levels in plasma observed 1-4 hours post-dose. Over 48 hours, [³H]-08-A01-C01 distributed mainly to liver, adrenal glands, spleen and ovaries, with maximum concentrations observed at 8-48 hours post-dose. Total recovery (% of injected dose) of [³H]-08-A01-C01 outside the injection site was greatest in the liver (up to 21.5%) and was much less in spleen (≤1.1%), adrenal glands (≤0.1%) and ovaries (≤0.1%). The mean concentrations and tissue distribution pattern were broadly similar between the sexes.

Blood:plasma ratios were generally between 0.5-0.6, indicating that the majority of the total radioactivity is associated with the plasma fraction and that [³H]-08-A01-C01 does not undergo appreciable accumulation in red blood cells.

In conclusion, the distribution of [³H]-08-A01-C01 (monitoring the [³H]-CHE lipid label) in blood, plasma and selected tissues was determined in male and female Wistar Han rats over 48 hours after a single intramuscular injection at 50 µg mRNA/animal (1.29 mg/animal lipid dose). The concentrations of [³H]-08-A01-C01 were greatest in the injection site at all time points, with levels peaking in the plasma by 1-4 hours post-dose and distribution mainly into liver, adrenal glands, spleen and ovaries over 48 hours. Total recovery of radioactivity outside of the injection site was greatest in the liver, with much lower total recovery in spleen, and very little recovery in adrenals glands and ovaries. The mean plasma, blood and tissue concentrations and tissue distribution patterns were broadly similar between the sexes and [³H]-08-A01-C01 did not associate with red blood cells.

5 INTRODUCTION

The objectives of this study were to:

1. Characterise the disposition of 08-A01-C01 containing a radiolabelled lipid marker in male and female Wistar Han rats following a single intramuscular administration
2. Determine the concentration and content of radioactivity in blood, plasma and tissues of rats (expressed as μg lipid eq/g (or per mL for plasma) and % injected dose/tissue, where appropriate)

The Wistar Han rat was chosen as the animal model for this study as it is an accepted rodent species for preclinical toxicity testing by regulatory agencies and has been used in all regulatory toxicology studies by the Sponsor.

The study was designed to be appropriate for submission to regulatory authorities. However, it is recognised that no detailed test guidelines for the conduct of drug distribution and pharmacokinetic studies are currently available.

Initially, 21 male rats were dosed at 100 μg mRNA/animal. Some adverse clinical signs were observed after approximately 24 hours post-dose and a subsequent review of the data showed concentrations were well detected in tissues. After discussions with the Sponsor, the target dose level was lowered to 50 μg mRNA/animal by amendment for the remainder of the study. Reference is made to the 100 μg mRNA /animal group in some sections of the report, however, the results are not discussed.

5.1 Study Location

The study was carried out at (b) (4) according to (b) (4) Protocol No. 185350 and Amendments 1 and 2.

5.2 Study Dates

The study was conducted according to the following timetable:

Study Initiation:	16 July 2020
Experimental Start Date:	17 July 2020
Experimental Completion Date:	24 September 2020
Study Completion Date:	See compliance page for date of Study Director's signature.

5.3 Archiving

All raw data generated and recorded during this study will be stored in the Scientific Archive of (b) (4) for 2 years after issue of the final report. After the 2-year period the Sponsor will be consulted regarding the disposal, transfer, or continued storage of the raw data. Electronic data generated by the Test Facility were archived as noted above, except reporting files stored on Shared Document Management System (SDMS), which were archived at the (b) (4)

The original signed copy of the final report will be stored indefinitely in the Scientific Archive of (b) (4)

The residual [³H]-08-A01-C01 dose (approximately 5 MBq) will be retained and stored in a fridge set to maintain 4°C at (b) (4)

Biological samples generated during the course of this study were held deep frozen until issue of the final report. (b) (4) will contact the Sponsor to discuss the fate of the samples (disposal, return or retain at (b) (4)) on issue of the final report. Samples will be disposed of unless (b) (4) receives written instruction regarding shipment of the samples to the Sponsor or continued storage at (b) (4)

6 EXPERIMENTAL PROCEDURE

6.1 Test Item

Identification:	[³ H]-08-A01-C01
Supplier:	Acuitas Therapeutics Inc
Lot Number:	NC-0552-1
Expiration Date:	July 7, 2021
Physical Description:	White to off-white, homogenous, opalescent liquid; no foreign particles
Concentration (mRNA):	1.0 mg/mL
Radioactive Concentration	0.864 mCi/mL, 1,900,000 dpm/μL

Concentration (Total Lipid)	25.7 mg/mL
Molecular weight	Not applicable for LNP
Purity:	94%
Radiochemical Purity	>97%
Specific Activity (mRNA):	0.864 mCi/mg (32.0 MBq/mg)
Correction Factor	None
Storage Conditions:	Frozen (-60°C to -90°C)

The test item contains trace amounts of radiolabelled [Cholesteryl-1,2-³H(N)]-Cholesteryl Hexadecyl Ether (³H]-CHE), a non-exchangeable, non-metabolisable lipid marker used to monitor the disposition of the lipid nanoparticles (containing encapsulated mRNA). Per the manufacturer's information, the radiochemical purity of [³H]-CHE was found to be >97% and the rate of decomposition is initially 2% for 6 months from the date of purification (16 December 2019). No radiochemical purity assessments were made as part of this study.

The Certificates of Analysis for [³H]-08-A01-C01 and [³H]-CHE are presented in [Appendix 1](#).

6.2 Other Materials

AquaSafe 500 Plus liquid scintillation fluid was obtained from Zinsser Inc.

Monophase® was used in conjunction with the Perkin Elmer Model 307 Automatic Sample Oxidiser and was supplied by Perkin Elmer Life Science and Analytical Instruments Inc, UK.

Spec-Chec™-³H used to estimate efficiencies of combustion was also obtained from Perkin Elmer Life Science and Analytical Instruments Inc, UK.

All other materials and chemicals used were of analytical grade where available and supplied by standard commercial suppliers.

6.3 Animals and Husbandry

Forty-two male and 21 female Wistar Han rats (8-11 weeks and body weight 179-270 g at the time of dosing) were used in the study and were supplied by (b) (4). The animals were acclimatised to the experimental unit for at least 5 days prior to use on the study. During the acclimatisation periods, the animals were closely observed by the animal technicians to ensure that they were in good health and suitable for inclusion in the study. During the study period the animals were closely observed twice daily by the animal technicians to ensure that they were in good health.

During the study period, the rats were housed in groups in polycarbonate and stainless steel cages with wire mesh floors. Animals used for excretion collection were housed singly in all-glass metabolism cages for the separate collection of urine and faeces.

A standard laboratory diet of known formulation (SDS Rat and Rat Maintenance Diet No.1, Special Diet Services, 1 Stepfield, Witham, Essex) and domestic mains tap water were available *ad libitum*.

Holding and study areas had automatic control of light cycles and temperature. Automatic 12 hours light and 12 hours dark. Ranges of temperature and humidity measured during the study were 21-23°C and 44-67%, respectively, with the exception of 31 July 2020 where the room temperature reached a maximum of 25°C.

6.4 Specific Activity

The specific activity value of 1.24 MBq/mg lipid (as calculated from the 0.864 mCi/mg mRNA specific activity value supplied and converted to per mg lipid) was used to calculate the amount of [³H]-08-A01-C01 dispensed in the dose formulation.

6.5 Dose Formulation

[³H]-08-A01-C01 was provided in PBS/sucrose buffer at the required dose concentration (1 mg mRNA/mL). No dilutions were therefore required. Four dose formulation vials were provided (3 x 1.5 mL and 1 x 1.2 mL).

The appropriate number of vials for each dosing occasion were defrosted for at least 30 minutes prior to dosing. Prior to use, each vial was inverted 3 times to mix. Once dosing was complete, each vial was stored in a fridge within 4 hours of removal from the -80°C freezer.

The radioactive concentration of the supplied dose formulation was determined by the removal of triplicate aliquots (50 µL) prior to and after the first dosing occasion. Appropriate

dilutions of each aliquot were prepared in distilled water and duplicate aliquots of each dilution were analysed by liquid scintillation counting (LSC).

The radioactive concentration determined by LSC was within 10% of the target value provided in the supplied Certificate of Analysis and was used in the dose determination calculations.

6.6 Dose Administration and Determination

Each animal received a single (one site) intramuscular administration of [³H]-08-A01-C01 at either 50 or 100 µL volume for the 50 and 100 µg mRNA/animal dose groups, respectively (target doses of 1.29 or 2.57 mg total lipid/animal, respectively).

The actual dose received by each animal was determined with reference to the dose concentration, the volume of dose administered and the specific activity of [³H]-08-A01-C01 in the formulated dose. Any undosed residue was also taken in to account. The actual dose received by each animal is documented in [Appendix 2](#).

6.7 Collection of Biological Samples

Three male and three female rats were sacrificed at the following times:

0.25, 1, 2, 4, 8, 24 and 48 hours post dose

From each animal, a terminal blood sample (*ca.* 5-10 mL) was collected by cardiac puncture into heparinised tubes. A portion (*ca.* 0.5 mL) was retained and plasma separated from the remainder of each sample by centrifugation (3000 rpm for 10 minutes in a centrifuge set to maintain a temperature of 4°C). Blood cells were discarded.

The following tissues were collected (where relevant for sex):

Adipose tissue	Ovaries
Adrenal glands	Pancreas
Bladder	Pituitary gland
Bone (femur)	Prostate
Bone marrow (femur)	Salivary glands
Brain	Skin
Eyes	Muscle
Heart	Small intestine
Injection site	Spinal cord
Kidneys	Spleen
Large intestine	Stomach
Liver	Testes
Lung	Thymus
Lymph node (mandibular)	Thyroid

Lymph node (mesenteric)

Uterus

Additionally, for animals 043M, 045M, 046M, 048M, 051M, 052M, 055M and 058M, the tibia/fibula bone was also collected but not analysed (refer to Section 6.11).

6.8 Sample Storage

Samples not analysed immediately were stored frozen in a freezer set to maintain a temperature of -20°C until taken for analysis, with the exception of urine and faeces samples which were stored at -80°C. After analysis, samples were returned to storage in a freezer set to maintain a temperature of -20°C.

Samples of cage wash, dose determinations and dose residues were stored at room temperature prior to and following analysis. These samples were discarded at the Study Director's discretion following acceptance of the study results.

6.9 Preparation of Samples for Total Radioactivity Analysis

Volumes or weights of all samples were measured where appropriate

6.9.1 Dose Formulation

Duplicate aliquots (0.1 mL) of each dilution of the dose formulation were diluted with water and dissolved in scintillation fluid (Aquasafe 500 Plus, Zinsser Inc.) and analysed directly by liquid scintillation counting.

6.9.2 Blood and Plasma

Duplicate weighed aliquots of whole blood (2 x *ca.* 0.15 g) were taken and then combusted using a Perkin Elmer Model 307 Sample Oxidiser. The resultant $^3\text{H}_2\text{O}$ generated was collected by absorption in Monophase® (15 mL).

Duplicate aliquots (100 µL) of plasma were allowed to air dry, diluted with water and dissolved in scintillation fluid (Aquasafe 500 Plus, Zinsser Inc.) and analysed directly by LSC.

6.9.3 Tissues

Tissue samples were finely chopped with scissors and duplicate, where appropriate, portions were combusted using a Perkin Elmer Model 307 Sample Oxidiser. Smaller tissues were aliquoted directly. The resultant $^3\text{H}_2\text{O}$ generated was collected by absorption in Monophase® S (15 mL).

Combustion of standards showed that recovery efficiencies were in excess of 95% throughout.

6.9.4 Urine, Faeces and Cage Wash

Urine, faeces and cage wash samples were collected but not analysed for total radioactivity. Urine and faeces sample weights were taken prior to storage. Urine and faeces samples were retained at -80°C for possible analysis of specific lipids by LC-MS/MS conducted and reported separately. The sample weights are presented in [Appendix 3](#).

6.10 Quantification of Radioactivity

6.10.1 Liquid Scintillation Counting

All samples prepared in scintillation fluid were subjected to liquid scintillation counting for 5 min, together with representative blank samples, using a Liquid Scintillation Analyser with automatic quench correction by an external standard method. Prior to analysis, samples were allowed to stabilise with regard to light and temperature. Self-normalisation and calibration (SNC) were conducted once a day. An unquenched tritium standard was used to initially calibrate the system to obtain optimal performance by adjusting the voltage on the photomultiplier tubes. Representative blank sample values were subtracted from sample count rates to give net disintegrations per minute (dpm) per sample. A limit of reliable measurement of 30 counts per minute (cpm) above background was instituted in these laboratories. Any results arising from data below the limit of reliable measurement were noted in the Results section of the report. Sample repeat analysis were in accordance with Standard Operating Procedures.

6.10.2 Data Presentation

Levels of radioactivity in all samples were quantified by LSC and the data captured into DEBRA® management software, Version 5.7 (LabLogic Ltd, UK). Plasma, blood and tissues concentrations of radioactivity in dpm/g and mass eq/g were calculated based on the measured specific activity (1.24 MBq/mg lipid) of radiolabelled test item in the dose formulation.

Individual and mean data were tabulated. The following information was reported:

- Radioactive content in tissues where a total organ weight is applicable was calculated as % administered (injected) dose
- Radioactive content in tissues, whole blood and plasma as µg equiv/g (or mL).
- Blood/plasma ratio

Data presented in results tables are computer generated in DEBRA and rounded appropriately for inclusion in the report. As a consequence, calculation of individual and mean values from data presented will, in some instances, yield slight differences from the results presented.

6.11 Protocol Deviations

Due to the unavailability of rats within specification at (b) (4) the rat supplier used in this study was Envigo, UK, deviating from Section 11 of the Protocol. In the opinion of the Study Director this had no impact on the study outcome since the correct age and strain of rats were used on this study.

In error, tibia/fibula bone were collected at necropsy for animals 043M, 045M, 046M, 048M, 051M, 052M, 055M, and 058M instead of femur bone, deviating from Section 14.1 of the Protocol. Once noticed, the femur bone was retrieved from the residual carcass stored in the -20°C freezer pending disposal and analysed after discussions with the Sponsor. The results appeared similar to the other animals in each timepoint and therefore this had no impact on the study outcome.

7 RESULTS

7.1 Clinical Observations

In the 100 µg mRNA male group, approximately 24 h following administration, animal 021M was noted to have decreased activity, ungroomed, brown staining on muzzle and irregular respiration. A decrease in bodyweight was noted in all remaining animals (approximately 16 g, equivalent to *ca.* 7% reduction of bodyweight) and food hoppers appeared untouched. By approximately 30 hours post-dose, animal 021M was also piloerect, hunched, and was hypersensitive to noise stimulus. Animal 021M was humanely killed and the diagnostic necropsy carried out showed one finding in the liver (prominent lobular architecture). Additionally, animals 019M and 020M were hunched and piloerect from approximately 30 h post-dose onwards.

In the 50 µg mRNA male group, following administration and for the duration of the study, no adverse effects were noted in any animal.

In the 50 µg mRNA female group, approximately 30 h following administration, animal 042F was noted to have decreased activity, and irregular respiration. At 48 h post dose animal 042F was additionally hunched and piloerect.

7.2 Body Weights

At the time of dosing, body weights were in the range of 217-270 g (males) and 179-224 g (females).

7.3 Tissue Distribution Following Intramuscular Administration

The mean (sex combined) concentration and recovery of total radioactivity in whole blood, plasma, injection site and tissues following a single intramuscular administration of [³H]-08-A01-C01 to Wistar Han rats at a target dose level of 50 µg mRNA/animal (1.29 mg/animal lipid) is presented in [Table 1](#). The mean concentration of total radioactivity in whole blood, plasma, injection site and tissues following a single intramuscular administration of [³H]-08-A01-C01 to male and female Wistar Han rats at a target dose level of 50 µg mRNA/animal (1.29 mg/animal lipid) is presented in [Table 2](#). The mean recovery in male and female individual tissues is presented in [Table 3](#).

Individual male and female concentration data is presented in [Appendix 4](#) and [Appendix 5](#), respectively. Individual male and female recovery data is presented in [Appendix 6](#) and [Appendix 7](#), respectively. The male 100 µg data is presented in [Appendix 8](#).

When analysing the injection site, there was often high inter-animal variability in concentration and % injected dose values at each time point. This may have been due to

difficulty in collecting the entirety of this sample since the total area that the injected bolus dose migrated to within the muscle was not visible. When dosing the male 50 µg mRNA group, the injection site was circled using a marker pen to help aid dissection of the injection area. The overall injection site concentrations and % dose values were higher in males than in females. Since concentrations in other tissues were broadly similar between the sexes, it is likely that the higher injection site values in males were a result of its more consistent identification and collection in males.

Following a single intramuscular administration of [³H]-08-A01-C01, the greatest mean tissue concentration and, in most instances, % of injected dose was found remaining in the injection site at each time point in both sexes. The injection site mean concentration and equivalent % dose values are presented in the table below.

Timepoint (h)	Injection site (µg equiv lipid/g)		Injection site (% dose)	
	Male	Female	Male	Female
0.25	219.940	36.566	32.887	6.815
1	587.670	199.950	68.829	36.411
2	529.210	93.144	39.053	24.094
4	619.850	56.227	47.710	9.056
8	299.590	125.930	18.731	24.993
24	267.170	122.540	31.957	26.295
48	268.770	61.088	32.823	16.426

The highest mean recovery of total radioactivity observed was 68.8% of the administered dose at 1-hour post-dose in males.

Low levels of radioactivity were detected in most tissues from the first time point (0.25 h), with the greatest level found circulating in plasma between 1-4 hours post-dose. The plasma and blood mean concentrations and blood:plasma ratios are presented in the table below.

Timepoint (h)	Blood (µg equiv lipid/g)		Plasma (µg equiv lipid/mL)		Blood:plasma ratio	
	Male	Female	Male	Female	Male	Female
0.25	3.003	0.936	6.035	1.894	0.48	1.15
1	2.809	5.928	5.379	10.884	0.49	0.54
2	4.028	6.773	8.714	9.091	0.46	0.64
4	3.400	2.698	8.755	4.251	0.42	0.60
8	2.000	0.628	3.573	1.147	0.56	0.55
24	1.274	0.544	2.621	0.945	0.49	0.57
48	0.535	0.305	1.085	0.524	0.50	0.58

Mean plasma concentrations peaked by 4 hours post-dose in males (8.755 µg equiv lipid/mL) and by 1 hour post-dose in females (10.884 µg equiv lipid/mL), before steadily decreasing. Concentrations were higher in plasma than in blood, with mean blood:plasma ratios generally

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ca. 0.5-0.6, indicating that the majority of the total radioactivity is associated with the plasma fraction.

Over 48 hours, [³H]-08-A01-C01 distributed from the injection site to most tissues, with the majority of tissues exhibiting low levels of radioactivity. The highest mean concentrations observed, and the equivalent % dose, are presented in the tables below.

Timepoint (h)	Values expressed as µg equiv lipid/g)						
	Liver		Spleen		Adrenal glands		Ovaries
	Male	Female	Male	Female	Male	Female	Female
0.25	1.151	0.323	0.354	0.313	0.302	0.240	0.104
1	4.006	5.244	2.140	2.801	0.580	2.388	1.339
2	9.574	12.370	5.255	10.213	1.206	4.232	1.638
4	18.525	14.569	8.945	11.646	2.569	3.206	2.341
8	27.916	25.172	24.434	19.747	6.387	7.218	3.088
24	23.360	15.119	22.819	17.341	19.948	7.595	5.240
48	18.164	30.411	19.550	27.155	21.476	14.942	12.261

=Mean includes results calculated from data less than 30 cpm above background

Timepoint (h)	Liver		Spleen		Adrenal glands		Ovaries
	Male	Female	Male	Female	Male	Female	Female
0.25	0.995	0.209	0.014	0.011	0.001	0.001	0.001
1	2.834	2.907	0.087	0.098	0.002	0.012	0.009
2	7.629	7.030	0.232	0.418	0.005	0.015	0.008
4	15.027	8.699	0.351	0.419	0.012	0.018	0.016
8	21.519	14.580	1.118	0.845	0.026	0.043	0.025
24	19.901	10.977	0.957	0.685	0.083	0.049	0.037
48	13.953	18.357	0.914	1.146	0.104	0.108	0.095

=Mean includes results calculated from data less than 30 cpm above background

Maximum concentrations (C_{max}) in liver and spleen were observed at 8 hours post-dose in males and 48 hours post dose in females, but were broadly similar and appeared to plateau at 8 hours post-dose when considering variability. The greatest mean concentration outside the injection site was observed in the liver, with values of 27.916 µg equiv lipid/g (equivalent to 21.5 % dose) in males and 30.411 µg equiv lipid/g (equivalent to 18.4 % dose) in females. In the spleen the highest concentrations were 24.434 µg equiv lipid/g in males and 27.155 µg equiv lipid/g (equivalent to 1.1% dose in both sexes).

In the adrenal glands and ovaries, the highest mean concentrations were observed at 48 hours post-dose. The highest mean concentrations in the adrenal glands were 21.476 and 14.942 µg equiv lipid/g in males and females, respectively (equivalent to 0.1% dose in both sexes). The highest mean ovaries concentration was 12.261 µg equiv lipid/g (equivalent to 0.1 % dose).

8 CONCLUSIONS

In conclusion, the distribution of [³H]-08-A01-C01 (monitoring the [³H]-CHE lipid label) in blood, plasma and selected tissues was determined in male and female Wistar Han rats over 48 hours after a single intramuscular injection at 50 µg mRNA/animal (1.29 mg/animal lipid dose). The concentrations of [³H]-08-A01-C01 were greatest in the injection site at all time points, with levels peaking in the plasma by 1-4 hours post-dose and distribution mainly into liver, adrenal glands, spleen and ovaries over 48 hours. Total recovery of radioactivity outside of the injection site was greatest in the liver, with much lower total recovery in spleen, and very little recovery in adrenals glands and ovaries. The mean plasma, blood and tissue concentrations and tissue distribution patterns were broadly similar between the sexes and [³H]-08-A01-C01 did not associate with red blood cells.

9 TABLES

Table 1 Mean (Sexes-Combined) Concentration and Recovery of Total Radioactivity in Whole Blood, Plasma and Tissues Following Single Intramuscular Administration of [³H]-08-A01-C01 to Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as total lipid concentration (µg lipid equiv/g (mL)) and % of administered dose

Sample	Total Lipid Concentration (µg lipid equiv/g (or mL))							% of Administered Dose						
	0.25 min	1 h	2 h	4 h	8 h	24 h	48 h	0.25 min	1 h	2 h	4 h	8 h	24 h	48 h
Adipose tissue	0.057	0.100	0.126	0.128	0.093	0.084	0.181	-	-	-	-	-	-	-
Adrenal glands	0.271	1.484	2.719	2.888	6.803	13.772	18.209	0.001	0.007	0.010	0.015	0.035	0.066	0.106
Bladder	0.041	0.130	0.146	0.167	0.148	0.247	0.365	0.000	0.001	0.001	0.001	0.001	0.002	0.002
Bone (femur)	0.091	0.195	0.266	0.276	0.340	0.342	0.687	-	-	-	-	-	-	-
Bone marrow (femur)	0.479	0.960	1.237	1.236	1.836	2.492	3.771	-	-	-	-	-	-	-
Brain	0.045	0.100	0.138	0.115	0.073	0.069	0.068	0.007	0.013	0.020	0.016	0.011	0.010	0.009
Eyes	0.010	0.035	0.052	0.067	0.059	0.091	0.112	0.000	0.001	0.001	0.002	0.002	0.002	0.003
Heart	0.282	1.029	1.402	0.987	0.790	0.451	0.546	0.018	0.056	0.084	0.060	0.042	0.027	0.030
Injection site	128.253	393.810	311.177	338.039	212.760	194.855	164.929	19.851	52.620	31.574	28.383	21.862	29.126	24.625
Kidneys	0.391	1.161	2.046	0.924	0.590	0.426	0.425	0.050	0.124	0.211	0.109	0.075	0.054	0.057
Large intestine	0.013	0.048	0.093	0.287	0.649	1.104	1.338	0.008	0.025	0.065	0.192	0.405	0.692	0.762
Liver	0.737	4.625	10.972	16.547	26.544	19.240	24.288	0.602	2.871	7.330	11.863	18.050	15.439	16.155
Lung	0.492	1.210	1.834	1.497	1.151	1.039	1.093	0.052	0.101	0.178	0.169	0.122	0.101	0.101
Lymph node (man)	0.064	0.189	0.290	0.408	0.534	0.554	0.727	-	-	-	-	-	-	-
Lymph node (mes)	0.050	0.146	0.530	0.489	0.689	0.985	1.366	-	-	-	-	-	-	-
Muscle	0.021	0.061	0.084	0.103	0.096	0.095	0.192	-	-	-	-	-	-	-
Ovaries (females)	0.104	1.339	1.638	2.341	3.088	5.240	12.261	0.001	0.009	0.008	0.016	0.025	0.037	0.095
Pancreas	0.081	0.207	0.414	0.380	0.294	0.358	0.599	0.003	0.007	0.014	0.015	0.015	0.011	0.019
Pituitary gland	0.339	0.645	0.868	0.854	0.405	0.478	0.694	0.000	0.001	0.001	0.001	0.000	0.000	0.001
Prostate (males)	0.061	0.091	0.128	0.157	0.150	0.183	0.170	0.001	0.001	0.002	0.003	0.003	0.004	0.003
Salivary glands	0.084	0.193	0.255	0.220	0.135	0.170	0.264	0.003	0.007	0.008	0.008	0.005	0.006	0.009
Skin	0.013	0.208	0.159	0.145	0.119	0.157	0.253	-	-	-	-	-	-	-

- =Partial tissue taken therefore not applicable

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Table 1 Mean (Sexes-Combined) Concentration of Total Radioactivity in Whole Blood, Plasma and
 (Continued) Tissues Following Single Intramuscular Administration of [³H]-08-A01-C01 to Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as total lipid concentration (µg lipid equiv/g (mL)) and % of administered dose

Sample	Total Lipid Concentration (µg lipid equiv/g (or mL))							% of Administered Dose						
	0.25 min	1 h	2 h	4 h	8 h	24 h	48 h	0.25 min	1 h	2 h	4 h	8 h	24 h	48 h
Small intestine	0.030	0.221	0.476	0.879	1.279	1.302	1.472	0.024	0.130	0.319	0.543	0.776	0.906	0.835
Spinal cord	0.043	0.097	0.169	0.250	0.106	0.085	0.112	0.001	0.002	0.002	0.003	0.001	0.001	0.001
Spleen	0.334	2.471	7.734	10.296	22.091	20.080	23.353	0.013	0.093	0.325	0.385	0.982	0.821	1.030
Stomach	0.017	0.065	0.115	0.144	0.268	0.152	0.215	0.006	0.019	0.034	0.030	0.040	0.037	0.039
Testes (males)	0.031	0.042	0.079	0.129	0.146	0.304	0.320	0.007	0.010	0.017	0.030	0.034	0.074	0.074
Thymus	0.088	0.243	0.340	0.335	0.196	0.207	0.331	0.004	0.007	0.010	0.012	0.008	0.007	0.008
Thyroid	0.155	0.536	0.842	0.851	0.544	0.578	1.000	0.000	0.001	0.001	0.001	0.001	0.001	0.001
Uterus (females)	0.043	0.203	0.305	0.140	0.287	0.289	0.456	0.002	0.011	0.015	0.008	0.016	0.018	0.022
Whole blood	1.970	4.369	5.401	3.049	1.314	0.909	0.420	-	-	-	-	-	-	-
Plasma	3.965	8.132	8.903	6.503	2.360	1.783	0.805	-	-	-	-	-	-	-
Blood:plasma ratio	0.815	0.515	0.550	0.510	0.555	0.530	0.540	-	-	-	-	-	-	-

- =Partial tissue taken therefore not applicable/not applicable

Table 2 Mean Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues Following Single Intramuscular Administration of [³H]-08-A01-C01 to Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	0.25 min		1 h		2 h		4 h		8 h		24 h		48 h	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Adipose tissue	0.040	°0.073	0.050	0.149	0.070	0.182	0.093	0.163	0.116	0.069	0.126	0.042	0.129	0.232
Adrenal glands	0.302	°0.240	0.580	2.388	1.206	4.232	2.569	3.206	6.387	7.218	19.948	7.595	21.476	14.942
Bladder	0.049	°0.033	0.095	0.165	0.137	0.155	0.227	0.106	0.211	0.085	0.323	0.171	0.340	0.389
Bone (femur)	0.126	0.056	0.148	0.241	0.235	0.296	0.335	0.217	0.502	0.177	0.504	0.180	0.520	0.854
Bone marrow (femur)	0.761	°0.196	0.910	1.010	1.136	1.337	1.557	0.915	2.397	1.274	3.579	1.405	3.690	3.851
Brain	0.073	°0.016	0.083	0.117	0.143	0.133	0.155	0.075	0.101	0.045	0.090	0.047	0.083	0.052
Eyes	0.014	°0.006	0.027	0.043	0.046	0.058	0.095	0.038	0.088	0.030	0.129	0.052	0.127	0.097
Heart	0.419	°0.144	0.631	1.426	1.122	1.682	1.049	0.925	1.189	0.391	0.583	0.318	0.672	0.420
Injection site	219.940	36.566	587.670	199.950	529.210	93.144	619.850	56.227	299.590	125.930	267.170	122.540	268.770	61.088
Kidneys	0.511	0.271	0.630	1.692	1.124	2.967	1.033	0.814	0.837	0.342	0.504	0.348	0.482	0.368
Large intestine	0.017	°0.008	0.031	0.065	0.080	0.106	0.350	0.224	0.690	0.608	1.741	0.466	1.426	1.249
Liver	1.151	0.323	4.006	5.244	9.574	12.370	18.525	14.569	27.916	25.172	23.360	15.119	18.164	30.411
Lung	0.737	0.247	0.845	1.574	1.594	2.074	1.772	1.222	1.674	0.628	1.316	0.762	1.288	0.898
Lymph node (man)	0.090	°0.038	0.154	0.223	0.217	0.362	0.424	0.391	0.695	0.372	0.744	0.363	0.820	0.633
Lymph node (mes)	0.052	°0.048	0.095	0.196	0.229	0.831	0.441	0.536	0.649	0.729	1.106	0.863	1.057	1.675
Muscle	°0.029	0.012	0.039	0.082	0.067	0.100	0.075	0.130	0.101	0.091	0.098	0.092	0.280	0.104
Ovaries (females)	-	°0.104	-	1.339	-	1.638	-	2.341	-	3.088	-	5.240	-	12.261
Pancreas	0.125	0.037	0.153	0.261	0.423	0.404	0.361	0.398	0.349	0.239	0.396	0.320	0.587	0.611
Pituitary gland	0.537	°0.141	0.446	0.844	0.781	0.955	1.249	0.458	0.669	0.141	0.656	0.300	0.543	0.845
Prostate (males)	0.061	-	0.091	-	0.128	-	0.157	-	0.150	-	0.183	-	0.170	-
Salivary glands	0.114	°0.054	0.148	0.237	0.214	0.295	0.270	0.169	0.176	0.094	0.243	0.096	0.297	0.231
Skin	°0.016	0.010	0.028	0.387	0.054	0.263	0.085	0.204	0.122	0.116	0.195	0.118	0.209	0.297

°=Mean includes results calculated from data less than 30 cpm above background

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Table 2 Mean Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues Following Single (Continued) Intramuscular Administration of [³H]-08-A01-C01 to Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	0.25 min		1 h		2 h		4 h		8 h		24 h		48 h	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Small intestine	0.038	°0.021	0.194	0.247	0.471	0.481	0.919	0.838	1.525	1.033	1.878	0.726	1.630	1.314
Spinal cord	0.061	°0.024	0.072	0.122	0.166	0.172	0.375	0.124	0.168	0.044	0.121	0.048	0.162	0.062
Spleen	0.354	°0.313	2.140	2.801	5.255	10.213	8.945	11.646	24.434	19.747	22.819	17.341	19.550	27.155
Stomach	0.018	°0.015	0.039	0.091	0.104	0.126	0.186	0.101	0.410	0.126	0.222	0.081	0.235	0.195
Testes (males)	0.031	-	0.042	-	0.079	-	0.129	-	0.146	-	0.304	-	0.320	-
Thymus	0.106	°0.069	0.187	0.298	0.220	0.459	0.461	0.209	0.292	0.100	0.255	0.159	0.296	0.366
Thyroid	0.217	°0.093	0.391	0.680	0.575	1.109	1.097	0.604	0.781	0.307	0.820	0.335	1.344	0.655
Uterus (females)	-	°0.043	-	0.203	-	0.305	-	0.140	-	0.287	-	0.289	-	0.456
Whole Blood	3.003	0.936	2.809	5.928	4.028	6.773	3.400	2.698	2.000	0.628	1.274	0.544	0.535	0.305
Plasma	6.035	1.894	5.379	10.884	8.714	9.091	8.755	4.251	3.573	1.147	2.621	0.945	1.085	0.524
Blood:plasma ratio	0.48	1.15	0.49	0.54	0.46	0.64	0.42	0.60	0.56	0.55	0.49	0.57	0.50	0.58

°=Mean includes results calculated from data less than 30 cpm above background

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Table 3 Mean Recovery of Total Radioactivity in Tissues Following Single Intramuscular Administration of [³H]-08-A01-C01 to Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	0.25 min		1 h		2 h		4 h		8 h		24 h		48 h	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Adrenal glands	0.001	°0.001	0.002	0.012	0.005	0.015	0.012	0.018	0.026	0.043	0.083	0.049	0.104	0.108
Bladder	0.000	°0.000	0.001	0.001	0.001	0.001	0.001	0.001	0.002	0.000	0.002	0.001	0.002	0.002
Brain	0.011	°0.002	0.010	0.016	0.021	0.019	0.021	0.011	0.014	0.007	0.012	0.007	0.011	0.007
Eyes	0.000	°0.000	0.000	0.001	0.001	0.001	0.002	0.001	0.002	0.001	0.002	0.001	0.003	0.002
Heart	0.028	°0.008	0.032	0.079	0.065	0.102	0.067	0.052	0.061	0.022	0.035	0.018	0.039	0.020
Injection site	32.887	6.815	68.829	36.411	39.053	24.094	47.710	9.056	18.731	24.993	31.957	26.295	32.823	16.426
Kidneys	0.069	0.030	0.077	0.171	0.149	0.272	0.136	0.082	0.109	0.040	0.068	0.039	0.071	0.042
Large intestine	0.011	°0.004	0.018	0.032	0.054	0.075	0.236	0.148	0.463	0.346	1.091	0.293	0.810	0.714
Liver	0.995	0.209	2.834	2.907	7.629	7.030	15.027	8.699	21.519	14.580	19.901	10.977	13.953	18.357
Lung	0.082	0.022	0.085	0.117	0.189	0.167	0.226	0.112	0.180	0.064	0.136	0.065	0.131	0.070
Ovaries (females)	-	°0.001	-	0.009	-	0.008	-	0.016	-	0.025	-	0.037	-	0.095
Pancreas	0.005	0.001	0.006	0.008	0.015	0.012	0.013	0.017	0.014	0.016	0.013	0.009	0.015	0.023
Pituitary gland	0.000	°0.000	0.000	0.001	0.000	0.001	0.001	0.000	0.000	0.000	0.000	0.000	0.000	0.001
Prostate (males)	0.001	-	0.001	-	0.002	-	0.003	-	0.003	-	0.004	-	0.003	-
Salivary glands	0.004	°0.002	0.005	0.008	0.007	0.009	0.009	0.006	0.007	0.003	0.008	0.003	0.010	0.007
Small intestine	0.032	°0.015	0.124	0.135	0.353	0.285	0.623	0.462	0.972	0.580	1.275	0.536	0.971	0.698
Spinal cord	0.001	°0.000	0.001	0.002	0.001	0.002	0.003	0.002	0.001	0.001	0.001	0.001	0.001	0.001
Spleen	0.014	°0.011	0.087	0.098	0.232	0.418	0.351	0.419	1.118	0.845	0.957	0.685	0.914	1.146
Stomach	0.008	°0.003	0.016	0.022	0.033	0.035	0.037	0.022	0.055	0.024	0.054	0.020	0.049	0.029
Testes (males)	0.007	-	0.010	-	0.017	-	0.030	-	0.034	-	0.074	-	0.074	-
Thymus	0.005	°0.002	0.006	0.008	0.008	0.012	0.018	0.006	0.012	0.003	0.009	0.004	0.008	0.007
Thyroid	0.000	°0.000	0.000	0.001	0.001	0.001	0.001	0.001	0.001	0.000	0.001	0.000	0.001	0.001
Uterus (females)	-	°0.002	-	0.011	-	0.015	-	0.008	-	0.016	-	0.018	-	0.022

°=Mean includes results calculated from data less than 30 cpm above background

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10 APPENDICES**Appendix 1 Certificates of Analysis for [³H]-08-A01-C01 and [³H]-CHE**

Confidential

**R&D Formulation Characterization Report**

Batch ID	LNP ID	Specific Activity	[Lipid]	Encaps	Encapsulated mRNA	Yield	mRNA/Lipid Ratio	Particle Diameter	Poly-dispersity
		dpm/uL	mg/mL	%	mg/mL	mg	mg/mg	nm	
NC-0552-1	08-A01-C01	1,900,000	25.7	94	1.0	6.05	0.039	89	0.062

Notes

Formulated July 6, 2020 for NC-0552 using BioNTech mRNA (AnSo luc 1041 CorVac) and trace labeled with 3H-CHE. Endotoxin below detection limit (<0.5 EU/mL). Sterile filtered using 0.2 µm pore-size filters.

Stored at -70°C. Thaw at room temperature and dilute on the day of use.

(b) (6)

(b) (6)

08-July-20

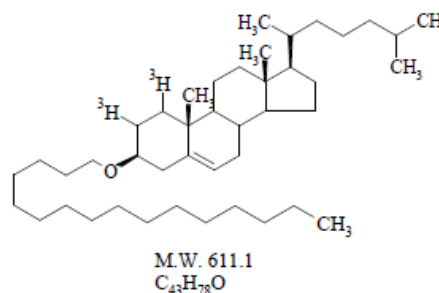
Date

Appendix 1 Certificates of Analysis for [³H]-08-A01-C01 and [³H]-CHE (continued)

TECHNICAL DATA SHEET	³H
Research Use Only. Not for use in diagnostic procedures	
CHOLESTERYL HEXADECYL ETHER, [CHOLESTERYL-1,2-³H(N)]-	
Product Number: NET859	

LOT SPECIFIC INFORMATION

Lot Number:	2656317
Specific Activity:	51.9 Ci/mmol
	1920 GBq/mmol
Production Date:	16-Dec-2019



PACKAGING: 1.0 mCi/ml (37 MBq/ml) in toluene, under argon in an ampoule. Shipped on dry ice.

STABILITY AND STORAGE RECOMMENDATIONS: When cholesteryl hexadecyl ether, [cholesteryl-1,2-³H(N)]- is stored at -20°C in its original solvent and at its original concentration, the rate of decomposition is initially 2% for 6 months from date of purification. Stability is nonlinear and not correlated to isotope half-life. Lot to lot variation may occur.

SPECIFIC ACTIVITY RANGE: 40-60 Ci/mmol (1480-2220 GBq/mmol)

RADIOCHEMICAL PURITY: This product was initially found to be greater than 97% when determined by the following methods. The rate of decomposition can accelerate. It is advisable to check purity prior to use:

High pressure liquid chromatography on a Zorbax C-8 column using the following mobile phase:
acetonitrile : isopropanol, (35:65).

Thin layer chromatography on silica gel using the following solvent system:
toluene : hexane, (1:9).

QUALITY CONTROL: The radiochemical purity of cholesteryl hexadecyl ether, [cholesteryl-1,2-³H(N)]- is checked at appropriate intervals using the first listed chromatography method.

The precursor used in the synthesis of NET-859 is synthetic.

HAZARD INFORMATION: WARNING: This product contains a chemical known to the state of California to cause cancer.

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NET859-REV-02



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Appendix 2 Individual Animal Dosing Summary

Males

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Animal ID	Body weight (g)	Dose Received		
		mg mRNA	mg lipid	MBq
043M	270	0.0514	1.32	1.63
044M	264	0.0518	1.33	1.65
045M	244	0.0521	1.34	1.66
046M	263	0.0525	1.35	1.68
047M	232	0.0514	1.32	1.64
048M	228	0.0525	1.35	1.67
049M	259	0.0514	1.32	1.64
050M	249	0.0518	1.33	1.66
051M	257	0.0533	1.37	1.70
052M	258	0.0521	1.34	1.66
053M	249	0.0529	1.36	1.69
054M	235	0.0525	1.35	1.68
055M	247	0.0502	1.29	1.60
056M	256	0.0514	1.32	1.64
057M	266	0.0521	1.34	1.66
058M	263	0.0521	1.34	1.66
059M	243	0.0525	1.35	1.67
060M	248	0.0518	1.33	1.65
061M	240	0.0521	1.34	1.66
062M	259	0.0521	1.34	1.66
063M	238	0.0521	1.34	1.66

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**Appendix 2 Individual Animal Dosing Summary
 (continued)**

Females

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Animal ID	Body weight (g)	Dose Received		
		mg mRNA	mg lipid	MBq
022F	215	0.0521	1.34	1.66
023F	206	0.0529	1.36	1.68
024F	206	0.0514	1.32	1.64
025F	212	0.0533	1.37	1.70
026F	213	0.0525	1.35	1.68
027F	207	0.0529	1.36	1.69
028F	198	0.0529	1.36	1.68
029F	208	0.0529	1.36	1.69
030F	214	0.0518	1.33	1.64
031F	204	0.0537	1.38	1.71
032F	207	0.0533	1.37	1.70
033F	209	0.0521	1.34	1.66
034F	224	0.0510	1.31	1.62
035F	179	0.0482	1.24	1.53
036F	211	0.0467	1.20	1.49
037F	205	0.0506	1.30	1.61
038F	225	0.0502	1.29	1.60
039F	213	0.0525	1.35	1.67
040F	199	0.0533	1.37	1.69
041F	218	0.0529	1.36	1.69
042F	193	0.0533	1.37	1.70

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**Appendix 2 Individual Animal Dosing Summary
 (continued)**

Males

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Animal ID	Body weight (g)	Dose Received		
		mg mRNA	mg lipid	MBq
001M	240	0.104	2.66	3.30
002M	243	0.106	2.73	3.38
003M	277	0.107	2.74	3.40
004M	247	0.106	2.72	3.37
005M	243	0.107	2.76	3.42
006M	237	0.107	2.74	3.39
007M	245	0.107	2.75	3.41
008M	237	0.106	2.73	3.39
009M	248	0.106	2.73	3.39
010M	227	0.101	2.60	3.22
011M	267	0.105	2.71	3.36
012M	237	0.106	2.72	3.37
013M	241	0.105	2.69	3.34
014M	264	0.107	2.76	3.42
015M	264	0.105	2.71	3.36
043M	241	0.106	2.73	3.39
017M	252	0.106	2.73	3.39
018M	263	0.105	2.70	3.35
019M	248	0.106	2.72	3.37
020M	246	0.106	2.73	3.39
021M	217	0.107	2.75	3.41

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Appendix 3 Urine and Faeces Sample Weights

Males

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed in g

Sample	Timepoint	061M	062M	063M
Urine	Pre-dose	6.860	18.617	14.228
	6 h	6.139	8.101	8.153
	24 h	21.208	29.766	40.276
	48 h	28.317	28.566	36.902
Faeces	Pre-dose	11.324	7.893	6.070
	24 h	4.716	14.327	8.659
	48 h	6.968	8.398	7.007

Appendix 3 Urine and Faeces Sample Weights
(continued)

Females

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed in g

Sample	Timepoint	040F	041F	042F
Urine	Pre-dose	3.963	9.453	7.513
	6 h	4.844	5.664	9.719
	24 h	20.736	29.176	21.294
	48 h	30.371	33.928	23.141
Faeces	Pre-dose	6.110	2.679	6.010
	24 h	8.887	9.193	5.619
	48 h	4.565	6.139	4.834

Appendix 3 Urine and Faeces Sample Weights
(continued)

Males

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed in g

Sample	Timepoint	019M	020M	021M
Urine	Pre-dose	7.519	4.094	13.159
	6 h	8.883	8.835	10.517
	24 h	29.916	22.983	12.664
	48 h	37.860	35.653	*6.931
Faeces	Pre-dose	9.491	9.292	4.882
	24 h	11.197	14.005	8.769
	48 h	6.950	8.229	*2.449

Note that for animal 021M the collection period was approximately 24-31 h.

Appendix 4 Individual Male Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 0.25 min Following Single Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	043M	044M	045M	Mean	SD
Adipose tissue	0.056	0.045	0.019	0.040	0.019
Adrenal glands	0.380	0.480	0.046	0.302	0.227
Bladder	0.096	0.045	0.007	0.049	0.045
Bone (femur)	0.172	0.085	0.119	0.126	0.044
Bone marrow (femur)	0.775	0.326	1.182	0.761	0.428
Brain	0.093	0.092	0.033	0.073	0.034
Eyes	0.025	0.013	0.005	0.014	0.010
Heart	0.710	0.474	0.074	0.419	0.322
Injection site	436.090	159.310	64.429	219.940	193.100
Kidneys	0.808	0.600	0.123	0.511	0.351
Large intestine	0.020	0.027	0.003	0.017	0.012
Liver	2.035	1.226	0.193	1.151	0.923
Lung	1.050	0.826	0.334	0.737	0.366
Lymph node (Man)	0.152	0.069	0.049	0.090	0.055
Lymph node (Mes)	0.087	0.054	0.016	0.052	0.036
Muscle	0.049	0.035	*0.003	°0.029	°0.024
Pancreas	0.156	0.201	0.019	0.125	0.095
Pituitary gland	0.962	0.535	0.115	0.537	0.424
Prostate	0.098	0.074	0.012	0.061	0.044
Salivary glands	0.169	0.145	0.028	0.114	0.076
Skin	0.030	0.015	*0.002	°0.016	°0.014
Small intestine	0.064	0.043	0.008	0.038	0.028
Spinal cord	0.108	0.063	0.013	0.061	0.047
Spleen	0.519	0.450	0.094	0.354	0.228
Stomach	0.022	0.027	0.005	0.018	0.012
Testes	0.053	0.036	0.006	0.031	0.024
Thymus	0.119	0.169	0.030	0.106	0.071
Thyroid	0.292	0.307	0.053	0.217	0.142
Whole Blood	5.631	2.526	0.852	3.003	2.425
Plasma	9.854	6.519	1.732	6.035	4.083
Blood:plasma ratio	0.57	0.39	0.49	0.48	0.09

*=Results calculated from data less than 30 cpm above background

°=Mean includes results calculated from data less than 30 cpm above background

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**Appendix 4 Individual Male Concentration Data
 (continued)**

**Concentration of Total Radioactivity in Whole Blood, Plasma and
 Tissues 1 hour Following Single Intramuscular Administration of
 [³H]-08-A01-C01 to Male Wistar Han Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	046M	047M	048M	Mean	SD
Adipose tissue	0.037	0.073	0.040	0.050	0.020
Adrenal glands	0.293	0.647	0.800	0.580	0.260
Bladder	0.111	0.087	0.088	0.095	0.013
Bone (femur)	0.115	0.085	0.246	0.148	0.085
Bone marrow (femur)	0.561	1.150	1.021	0.910	0.310
Brain	0.033	0.108	0.107	0.083	0.043
Eyes	0.014	0.019	0.049	0.027	0.019
Heart	0.266	0.780	0.847	0.631	0.318
Injection site	503.490	593.230	666.280	587.670	81.536
Kidneys	0.322	0.710	0.857	0.630	0.276
Large intestine	0.026	0.032	0.037	0.031	0.005
Liver	2.667	3.571	5.780	4.006	1.602
Lung	0.428	1.203	0.903	0.845	0.391
Lymph node (Man)	0.151	0.166	0.145	0.154	0.011
Lymph node (Mes)	0.076	0.100	0.109	0.095	0.017
Muscle	0.030	0.036	0.050	0.039	0.010
Pancreas	0.076	0.189	0.193	0.153	0.067
Pituitary gland	0.202	0.502	0.634	0.446	0.221
Prostate	0.063	0.105	0.105	0.091	0.024
Salivary glands	0.084	0.151	0.208	0.148	0.062
Skin	0.020	0.027	0.039	0.028	0.010
Small intestine	0.144	0.214	0.223	0.194	0.043
Spinal cord	0.062	0.070	0.084	0.072	0.011
Spleen	3.314	1.388	1.720	2.140	1.029
Stomach	0.024	0.043	0.049	0.039	0.013
Testes	0.026	0.041	0.057	0.042	0.015
Thymus	0.201	0.133	0.226	0.187	0.048
Thyroid	0.126	0.599	0.448	0.391	0.241
Whole Blood	0.873	4.534	3.018	2.809	1.840
Plasma	2.937	6.047	7.153	5.379	2.186
Blood:plasma ratio	0.30	0.75	0.42	0.49	0.23

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Appendix 4 Individual Male Concentration Data
 (continued)

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 2 hours Following Single Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	049M	050M	051M	Mean	SD
Adipose tissue	0.084	0.034	0.090	0.070	0.031
Adrenal glands	1.809	0.584	1.226	1.206	0.613
Bladder	0.152	0.080	0.179	0.137	0.051
Bone (femur)	0.250	0.180	0.273	0.235	0.048
Bone marrow (femur)	1.526	0.559	1.323	1.136	0.510
Brain	0.220	0.088	0.121	0.143	0.069
Eyes	0.036	0.023	0.077	0.046	0.028
Heart	1.782	0.682	0.901	1.122	0.582
Injection site	445.930	1052.800	88.843	529.210	487.370
Kidneys	1.467	0.785	1.120	1.124	0.341
Large intestine	0.074	0.056	0.109	0.080	0.027
Liver	12.023	5.816	10.885	9.574	3.304
Lung	2.397	0.968	1.419	1.594	0.730
Lymph node (Man)	0.328	0.112	0.210	0.217	0.108
Lymph node (Mes)	0.312	0.180	0.194	0.229	0.073
Muscle	0.083	0.060	0.057	0.067	0.014
Pancreas	0.296	0.179	0.792	0.423	0.325
Pituitary gland	1.175	0.405	0.764	0.781	0.385
Prostate	0.150	0.095	0.139	0.128	0.029
Salivary glands	0.279	0.113	0.251	0.214	0.089
Skin	0.083	0.032	0.048	0.054	0.026
Small intestine	0.455	0.458	0.500	0.471	0.025
Spinal cord	0.184	0.150	0.163	0.166	0.017
Spleen	6.771	2.590	6.403	5.255	2.315
Stomach	0.121	0.059	0.133	0.104	0.040
Testes	0.120	0.039	0.077	0.079	0.040
Thymus	0.248	0.146	0.265	0.220	0.065
Thyroid	0.749	0.361	0.615	0.575	0.197
Whole Blood	4.913	2.788	4.384	4.028	1.106
Plasma	10.623	6.177	9.341	8.714	2.288
Blood:plasma ratio	0.46	0.45	0.47	0.46	0.01

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Appendix 4 Individual Male Concentration Data
 (continued)

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 4 hours Following Single Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	052M	053M	054M	Mean	SD
Adipose tissue	0.062	0.092	0.124	0.093	0.031
Adrenal glands	2.252	1.999	3.456	2.569	0.779
Bladder	0.207	0.239	0.234	0.227	0.017
Bone (femur)	0.264	0.234	0.506	0.335	0.149
Bone marrow (femur)	1.318	1.364	1.987	1.557	0.374
Brain	0.136	0.112	0.217	0.155	0.055
Eyes	0.084	0.133	0.067	0.095	0.034
Heart	0.993	0.669	1.484	1.049	0.411
Injection site	445.970	1001.000	412.620	619.850	330.480
Kidneys	0.967	0.737	1.395	1.033	0.334
Large intestine	0.413	0.311	0.327	0.350	0.055
Liver	14.739	16.391	24.445	18.525	5.193
Lung	2.047	1.003	2.265	1.772	0.675
Lymph node (Man)	0.283	0.564	0.426	0.424	0.140
Lymph node (Mes)	0.287	0.258	0.780	0.441	0.293
Muscle	0.064	0.057	0.104	0.075	0.025
Pancreas	0.277	0.413	0.393	0.361	0.073
Pituitary gland	0.933	2.418	0.397	1.249	1.047
Prostate	0.161	0.121	0.190	0.157	0.035
Salivary glands	0.232	0.197	0.380	0.270	0.097
Skin	0.073	0.052	0.131	0.085	0.041
Small intestine	0.822	0.698	1.235	0.919	0.281
Spinal cord	0.193	0.745	0.188	0.375	0.320
Spleen	6.146	11.159	9.529	8.945	2.557
Stomach	0.324	0.058	0.176	0.186	0.134
Testes	0.105	0.098	0.185	0.129	0.049
Thymus	0.210	0.371	0.800	0.461	0.305
Thyroid	1.055	1.301	0.936	1.097	0.186
Whole Blood	3.547	2.519	4.133	3.400	0.817
Plasma	8.820	4.802	12.644	8.755	3.922
Blood:plasma ratio	0.40	0.52	0.33	0.42	0.10

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Appendix 4 Individual Male Concentration Data
 (continued)

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 8 hours Following Single Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	055M	056M	057M	Mean	SD
Adipose tissue	0.076	0.163	0.109	0.116	0.044
Adrenal glands	4.440	4.886	9.835	6.387	2.995
Bladder	N.S.	0.198	0.224	0.211	N.A.
Bone (femur)	0.510	0.355	0.639	0.502	0.142
Bone marrow (femur)	3.050	1.943	2.199	2.397	0.579
Brain	0.105	0.096	0.103	0.101	0.005
Eyes	N.S.	0.071	0.104	0.088	N.A.
Heart	1.418	1.008	1.142	1.189	0.209
Injection site	181.620	497.270	219.870	299.590	172.260
Kidneys	0.934	0.795	0.783	0.837	0.084
Large intestine	0.735	0.665	0.672	0.690	0.039
Liver	23.158	22.178	38.412	27.916	9.103
Lung	1.679	1.643	1.701	1.674	0.029
Lymph node (Man)	0.432	1.053	0.601	0.695	0.321
Lymph node (Mes)	0.444	0.609	0.892	0.649	0.226
Muscle	0.082	0.096	0.127	0.101	0.023
Pancreas	0.352	0.418	0.276	0.349	0.071
Pituitary gland	0.635	0.477	0.894	0.669	0.211
Prostate	0.184	0.127	0.139	0.150	0.030
Salivary glands	0.170	0.157	0.202	0.176	0.023
Skin	0.138	0.111	0.117	0.122	0.014
Small intestine	1.423	1.518	1.634	1.525	0.106
Spinal cord	0.146	0.119	0.239	0.168	0.063
Spleen	21.122	24.073	28.107	24.434	3.507
Stomach	0.345	0.107	0.777	0.410	0.340
Testes	0.153	0.107	0.179	0.146	0.037
Thymus	0.317	0.278	0.282	0.292	0.021
Thyroid	0.940	0.611	0.792	0.781	0.165
Whole Blood	2.215	1.968	1.817	2.000	0.201
Plasma	3.978	3.465	3.275	3.573	0.364
Blood:plasma ratio	0.56	0.57	0.55	0.56	0.01

N.S. = No sample due to oxidiser failure

N.A. = Not applicable

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Appendix 4 Individual Male Concentration Data
 (continued)

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 24 hours Following Single Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	058M	059M	060M	Mean	SD
Adipose tissue	0.079	0.116	0.182	0.126	0.053
Adrenal glands	10.795	21.060	27.988	19.948	8.650
Bladder	0.211	0.394	0.365	0.323	0.099
Bone (femur)	0.456	0.408	0.649	0.504	0.127
Bone marrow (femur)	2.286	3.625	4.824	3.579	1.270
Brain	0.049	0.099	0.124	0.090	0.038
Eyes	0.098	0.113	0.178	0.129	0.042
Heart	0.640	0.590	0.520	0.583	0.060
Injection site	178.010	330.550	292.960	267.170	79.471
Kidneys	0.522	0.407	0.584	0.504	0.090
Large intestine	0.592	1.611	3.019	1.741	1.219
Liver	17.750	21.966	30.365	23.360	6.422
Lung	0.942	1.334	1.672	1.316	0.365
Lymph node (Man)	0.577	0.689	0.965	0.744	0.200
Lymph node (Mes)	0.905	1.040	1.373	1.106	0.241
Muscle	0.092	0.068	0.133	0.098	0.033
Pancreas	0.294	0.382	0.513	0.396	0.110
Pituitary gland	0.489	0.768	0.711	0.656	0.147
Prostate	0.150	0.183	0.215	0.183	0.032
Salivary glands	0.168	0.243	0.317	0.243	0.075
Skin	0.134	0.166	0.287	0.195	0.081
Small intestine	0.971	1.994	2.670	1.878	0.855
Spinal cord	0.091	0.144	0.127	0.121	0.027
Spleen	19.140	15.796	33.523	22.819	9.419
Stomach	0.110	0.168	0.386	0.222	0.145
Testes	0.234	0.286	0.392	0.304	0.080
Thymus	0.163	0.235	0.368	0.255	0.104
Thyroid	0.721	0.660	1.081	0.820	0.228
Whole Blood	1.473	1.237	1.112	1.274	0.183
Plasma	2.584	2.935	2.345	2.621	0.297
Blood:plasma ratio	0.57	0.42	0.47	0.49	0.08

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Appendix 4 Individual Male Concentration Data
 (continued)

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 48 hours Following Single Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	061M	062M	063M	Mean	SD
Adipose tissue	0.104	0.162	0.121	0.129	0.030
Adrenal glands	13.913	35.091	15.424	21.476	11.815
Bladder	0.274	0.447	0.298	0.340	0.094
Bone (femur)	0.344	0.577	0.639	0.520	0.155
Bone marrow (femur)	2.566	5.049	3.455	3.690	1.258
Brain	0.051	0.112	0.087	0.083	0.031
Eyes	0.100	0.121	0.160	0.127	0.031
Heart	0.418	0.955	0.642	0.672	0.270
Injection site	292.370	196.910	317.030	268.770	63.446
Kidneys	0.309	0.673	0.463	0.482	0.182
Large intestine	0.998	1.235	2.045	1.426	0.549
Liver	17.734	20.580	16.177	18.164	2.233
Lung	0.809	1.885	1.170	1.288	0.548
Lymph node (Man)	0.728	1.078	0.656	0.820	0.226
Lymph node (Mes)	0.924	1.620	0.626	1.057	0.510
Muscle	0.078	0.115	0.647	0.280	0.318
Pancreas	0.291	0.506	0.964	0.587	0.344
Pituitary gland	0.431	0.610	0.588	0.543	0.098
Prostate	0.110	0.265	0.135	0.170	0.083
Salivary glands	0.286	0.370	0.234	0.297	0.069
Skin	0.177	0.267	0.183	0.209	0.051
Small intestine	1.178	2.030	1.681	1.630	0.428
Spinal cord	0.089	0.129	0.267	0.162	0.093
Spleen	12.073	25.689	20.887	19.550	6.906
Stomach	0.122	0.315	0.268	0.235	0.101
Testes	0.214	0.471	0.275	0.320	0.134
Thymus	0.226	0.362	0.299	0.296	0.068
Thyroid	0.830	1.797	1.406	1.344	0.486
Whole Blood	0.594	0.473	0.536	0.535	0.060
Plasma	1.021	1.003	1.230	1.085	0.126
Blood:plasma ratio	0.58	0.47	0.44	0.50	0.08

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Appendix 5 Individual Female Concentration Data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 0.25 min Following Single Intramuscular Administration of [³H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	022F	023F ^A	024F	Mean	SD
Adipose tissue	0.203	*0.002	0.015	°0.073	°0.113
Adrenal glands	0.578	*0.000	0.143	°0.240	°0.301
Bladder	0.050	*0.000	0.048	°0.033	°0.029
Bone (femur)	0.146	0.003	0.019	0.056	0.079
Bone marrow (femur)	N.S.	0.264	*0.128	°0.196	N.A.
Brain	0.036	*0.002	0.011	°0.016	°0.018
Eyes	0.015	*0.000	0.004	°0.006	°0.008
Injection site	27.519	77.480	4.697	36.566	37.225
Heart	0.310	*0.001	0.121	°0.144	°0.156
Kidneys	0.544	0.126	0.143	0.271	0.236
Large intestine	0.019	*0.001	0.004	°0.008	°0.010
Liver	0.635	0.018	0.316	0.323	0.309
Lung	0.550	0.012	0.177	0.247	0.275
Lymph node (Man)	0.088	*0.000	0.025	°0.038	°0.045
Lymph node (Mes)	0.127	*0.000	0.018	°0.048	°0.069
Muscle	0.024	0.006	0.007	0.012	0.010
Ovaries	0.206	*0.000	0.106	°0.104	°0.103
Pancreas	0.072	0.008	0.030	0.037	0.033
Pituitary gland	0.310	*0.000	0.113	°0.141	°0.157
Salivary glands	0.133	*0.000	0.028	°0.054	°0.070
Skin	0.018	0.004	0.009	0.010	0.007
Small intestine	0.051	*0.001	0.010	°0.021	°0.026
Spinal cord	0.057	*0.000	0.016	°0.024	°0.029
Spleen	0.366	*0.004	0.570	°0.313	°0.287
Stomach	0.032	*0.001	0.013	°0.015	°0.016
Thymus	0.159	*0.003	0.047	°0.069	°0.080
Thyroid	0.181	*0.000	0.097	°0.093	°0.091
Uterus	0.090	*0.000	0.037	°0.043	°0.045
Whole Blood	2.016	0.013	0.778	0.936	1.011
Plasma	4.189	0.005	1.487	1.894	2.121
Blood:plasma ratio	0.48	2.43	0.52	1.15	1.12

N.S. = No sample due to analysis error (the bone marrow was not able to be removed from the bone since the bone was initially crushed for analysis)

A = Animal 023F appeared to have a slow distribution compared with the other animals

*=Results calculated from data less than 30 cpm above background

°=Mean includes results calculated from data less than 30 cpm above background

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Appendix 5 Individual Female Concentration Data
 (continued)

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 1 hour Following Single Intramuscular Administration of [³H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	025F	026F	027F	Mean	SD
Adipose tissue	0.145	0.234	0.069	0.149	0.083
Adrenal glands	1.779	2.131	3.254	2.388	0.770
Bladder	0.123	0.206	0.166	0.165	0.042
Bone (femur)	0.216	0.285	0.223	0.241	0.038
Bone marrow (femur)	0.886	1.219	0.926	1.010	0.182
Brain	0.096	0.139	0.115	0.117	0.022
Eyes	0.052	0.052	0.027	0.043	0.015
Heart	1.273	1.884	1.120	1.426	0.404
Injection site	31.021	202.720	366.100	199.950	167.560
Kidneys	1.568	2.396	1.112	1.692	0.651
Large intestine	0.060	0.065	0.070	0.065	0.005
Liver	6.342	4.717	4.674	5.244	0.951
Lung	1.455	1.954	1.313	1.574	0.336
Lymph node (Man)	0.226	0.266	0.176	0.223	0.045
Lymph node (Mes)	0.207	0.226	0.155	0.196	0.037
Muscle	0.080	0.093	0.072	0.082	0.011
Ovaries	1.630	1.650	0.736	1.339	0.522
Pancreas	0.208	0.343	0.234	0.261	0.072
Pituitary gland	0.607	1.114	0.810	0.844	0.255
Salivary glands	0.245	0.327	0.140	0.237	0.094
Skin	0.056	0.956	0.148	0.387	0.495
Small intestine	0.281	0.223	0.235	0.247	0.031
Spinal cord	0.111	0.119	0.137	0.122	0.013
Spleen	2.423	2.626	3.355	2.801	0.490
Stomach	0.085	0.118	0.070	0.091	0.025
Thymus	0.248	0.483	0.164	0.298	0.165
Thyroid	0.510	0.997	0.533	0.680	0.275
Uterus	0.194	0.251	0.164	0.203	0.044
Whole Blood	5.057	8.484	4.243	5.928	2.251
Plasma	9.655	14.318	8.680	10.884	3.014
Blood:plasma ratio	0.52	0.59	0.49	0.54	0.05

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Appendix 5 Individual Female Concentration Data
 (continued)

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 2 hours Following Single Intramuscular Administration of [³H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	028F	029F	030F	Mean	SD
Adipose tissue	0.110	0.274	0.162	0.182	0.084
Adrenal glands	1.429	8.981	2.285	4.232	4.135
Bladder	0.062	0.289	0.114	0.155	0.119
Bone (femur)	0.132	0.566	0.189	0.296	0.236
Bone marrow (femur)	0.575	1.722	1.714	1.337	0.660
Brain	0.063	0.241	0.095	0.133	0.095
Eyes	0.034	0.117	0.023	0.058	0.051
Heart	0.554	3.221	1.272	1.682	1.380
Injection site	0.092	1.744	277.600	93.144	159.740
Kidneys	0.623	2.870	5.408	2.967	2.394
Large intestine	0.027	0.198	0.092	0.106	0.086
Liver	5.209	21.794	10.108	12.370	8.521
Lung	0.908	4.000	1.313	2.074	1.681
Lymph node (Man)	0.198	0.701	0.188	0.362	0.293
Lymph node (Mes)	1.473	0.640	0.381	0.831	0.571
Muscle	0.045	0.140	0.114	0.100	0.049
Ovaries	0.474	2.683	1.756	1.638	1.109
Pancreas	0.116	0.825	0.270	0.404	0.373
Pituitary gland	0.414	1.853	0.599	0.955	0.783
Salivary glands	0.141	0.562	0.182	0.295	0.232
Skin	0.040	0.263	0.486	0.263	0.223
Small intestine	0.305	0.664	0.473	0.481	0.180
Spinal cord	0.109	0.289	0.118	0.172	0.102
Spleen	2.066	23.785	4.788	10.213	11.832
Stomach	0.088	0.211	0.077	0.126	0.074
Thymus	0.109	1.108	0.160	0.459	0.562
Thyroid	0.371	1.791	1.163	1.109	0.711
Uterus	0.169	0.568	0.178	0.305	0.228
Whole Blood	2.194	14.470	3.655	6.773	6.706
Plasma	4.442	15.480	7.350	9.091	5.721
Blood:plasma ratio	0.49	0.93	0.50	0.64	0.25

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Appendix 5 Individual Female Concentration Data
 (continued)

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 4 hours Following Single Intramuscular Administration of [³H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	031F	032F	033F	Mean	SD
Adipose tissue	0.134	0.061	0.296	0.163	0.121
Adrenal glands	1.879	3.483	4.255	3.206	1.212
Bladder	0.043	0.101	0.175	0.106	0.066
Bone (femur)	0.136	0.194	0.321	0.217	0.095
Bone marrow (femur)	0.448	0.818	1.480	0.915	0.522
Brain	0.033	0.058	0.133	0.075	0.052
Eyes	0.022	0.046	0.048	0.038	0.015
Heart	0.296	0.746	1.734	0.925	0.735
Injection site	8.920	103.630	56.133	56.227	47.355
Kidneys	0.328	0.627	1.486	0.814	0.601
Large intestine	0.165	0.222	0.283	0.224	0.059
Liver	8.503	14.685	20.519	14.569	6.009
Lung	0.610	1.159	1.898	1.222	0.646
Lymph node (Man)	0.173	0.454	0.546	0.391	0.194
Lymph node (Mes)	0.316	0.598	0.695	0.536	0.197
Muscle	0.033	0.057	0.301	0.130	0.148
Ovaries	0.555	2.916	3.552	2.341	1.579
Pancreas	0.358	0.270	0.568	0.398	0.153
Pituitary gland	0.251	0.317	0.805	0.458	0.303
Salivary glands	0.087	0.156	0.262	0.169	0.088
Skin	0.043	0.371	0.197	0.204	0.164
Small intestine	0.684	0.739	1.089	0.838	0.220
Spinal cord	0.073	0.061	0.236	0.124	0.098
Spleen	9.910	11.442	13.587	11.646	1.847
Stomach	0.050	0.113	0.141	0.101	0.047
Thymus	0.130	0.267	0.231	0.209	0.071
Thyroid	0.225	0.718	0.867	0.604	0.336
Uterus	0.080	0.096	0.246	0.140	0.091
Whole Blood	1.090	1.981	5.022	2.698	2.062
Plasma	2.037	3.442	7.274	4.251	2.711
Blood:plasma ratio	0.53	0.58	0.69	0.60	0.08

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**Appendix 5 Individual Female Concentration Data
 (continued)**

**Concentration of Total Radioactivity in Whole Blood, Plasma and
 Tissues 8 hours Following Single Intramuscular Administration of
 [³H]-08-A01-C01 to Female Wistar Han Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	034F	035F	036F	Mean	SD
Adipose tissue	0.095	0.041	0.072	0.069	0.027
Adrenal glands	7.562	6.554	7.538	7.218	0.575
Bladder	0.047	0.080	0.127	0.085	0.040
Bone (femur)	0.243	0.143	0.144	0.177	0.057
Bone marrow (femur)	1.262	1.350	1.210	1.274	0.071
Brain	0.047	0.030	0.058	0.045	0.014
Eyes	0.046	0.013	0.032	0.030	0.016
Heart	0.532	0.193	0.448	0.391	0.177
Injection site	30.227	174.950	172.620	125.930	82.890
Kidneys	0.416	0.239	0.372	0.342	0.092
Large intestine	0.679	0.381	0.764	0.608	0.201
Liver	22.242	25.442	27.834	25.172	2.806
Lung	0.661	0.378	0.846	0.628	0.236
Lymph node (Man)	0.315	0.251	0.551	0.372	0.158
Lymph node (Mes)	0.790	0.481	0.915	0.729	0.223
Muscle	0.040	0.160	0.075	0.091	0.062
Ovaries	2.960	1.276	5.029	3.088	1.880
Pancreas	0.390	0.087	0.241	0.239	0.151
Pituitary gland	0.169	0.099	0.157	0.141	0.037
Salivary glands	0.124	0.074	0.082	0.094	0.027
Skin	0.137	0.057	0.155	0.116	0.052
Small intestine	1.162	0.839	1.098	1.033	0.171
Spinal cord	0.051	0.021	0.060	0.044	0.020
Spleen	19.387	16.090	23.763	19.747	3.849
Stomach	0.243	0.040	0.094	0.126	0.105
Thymus	0.111	0.086	0.102	0.100	0.013
Thyroid	0.395	0.131	0.395	0.307	0.152
Uterus	0.584	0.055	0.223	0.287	0.270
Whole Blood	0.731	0.319	0.833	0.628	0.272
Plasma	1.421	0.574	1.447	1.147	0.496
Blood:plasma ratio	0.51	0.56	0.58	0.55	0.03

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Appendix 5 Individual Female Concentration Data
 (continued)

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 24 hours Following Single Intramuscular Administration of [³H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	037F	038F	039F	Mean	SD
Adipose tissue	0.031	0.042	0.053	0.042	0.011
Adrenal glands	9.718	3.981	9.084	7.595	3.145
Bladder	0.141	0.135	0.235	0.171	0.056
Bone (femur)	0.158	0.105	0.278	0.180	0.089
Bone marrow (femur)	1.180	1.058	1.978	1.405	0.500
Brain	0.040	0.039	0.063	0.047	0.014
Eyes	0.063	0.037	0.057	0.052	0.014
Heart	0.342	0.259	0.355	0.318	0.052
Injection site	2.568	202.540	162.510	122.540	105.810
Kidneys	0.270	0.412	0.361	0.348	0.072
Large intestine	0.561	0.370	0.465	0.466	0.095
Liver	13.368	10.520	21.469	15.119	5.681
Lung	0.519	0.822	0.945	0.762	0.219
Lymph node (Man)	0.259	0.242	0.589	0.363	0.195
Lymph node (Mes)	0.944	0.550	1.095	0.863	0.281
Muscle	0.028	0.114	0.133	0.092	0.056
Ovaries	4.091	5.266	6.363	5.240	1.136
Pancreas	0.176	0.362	0.422	0.320	0.128
Pituitary gland	0.309	0.213	0.379	0.300	0.083
Salivary glands	0.084	0.083	0.119	0.096	0.021
Skin	0.047	0.156	0.151	0.118	0.062
Small intestine	0.748	0.661	0.769	0.726	0.057
Spinal cord	0.047	0.034	0.064	0.048	0.015
Spleen	15.606	12.977	23.440	17.341	5.443
Stomach	0.094	0.054	0.096	0.081	0.024
Thymus	0.154	0.190	0.135	0.159	0.028
Thyroid	0.302	0.294	0.410	0.335	0.065
Uterus	0.307	0.207	0.354	0.289	0.075
Whole Blood	0.475	0.380	0.779	0.544	0.208
Plasma	0.930	0.681	1.223	0.945	0.271
Blood:plasma ratio	0.51	0.56	0.64	0.57	0.06

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**Appendix 5 Individual Female Concentration Data
 (continued)**

**Concentration of Total Radioactivity in Whole Blood, Plasma and
 Tissues 48 hours Following Single Intramuscular Administration of
³H]-08-A01-C01 to Female Wistar Han Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	040F	041F	042F	Mean	SD
Adipose tissue	0.081	0.201	0.414	0.232	0.168
Adrenal glands	12.979	15.142	16.707	14.942	1.872
Bladder	0.234	0.640	0.293	0.389	0.219
Bone (femur)	0.299	1.911	0.351	0.854	0.916
Bone marrow (femur)	2.096	1.993	7.463	3.851	3.129
Brain	0.038	0.046	0.072	0.052	0.018
Eyes	0.064	0.105	0.121	0.097	0.029
Heart	0.352	0.369	0.539	0.420	0.103
Injection site	93.643	27.547	62.073	61.088	33.059
Kidneys	0.314	0.378	0.412	0.368	0.050
Large intestine	1.210	1.507	1.031	1.249	0.241
Liver	24.416	20.707	46.111	30.411	13.722
Lung	0.921	0.719	1.053	0.898	0.168
Lymph node (Man)	0.600	0.516	0.784	0.633	0.137
Lymph node (Mes)	1.557	1.669	1.800	1.675	0.122
Muscle	0.126	0.068	0.119	0.104	0.032
Ovaries	9.305	13.544	13.933	12.261	2.567
Pancreas	0.364	0.298	1.170	0.611	0.485
Pituitary gland	0.910	0.816	0.810	0.845	0.056
Salivary glands	0.200	0.204	0.288	0.231	0.049
Skin	0.303	0.173	0.416	0.297	0.122
Small intestine	1.142	1.461	1.339	1.314	0.161
Spinal cord	0.043	0.075	0.069	0.062	0.017
Spleen	19.456	16.775	45.234	27.155	15.714
Stomach	0.154	0.197	0.233	0.195	0.040
Thymus	0.314	0.248	0.536	0.366	0.151
Thyroid	0.584	0.870	0.512	0.655	0.190
Uterus	0.267	0.521	0.581	0.456	0.167
Whole Blood	0.258	0.338	0.320	0.305	0.042
Plasma	0.429	0.598	0.546	0.524	0.087
Blood:plasma ratio	0.60	0.57	0.59	0.58	0.02

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Appendix 6 Individual Male Recovery Data

Recovery of Total Radioactivity in Tissues 0.25 min Following Single Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	043M	044M	045M	Mean	SD
Adrenal glands	0.002	0.002	0.000	0.001	0.001
Bladder	0.001	0.000	0.000	0.000	0.000
Brain	0.013	0.014	0.005	0.011	0.005
Eyes	0.001	0.000	0.000	0.000	0.000
Heart	0.056	0.024	0.004	0.028	0.026
Injection site	82.460	6.097	10.103	32.887	42.978
Kidneys	0.103	0.087	0.016	0.069	0.046
Large intestine	0.012	0.018	0.002	0.011	0.008
Liver	1.735	1.083	0.167	0.995	0.787
Lung	0.133	0.082	0.031	0.082	0.051
Pancreas	0.004	0.010	0.001	0.005	0.005
Pituitary gland	0.001	0.000	0.000	0.000	0.000
Prostate	0.002	0.002	0.000	0.001	0.001
Salivary glands	0.007	0.005	0.001	0.004	0.003
Small intestine	0.051	0.040	0.005	0.032	0.024
Spinal cord	0.002	0.001	0.000	0.001	0.001
Spleen	0.020	0.019	0.003	0.014	0.009
Stomach	0.008	0.013	0.002	0.008	0.006
Testes	0.012	0.008	0.001	0.007	0.005
Thymus	0.005	0.010	0.001	0.005	0.005
Thyroid	0.000	0.000	0.000	0.000	0.000

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**Appendix 6 Individual Male Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 1 hour Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han
 Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	046M	047M	048M	Mean	SD
Adrenal glands	0.001	0.003	0.002	0.002	0.001
Bladder	0.001	0.001	0.000	0.001	0.000
Brain	0.005	0.014	0.013	0.010	0.005
Eyes	0.000	0.000	0.001	0.000	0.000
Heart	0.015	0.036	0.045	0.032	0.015
Injection site	74.148	46.614	85.725	68.829	20.090
Kidneys	0.047	0.086	0.098	0.077	0.027
Large intestine	0.016	0.017	0.021	0.018	0.002
Liver	2.218	2.607	3.676	2.834	0.755
Lung	0.043	0.131	0.081	0.085	0.044
Pancreas	0.004	0.009	0.006	0.006	0.003
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.001	0.002	0.001	0.001	0.001
Salivary glands	0.003	0.005	0.006	0.005	0.002
Small intestine	0.102	0.133	0.136	0.124	0.019
Spinal cord	0.001	0.000	0.001	0.001	0.000
Spleen	0.115	0.063	0.082	0.087	0.026
Stomach	0.007	0.019	0.023	0.016	0.008
Testes	0.007	0.009	0.013	0.010	0.003
Thymus	0.008	0.004	0.007	0.006	0.002
Thyroid	0.000	0.001	0.000	0.000	0.000

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**Appendix 6 Individual Male Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 2 hours Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han
 Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	049M	050M	051M	Mean	SD
Adrenal glands	0.006	0.003	0.005	0.005	0.001
Bladder	0.001	0.001	0.001	0.001	0.000
Brain	0.033	0.013	0.016	0.021	0.011
Eyes	0.001	0.000	0.002	0.001	0.001
Heart	0.109	0.036	0.051	0.065	0.039
Injection site	53.157	53.477	10.525	39.053	24.707
Kidneys	0.203	0.096	0.148	0.149	0.054
Large intestine	0.063	0.035	0.063	0.054	0.016
Liver	10.166	4.262	8.460	7.629	3.038
Lung	0.313	0.094	0.160	0.189	0.113
Pancreas	0.011	0.006	0.028	0.015	0.012
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.002	0.002	0.003	0.002	0.000
Salivary glands	0.010	0.004	0.008	0.007	0.003
Small intestine	0.418	0.305	0.336	0.353	0.058
Spinal cord	0.001	0.001	0.002	0.001	0.001
Spleen	0.296	0.101	0.299	0.232	0.114
Stomach	0.034	0.017	0.047	0.033	0.015
Testes	0.027	0.008	0.017	0.017	0.009
Thymus	0.010	0.005	0.008	0.008	0.002
Thyroid	0.001	0.001	0.000	0.001	0.000

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**Appendix 6 Individual Male Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 4 hours Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han
 Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	052M	053M	054M	Mean	SD
Adrenal glands	0.013	0.009	0.014	0.012	0.002
Bladder	0.001	0.002	0.001	0.001	0.000
Brain	0.019	0.015	0.029	0.021	0.007
Eyes	0.002	0.002	0.001	0.002	0.001
Heart	0.071	0.033	0.096	0.067	0.032
Injection site	61.619	36.450	45.061	47.710	12.792
Kidneys	0.151	0.088	0.169	0.136	0.042
Large intestine	0.271	0.219	0.216	0.236	0.031
Liver	12.655	13.898	18.528	15.027	3.095
Lung	0.356	0.080	0.241	0.226	0.139
Pancreas	0.007	0.020	0.011	0.013	0.007
Pituitary gland	0.001	0.001	0.000	0.001	0.000
Prostate	0.003	0.002	0.003	0.003	0.001
Salivary glands	0.009	0.007	0.012	0.009	0.002
Small intestine	0.632	0.499	0.737	0.623	0.120
Spinal cord	0.002	0.004	0.002	0.003	0.001
Spleen	0.309	0.410	0.334	0.351	0.052
Stomach	0.053	0.027	0.033	0.037	0.013
Testes	0.028	0.021	0.039	0.030	0.009
Thymus	0.010	0.011	0.033	0.018	0.013
Thyroid	0.001	0.001	0.001	0.001	0.000

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**Appendix 6 Individual Male Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 8 hours Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han
 Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	055M	056M	057M	Mean	SD
Adrenal glands	0.013	0.023	0.042	0.026	0.015
Bladder	N.S.	0.001	0.002	0.002	N.A.
Brain	0.014	0.013	0.014	0.014	0.001
Eyes	N.S.	0.001	0.002	0.002	N.A.
Heart	0.071	0.051	0.061	0.061	0.010
Injection site	18.863	19.984	17.346	18.731	1.324
Kidneys	0.114	0.107	0.108	0.109	0.004
Large intestine	0.536	0.424	0.430	0.463	0.063
Liver	17.280	17.862	29.414	21.519	6.844
Lung	0.226	0.146	0.169	0.180	0.042
Pancreas	0.010	0.021	0.012	0.014	0.006
Pituitary gland	0.000	0.000	0.001	0.000	0.000
Prostate	0.004	0.002	0.001	0.003	0.001
Salivary glands	0.008	0.006	0.007	0.007	0.001
Small intestine	0.850	1.034	1.031	0.972	0.106
Spinal cord	0.001	0.001	0.001	0.001	0.000
Spleen	1.037	1.022	1.293	1.118	0.152
Stomach	0.043	0.026	0.097	0.055	0.037
Testes	0.034	0.022	0.045	0.034	0.012
Thymus	0.013	0.010	0.012	0.012	0.001
Thyroid	0.001	0.001	0.001	0.001	0.000

N.S. = No sample due to oxidiser failure

N.A. = Not applicable

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**Appendix 6 Individual Male Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 24 hours Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han
 Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	058M	059M	060M	Mean	SD
Adrenal glands	0.052	0.059	0.137	0.083	0.047
Bladder	0.002	0.002	0.002	0.002	0.000
Brain	0.006	0.013	0.017	0.012	0.006
Eyes	0.002	0.002	0.004	0.002	0.001
Heart	0.051	0.026	0.026	0.035	0.014
Injection site	39.854	26.623	29.394	31.957	6.978
Kidneys	0.075	0.053	0.075	0.068	0.012
Large intestine	0.332	0.895	2.045	1.091	0.873
Liver	14.444	16.303	28.957	19.901	7.897
Lung	0.109	0.118	0.179	0.136	0.038
Pancreas	0.007	0.017	0.015	0.013	0.005
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.003	0.004	0.005	0.004	0.001
Salivary glands	0.005	0.008	0.012	0.008	0.004
Small intestine	0.693	1.198	1.934	1.275	0.624
Spinal cord	0.001	0.002	0.002	0.001	0.001
Spleen	0.977	0.660	1.234	0.957	0.287
Stomach	0.021	0.033	0.107	0.054	0.046
Testes	0.057	0.058	0.105	0.074	0.028
Thymus	0.007	0.010	0.009	0.009	0.002
Thyroid	0.001	0.001	0.001	0.001	0.000

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**Appendix 6 Individual Male Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 48 hours Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han
 Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	061M	062M	063M	Mean	SD
Adrenal glands	0.078	0.157	0.078	0.104	0.046
Bladder	0.001	0.002	0.002	0.002	0.000
Brain	0.006	0.016	0.012	0.011	0.005
Eyes	0.002	0.003	0.003	0.003	0.000
Heart	0.024	0.055	0.037	0.039	0.016
Injection site	49.053	18.355	31.059	32.823	15.425
Kidneys	0.045	0.104	0.063	0.071	0.031
Large intestine	0.541	0.624	1.264	0.810	0.395
Liver	12.962	17.164	11.734	13.953	2.848
Lung	0.088	0.173	0.133	0.131	0.043
Pancreas	0.010	0.013	0.023	0.015	0.007
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.002	0.004	0.004	0.003	0.001
Salivary glands	0.010	0.012	0.008	0.010	0.002
Small intestine	0.635	1.258	1.020	0.971	0.314
Spinal cord	0.001	0.001	0.002	0.001	0.001
Spleen	0.544	1.271	0.926	0.914	0.364
Stomach	0.027	0.065	0.056	0.049	0.019
Testes	0.053	0.109	0.060	0.074	0.030
Thymus	0.004	0.012	0.009	0.008	0.004
Thyroid	0.001	0.002	0.001	0.001	0.001

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Appendix 7 Individual Female Recovery Data

Recovery of Total Radioactivity in Tissues 0.25 min Following Single Intramuscular Administration of [³H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	022F	023F	024F	Mean	SD
Adrenal glands	0.003	*0.000	0.001	°0.001	°0.002
Bladder	0.000	*0.000	0.000	°0.000	°0.000
Brain	0.005	*0.000	0.002	°0.002	°0.002
Eyes	0.000	*0.000	0.000	°0.000	°0.000
Heart	0.017	*0.000	0.006	°0.008	°0.008
Injection site	8.145	11.578	0.723	6.815	5.549
Kidneys	0.063	0.012	0.014	0.030	0.028
Large intestine	0.010	*0.000	0.002	°0.004	°0.005
Liver	0.435	0.010	0.180	0.209	0.214
Lung	0.051	0.001	0.013	0.022	0.026
Ovaries	0.002	*0.000	0.001	°0.001	°0.001
Pancreas	0.002	0.000	0.001	0.001	0.001
Pituitary gland	0.000	*0.000	0.000	°0.000	°0.000
Salivary glands	0.004	*0.000	0.001	°0.002	°0.002
Small intestine	0.038	*0.001	0.005	°0.015	°0.020
Spinal cord	0.000	*0.000	0.000	°0.000	°0.000
Spleen	0.014	*0.000	0.017	°0.011	°0.009
Stomach	0.007	*0.000	0.002	°0.003	°0.003
Thymus	0.005	*0.000	0.002	°0.002	°0.002
Thyroid	0.000	*0.000	0.000	°0.000	°0.000
Uterus	0.004	*0.000	0.002	°0.002	°0.002

*=Results calculated from data less than 30 cpm above background

°=Mean includes results calculated from data less than 30 cpm above background

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**Appendix 7 Individual Female Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 1 hour Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Female Wistar
 Han Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	025F	026F	027F	Mean	SD
Adrenal glands	0.010	0.011	0.015	0.012	0.003
Bladder	0.001	0.001	0.001	0.001	0.000
Brain	0.013	0.019	0.015	0.016	0.003
Eyes	0.001	0.001	0.001	0.001	0.000
Heart	0.066	0.109	0.062	0.079	0.026
Injection site	10.609	47.776	50.847	36.411	22.398
Kidneys	0.162	0.250	0.102	0.171	0.074
Large intestine	0.030	0.035	0.029	0.032	0.003
Liver	3.586	2.713	2.421	2.907	0.606
Lung	0.112	0.131	0.106	0.117	0.013
Ovaries	0.012	0.010	0.004	0.009	0.004
Pancreas	0.009	0.009	0.007	0.008	0.001
Pituitary gland	0.000	0.001	0.001	0.001	0.000
Salivary glands	0.008	0.009	0.006	0.008	0.002
Small intestine	0.153	0.130	0.121	0.135	0.017
Spinal cord	0.002	0.002	0.001	0.002	0.001
Spleen	0.082	0.099	0.112	0.098	0.015
Stomach	0.024	0.021	0.023	0.022	0.002
Thymus	0.007	0.013	0.004	0.008	0.005
Thyroid	0.001	0.001	0.001	0.001	0.000
Uterus	0.008	0.010	0.015	0.011	0.004

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**Appendix 7 Individual Female Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 2 hours Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Female Wistar
 Han Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	028F	029F	030F	Mean	SD
Adrenal glands	0.010	0.022	0.012	0.015	0.006
Bladder	0.000	0.001	0.001	0.001	0.001
Brain	0.008	0.034	0.014	0.019	0.014
Eyes	0.001	0.003	0.000	0.001	0.001
Heart	0.028	0.201	0.077	0.102	0.089
Injection site	0.018	0.236	72.027	24.094	41.511
Kidneys	0.056	0.264	0.497	0.272	0.221
Large intestine	0.018	0.142	0.065	0.075	0.063
Liver	3.203	12.436	5.452	7.030	4.815
Lung	0.080	0.311	0.110	0.167	0.125
Ovaries	0.003	0.012	0.009	0.008	0.004
Pancreas	0.003	0.022	0.010	0.012	0.010
Pituitary gland	0.000	0.002	0.000	0.001	0.001
Salivary glands	0.005	0.015	0.007	0.009	0.006
Small intestine	0.205	0.367	0.283	0.285	0.081
Spinal cord	0.002	0.004	0.001	0.002	0.002
Spleen	0.063	1.010	0.180	0.418	0.516
Stomach	0.027	0.057	0.022	0.035	0.019
Thymus	0.003	0.028	0.004	0.012	0.014
Thyroid	0.000	0.002	0.001	0.001	0.001
Uterus	0.008	0.025	0.011	0.015	0.009

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**Appendix 7 Individual Female Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 4 hours Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Female Wistar
 Han Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	031F	032F	033F	Mean	SD
Adrenal glands	0.011	0.019	0.023	0.018	0.006
Bladder	0.000	0.001	0.001	0.001	0.000
Brain	0.005	0.007	0.020	0.011	0.008
Eyes	0.001	0.001	0.001	0.001	0.000
Heart	0.013	0.046	0.097	0.052	0.042
Injection site	2.619	19.042	5.508	9.056	8.768
Kidneys	0.031	0.062	0.154	0.082	0.064
Large intestine	0.111	0.136	0.198	0.148	0.045
Liver	5.207	8.846	12.045	8.699	3.421
Lung	0.054	0.093	0.188	0.112	0.069
Ovaries	0.003	0.022	0.022	0.016	0.011
Pancreas	0.016	0.009	0.027	0.017	0.009
Pituitary gland	0.000	0.000	0.001	0.000	0.000
Salivary glands	0.003	0.005	0.011	0.006	0.005
Small intestine	0.354	0.435	0.596	0.462	0.123
Spinal cord	0.001	0.001	0.003	0.002	0.001
Spleen	0.390	0.421	0.447	0.419	0.028
Stomach	0.014	0.022	0.029	0.022	0.008
Thymus	0.004	0.007	0.006	0.006	0.002
Thyroid	0.000	0.001	0.001	0.001	0.000
Uterus	0.005	0.004	0.016	0.008	0.007

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**Appendix 7 Individual Female Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 8 hours Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Female Wistar
 Han Rats**

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	034F	035F	036F	Mean	SD
Adrenal glands	0.048	0.031	0.051	0.043	0.011
Bladder	0.000	0.000	0.001	0.000	0.000
Brain	0.007	0.004	0.009	0.007	0.002
Eyes	0.001	0.000	0.001	0.001	0.000
Heart	0.029	0.010	0.027	0.022	0.011
Injection site	10.296	26.182	38.500	24.993	14.139
Kidneys	0.056	0.022	0.042	0.040	0.017
Large intestine	0.409	0.233	0.397	0.346	0.098
Liver	13.264	12.033	18.443	14.580	3.402
Lung	0.089	0.028	0.074	0.064	0.031
Ovaries	0.022	0.010	0.042	0.025	0.016
Pancreas	0.034	0.002	0.011	0.016	0.016
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Salivary glands	0.005	0.002	0.003	0.003	0.001
Small intestine	0.718	0.308	0.714	0.580	0.235
Spinal cord	0.001	0.000	0.001	0.001	0.000
Spleen	0.853	0.601	1.082	0.845	0.241
Stomach	0.043	0.005	0.023	0.024	0.019
Thymus	0.004	0.002	0.003	0.003	0.001
Thyroid	0.001	0.000	0.001	0.000	0.000
Uterus	0.030	0.004	0.014	0.016	0.013

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**Appendix 7 Individual Female Recovery Data
 (continued)**

Recovery of Total Radioactivity in Tissues 24 hours Following Single Intramuscular Administration of [³H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	037F	038F	039F	Mean	SD
Adrenal glands	0.064	0.032	0.050	0.049	0.016
Bladder	0.001	0.001	0.001	0.001	0.000
Brain	0.005	0.006	0.009	0.007	0.002
Eyes	0.001	0.001	0.001	0.001	0.000
Heart	0.019	0.014	0.020	0.018	0.003
Injection site	0.444	39.677	38.765	26.295	22.392
Kidneys	0.029	0.053	0.035	0.039	0.013
Large intestine	0.334	0.283	0.263	0.293	0.037
Liver	9.112	9.776	14.042	10.977	2.675
Lung	0.053	0.071	0.072	0.065	0.010
Ovaries	0.031	0.038	0.043	0.037	0.006
Pancreas	0.005	0.007	0.014	0.009	0.004
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Salivary glands	0.003	0.003	0.004	0.003	0.001
Small intestine	0.575	0.601	0.432	0.536	0.091
Spinal cord	0.001	0.001	0.001	0.001	0.000
Spleen	0.591	0.508	0.955	0.685	0.237
Stomach	0.019	0.011	0.029	0.020	0.009
Thymus	0.003	0.005	0.003	0.004	0.001
Thyroid	0.000	0.000	0.001	0.000	0.000
Uterus	0.027	0.009	0.017	0.018	0.009

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**Appendix 7 Individual Female Recovery Data
 (continued)**

Recovery of Total Radioactivity in Tissues 48 hours Following Single Intramuscular Administration of [³H]-08-A01-C01 to Female Wistar Han Rats

Target Dose Level: 50 µg mRNA/Animal; 1.29 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	040F	041F	042F	Mean	SD
Adrenal glands	0.085	0.126	0.114	0.108	0.021
Bladder	0.001	0.004	0.002	0.002	0.001
Brain	0.005	0.006	0.010	0.007	0.002
Eyes	0.001	0.003	0.003	0.002	0.001
Heart	0.018	0.017	0.024	0.020	0.004
Injection site	20.139	5.852	23.287	16.426	9.292
Kidneys	0.036	0.045	0.044	0.042	0.005
Large intestine	0.570	0.928	0.644	0.714	0.189
Liver	15.122	13.811	26.137	18.357	6.770
Lung	0.066	0.066	0.076	0.070	0.006
Ovaries	0.075	0.113	0.097	0.095	0.019
Pancreas	0.011	0.007	0.050	0.023	0.024
Pituitary gland	0.001	0.001	0.000	0.001	0.000
Salivary glands	0.007	0.005	0.009	0.007	0.002
Small intestine	0.540	0.825	0.729	0.698	0.145
Spinal cord	0.001	0.002	0.001	0.001	0.000
Spleen	0.772	0.848	1.818	1.146	0.583
Stomach	0.023	0.028	0.035	0.029	0.006
Thymus	0.007	0.005	0.009	0.007	0.002
Thyroid	0.001	0.001	0.001	0.001	0.000
Uterus	0.010	0.031	0.025	0.022	0.010

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Appendix 8 Individual Male 100 µg mRNA data

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 0.25 min Following Single Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	001M	002M	003M	Mean	SD
Adipose tissue	0.075	0.108	0.018	0.067	0.046
Adrenal glands	0.193	0.192	0.184	0.190	0.005
Bladder	0.035	0.079	0.026	0.047	0.028
Bone (femur)	0.195	0.054	0.044	0.098	0.085
Bone marrow (femur)	0.312	0.163	0.229	0.234	0.075
Brain	0.050	0.047	0.046	0.048	0.002
Eyes	0.015	0.021	0.007	0.014	0.007
Heart	0.394	0.365	0.460	0.406	0.048
Injection site	16.832	24.313	179.840	73.662	92.030
Kidneys	0.576	0.552	0.273	0.467	0.169
Large intestine	0.016	0.012	0.051	0.026	0.022
Liver	0.963	0.503	0.670	0.712	0.233
Lung	0.689	0.497	0.410	0.532	0.143
Lymph node (Man)	0.043	0.046	0.042	0.044	0.002
Lymph node (Mes)	0.045	0.020	0.018	0.028	0.015
Muscle	0.035	0.040	0.285	0.120	0.143
Pancreas	0.088	0.068	0.068	0.075	0.012
Pituitary gland	0.787	0.796	0.225	0.603	0.327
Prostate	0.035	0.045	0.047	0.042	0.006
Salivary glands	0.087	0.087	0.049	0.074	0.022
Skin	2.094	3.233	12.691	6.499	6.668
Small intestine	0.046	0.030	0.016	0.031	0.015
Spinal cord	0.091	0.064	0.068	0.074	0.015
Spleen	0.426	1.463	0.221	0.704	0.666
Stomach	0.032	0.026	*0.007	°0.022	°0.013
Testes	0.033	0.030	0.020	0.028	0.007
Thymus	0.121	0.161	0.216	0.166	0.048
Thyroid	0.175	0.498	0.105	0.259	0.209
Whole Blood	2.291	2.426	1.678	2.132	0.398
Plasma	5.640	5.530	3.924	5.031	0.960
Blood:plasma ratio	0.41	0.44	0.43	0.42	0.02

*=Results calculated from data less than 30 cpm above background

°=Mean includes results calculated from data less than 30 cpm above background

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Appendix 8 Individual Male 100 µg mRNA Data
 (continued)

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 1 hour Following Single Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	004M	005M	006M	Mean	SD
Adipose tissue	0.193	0.307	0.350	0.283	0.081
Adrenal glands	1.775	1.877	2.208	1.953	0.227
Bladder	0.224	0.098	0.264	0.195	0.086
Bone (femur)	1.102	0.530	0.566	0.733	0.320
Bone marrow (femur)	2.111	4.732	2.456	3.100	1.424
Brain	0.253	0.297	0.296	0.282	0.025
Eyes	0.229	0.070	0.093	0.131	0.086
Heart	1.948	3.461	2.496	2.635	0.766
Injection site	152.370	78.654	150.890	127.300	42.139
Kidneys	3.017	3.096	3.170	3.094	0.077
Large intestine	0.090	0.091	0.152	0.111	0.035
Liver	13.805	10.906	16.323	13.678	2.711
Lung	3.523	3.532	2.901	3.319	0.362
Lymph node (Man)	0.366	0.379	0.437	0.394	0.038
Lymph node (Mes)	0.268	0.412	0.389	0.356	0.077
Muscle	0.184	0.213	0.195	0.198	0.015
Pancreas	0.335	0.375	0.469	0.393	0.069
Pituitary gland	1.389	1.810	1.717	1.639	0.221
Prostate	0.328	0.363	0.380	0.357	0.027
Salivary glands	0.471	0.613	0.493	0.526	0.076
Skin	3.043	0.407	1.179	1.543	1.355
Small intestine	0.393	3.191	3.563	2.382	1.733
Spinal cord	0.216	0.356	0.303	0.292	0.071
Spleen	4.066	4.402	4.868	4.445	0.402
Stomach	0.332	2.377	8.099	3.603	4.026
Testes	0.185	0.196	0.486	0.289	0.171
Thymus	0.332	0.343	0.596	0.424	0.149
Thyroid	1.219	1.909	1.266	1.465	0.385
Whole Blood	7.985	11.835	10.357	10.059	1.942
Plasma	23.703	26.782	26.070	25.518	1.612
Blood:plasma ratio	0.34	0.44	0.40	0.39	0.05

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Appendix 8 Individual Male 100 µg mRNA Data
 (continued)

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 2 hours Following Single Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	007M	008M	009M	Mean	SD
Adipose tissue	0.311	0.211	0.486	0.336	0.140
Adrenal glands	3.152	3.337	2.559	3.016	0.406
Bladder	0.310	0.241	0.479	0.343	0.122
Bone (femur)	0.835	0.462	0.385	0.561	0.241
Bone marrow (femur)	3.322	2.694	2.057	2.691	0.632
Brain	0.348	0.310	0.250	0.302	0.049
Eyes	0.126	0.104	0.064	0.098	0.031
Heart	2.866	3.359	3.481	3.235	0.326
Injection site	6.971	61.485	30.751	33.069	27.331
Kidneys	2.887	2.858	2.679	2.808	0.113
Large intestine	0.283	0.125	0.148	0.185	0.085
Liver	33.320	24.542	22.034	26.632	5.926
Lung	3.839	2.982	3.769	3.530	0.476
Lymph node (Man)	0.784	0.413	0.474	0.557	0.199
Lymph node (Mes)	0.859	0.503	0.333	0.565	0.268
Muscle	0.220	0.182	0.189	0.197	0.020
Pancreas	0.595	0.512	0.557	0.554	0.041
Pituitary gland	1.998	1.921	1.729	1.883	0.139
Prostate	0.458	0.354	0.461	0.424	0.061
Salivary glands	0.740	0.597	0.539	0.625	0.104
Skin	0.524	0.353	0.454	0.444	0.086
Small intestine	1.147	0.887	0.755	0.930	0.199
Spinal cord	0.396	0.373	0.360	0.377	0.018
Spleen	14.103	8.227	7.803	10.044	3.521
Stomach	0.234	0.142	0.143	0.173	0.053
Testes	0.239	0.402	0.317	0.320	0.081
Thymus	0.447	0.424	0.371	0.414	0.039
Thyroid	1.906	1.397	1.481	1.595	0.273
Whole Blood	11.413	10.005	10.736	10.718	0.704
Plasma	25.479	22.927	22.340	23.582	1.669
Blood:plasma ratio	0.45	0.44	0.48	0.45	0.02

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**Appendix 8 Individual Male 100 µg mRNA Data
 (continued)**

**Concentration of Total Radioactivity in Whole Blood, Plasma and
 Tissues 4 hours Following Single Intramuscular Administration of
 [³H]-08-A01-C01 to Male Wistar Han Rats**

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	010M	011M	012M	Mean	SD
Adipose tissue	0.222	0.262	0.105	0.196	0.082
Adrenal glands	5.481	2.469	2.491	3.480	1.732
Bladder	0.237	0.151	0.156	0.181	0.048
Bone (femur)	1.452	1.249	0.348	1.016	0.588
Bone marrow (femur)	1.880	3.875	1.459	2.405	1.291
Brain	0.373	0.123	0.090	0.195	0.155
Eyes	0.095	0.056	0.042	0.065	0.027
Heart	1.233	1.095	1.064	1.131	0.090
Injection site	55.286	464.630	257.860	259.260	204.680
Kidneys	2.190	1.607	1.007	1.601	0.591
Large intestine	0.180	0.713	0.338	0.410	0.274
Liver	38.606	14.955	19.426	24.329	12.565
Lung	1.255	3.060	1.398	1.904	1.003
Lymph node (Man)	0.694	0.271	0.242	0.402	0.253
Lymph node (Mes)	0.970	0.427	0.502	0.633	0.294
Muscle	0.129	0.076	0.085	0.097	0.029
Pancreas	0.189	0.419	0.299	0.302	0.115
Pituitary gland	0.870	0.599	0.480	0.649	0.200
Prostate	0.244	0.133	0.133	0.170	0.064
Salivary glands	0.334	0.192	0.170	0.232	0.089
Skin	0.931	0.178	2.172	1.094	1.007
Small intestine	0.758	1.381	1.189	1.110	0.319
Spinal cord	0.154	0.094	0.111	0.120	0.031
Spleen	9.286	27.731	9.780	15.599	10.510
Stomach	0.057	0.131	0.302	0.163	0.125
Testes	0.397	0.134	0.110	0.214	0.159
Thymus	0.164	0.229	0.185	0.193	0.033
Thyroid	1.256	0.565	0.742	0.854	0.359
Whole Blood	4.741	2.416	2.502	3.220	1.318
Plasma	11.200	5.253	5.862	7.438	3.272
Blood:plasma ratio	0.42	0.46	0.43	0.44	0.02

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Appendix 8 Individual Male 100 µg mRNA Data
 (continued)

Concentration of Total Radioactivity in Whole Blood, Plasma and Tissues 8 hours Following Single Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	013M	014M	015M	Mean	SD
Adipose tissue	0.134	0.147	0.269	0.184	0.075
Adrenal glands	6.445	9.564	32.615	16.208	14.294
Bladder	0.741	0.264	0.499	0.501	0.238
Bone (femur)	0.835	0.274	0.855	0.655	0.330
Bone marrow (femur)	1.920	1.495	2.225	1.880	0.367
Brain	0.165	0.120	0.214	0.166	0.047
Eyes	0.188	0.146	0.229	0.188	0.041
Heart	2.084	1.104	2.398	1.862	0.675
Injection site	126.340	106.800	2.416	78.521	66.629
Kidneys	2.145	1.122	1.472	1.580	0.520
Large intestine	1.713	1.199	1.781	1.564	0.318
Liver	34.463	41.789	61.002	45.751	13.706
Lung	2.999	1.707	3.360	2.689	0.869
Lymph node (Man)	1.158	0.644	1.099	0.967	0.282
Lymph node (Mes)	1.076	1.409	1.701	1.395	0.313
Muscle	0.158	0.096	0.196	0.150	0.051
Pancreas	0.433	0.326	0.579	0.446	0.127
Pituitary gland	0.858	0.517	0.994	0.790	0.246
Prostate	0.314	0.176	0.386	0.292	0.107
Salivary glands	0.242	0.168	0.386	0.265	0.111
Skin	0.295	0.285	0.547	0.376	0.148
Small intestine	2.012	1.963	1.865	1.946	0.075
Spinal cord	0.185	0.148	0.252	0.195	0.053
Spleen	24.956	16.693	35.344	25.664	9.345
Stomach	0.113	0.187	2.187	0.829	1.177
Testes	0.269	0.328	0.361	0.319	0.047
Thymus	0.110	0.295	0.481	0.295	0.185
Thyroid	1.544	0.885	2.170	1.533	0.642
Whole Blood	3.450	2.106	4.202	3.253	1.062
Plasma	7.541	4.597	8.168	6.768	1.907
Blood:plasma ratio	0.46	0.46	0.51	0.48	0.03

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**Appendix 8 Individual Male 100 µg mRNA Data
 (continued)**

**Concentration of Total Radioactivity in Whole Blood, Plasma and
 Tissues 24 hours Following Single Intramuscular Administration of
 [³H]-08-A01-C01 to Male Wistar Han Rats**

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	016M	017M	018M	Mean	SD
Adipose tissue	0.268	0.219	0.261	0.249	0.027
Adrenal glands	63.795	42.538	52.924	53.085	10.629
Bladder	0.609	0.643	0.373	0.542	0.147
Bone (femur)	1.254	2.075	0.950	1.426	0.582
Bone marrow (femur)	5.002	4.711	7.513	5.742	1.541
Brain	0.186	0.221	0.255	0.221	0.034
Eyes	0.342	0.247	0.360	0.316	0.061
Heart	1.613	1.877	1.760	1.750	0.132
Injection site	50.606	70.405	268.240	129.750	120.340
Kidneys	1.971	1.774	2.460	2.068	0.353
Large intestine	5.083	2.282	3.210	3.525	1.427
Liver	51.485	71.224	45.827	56.179	13.334
Lung	3.831	3.615	3.360	3.602	0.236
Lymph node (Man)	3.227	1.555	1.570	2.117	0.961
Lymph node (Mes)	5.835	3.496	3.765	4.366	1.279
Muscle	0.208	0.263	0.247	0.239	0.028
Pancreas	0.767	0.966	0.781	0.838	0.111
Pituitary gland	1.320	1.362	1.603	1.428	0.152
Prostate	0.407	0.446	0.481	0.445	0.037
Salivary glands	0.617	0.561	0.701	0.626	0.071
Skin	0.833	0.937	0.645	0.805	0.148
Small intestine	3.736	3.157	3.433	3.442	0.289
Spinal cord	0.229	0.200	0.326	0.252	0.066
Spleen	47.746	74.940	44.431	55.706	16.739
Stomach	0.572	0.802	0.489	0.621	0.162
Testes	0.638	0.502	0.616	0.585	0.073
Thymus	0.473	0.568	0.506	0.516	0.048
Thyroid	1.845	1.890	2.651	2.129	0.453
Whole Blood	2.448	1.756	3.404	2.536	0.827
Plasma	5.639	5.297	8.191	6.376	1.581
Blood:plasma ratio	0.43	0.33	0.42	0.39	0.05

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**Appendix 8
 (continued)**

Individual Male 100 µg mRNA Data

**Concentration of Total Radioactivity in Whole Blood, Plasma and
 Tissues 48 hours Following Single Intramuscular Administration of
 [³H]-08-A01-C01 to Male Wistar Han Rats**

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as µg lipid equiv/g (mL)

Sample	019M	020M	Mean
Adipose tissue	0.276	0.234	0.255
Adrenal glands	52.496	45.684	49.090
Bladder	0.779	0.849	0.814
Bone (femur)	0.639	0.867	0.753
Bone marrow (femur)	3.233	2.890	3.062
Brain	0.477	0.173	0.325
Eyes	0.239	0.260	0.249
Heart	1.132	1.158	1.145
Injection site	48.800	59.876	54.338
Kidneys	0.971	1.131	1.051
Large intestine	4.144	2.190	3.167
Liver	48.512	36.690	42.601
Lung	1.853	2.477	2.165
Lymph node (Man)	2.418	1.157	1.788
Lymph node (Mes)	5.067	3.297	4.182
Muscle	0.166	0.926	0.546
Pancreas	0.540	0.701	0.620
Pituitary gland	0.987	0.884	0.936
Prostate	0.308	0.285	0.296
Salivary glands	0.488	0.588	0.538
Skin	0.640	0.699	0.670
Small intestine	3.644	3.750	3.697
Spinal cord	0.212	0.237	0.224
Spleen	35.545	33.899	34.722
Stomach	0.794	1.011	0.903
Testes	0.523	0.555	0.539
Thymus	0.514	0.655	0.584
Thyroid	1.604	1.523	1.564
Whole Blood	0.967	1.011	0.989
Plasma	1.451	1.493	1.472
Blood:plasma ratio	0.67	0.68	0.67

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Appendix 8 Individual Male 100 µg mRNA Data
 (continued)

Recovery of Total Radioactivity in Tissues 0.25 min Following Single Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	001M	002M	003M	Mean	SD
Adrenal glands	0.000	0.000	0.000	0.000	0.000
Bladder	0.000	0.000	0.000	0.000	0.000
Brain	0.003	0.003	0.003	0.003	0.000
Eyes	0.000	0.000	0.000	0.000	0.000
Heart	0.011	0.009	0.017	0.013	0.004
Injection site	1.865	3.345	18.252	7.821	9.064
Kidneys	0.037	0.033	0.019	0.030	0.010
Large intestine	0.006	0.004	0.018	0.009	0.008
Liver	0.368	0.185	0.278	0.277	0.091
Lung	0.028	0.017	0.023	0.023	0.005
Pancreas	0.001	0.001	0.002	0.001	0.000
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.000	0.000	0.000	0.000	0.000
Salivary glands	0.001	0.002	0.001	0.001	0.000
Small intestine	0.016	0.009	0.006	0.010	0.005
Spinal cord	0.001	0.001	0.000	0.001	0.000
Spleen	0.010	0.026	0.006	0.014	0.011
Stomach	0.005	0.004	*0.002	°0.003	°0.002
Testes	0.004	0.003	0.003	0.003	0.001
Thymus	0.003	0.003	0.004	0.003	0.001
Thyroid	0.000	0.000	0.000	0.000	0.000

*=Results calculated from data less than 30 cpm above background

°=Mean includes results calculated from data less than 30 cpm above background

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**Appendix 8 Individual Male 100 µg mRNA Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 1 hour Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han
 Rats**

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	004M	005M	006M	Mean	SD
Adrenal glands	0.005	0.003	0.004	0.004	0.001
Bladder	0.001	0.000	0.001	0.001	0.000
Brain	0.019	0.020	0.020	0.019	0.001
Eyes	0.002	0.001	0.001	0.001	0.001
Heart	0.049	0.103	0.074	0.075	0.027
Injection site	15.619	13.609	16.094	15.107	1.319
Kidneys	0.191	0.176	0.188	0.185	0.008
Large intestine	0.024	0.027	0.050	0.034	0.014
Liver	5.198	3.856	5.564	4.873	0.899
Lung	0.148	0.159	0.103	0.137	0.030
Pancreas	0.004	0.006	0.007	0.006	0.002
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.003	0.003	0.003	0.003	0.000
Salivary glands	0.007	0.009	0.011	0.009	0.002
Small intestine	0.132	1.003	1.062	0.732	0.521
Spinal cord	0.001	0.003	0.001	0.002	0.001
Spleen	0.090	0.087	0.089	0.089	0.001
Stomach	0.075	0.362	1.259	0.565	0.618
Testes	0.020	0.021	0.057	0.033	0.021
Thymus	0.007	0.005	0.006	0.006	0.001
Thyroid	0.001	0.001	0.001	0.001	0.000

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**Appendix 8 Individual Male Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 2 hours Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han
 Rats**

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	007M	008M	009M	Mean	SD
Adrenal glands	0.008	0.006	0.007	0.007	0.001
Bladder	0.001	0.001	0.001	0.001	0.000
Brain	0.024	0.021	0.018	0.021	0.003
Eyes	0.001	0.001	0.001	0.001	0.000
Heart	0.078	0.095	0.115	0.096	0.019
Injection site	0.598	9.070	3.532	4.400	4.302
Kidneys	0.180	0.148	0.160	0.163	0.016
Large intestine	0.088	0.038	0.055	0.061	0.025
Liver	11.802	8.114	8.654	9.523	1.992
Lung	0.147	0.112	0.153	0.137	0.022
Pancreas	0.008	0.007	0.011	0.009	0.002
Pituitary gland	0.001	0.000	0.000	0.000	0.000
Prostate	0.003	0.004	0.004	0.004	0.001
Salivary glands	0.012	0.010	0.013	0.011	0.002
Small intestine	0.434	0.294	0.281	0.336	0.085
Spinal cord	0.003	0.004	0.002	0.003	0.001
Spleen	0.271	0.155	0.192	0.206	0.059
Stomach	0.036	0.023	0.026	0.028	0.007
Testes	0.025	0.045	0.036	0.035	0.010
Thymus	0.010	0.008	0.007	0.008	0.001
Thyroid	0.001	0.001	0.001	0.001	0.000

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**Appendix 8 Individual Male Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 4 hours Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han
 Rats**

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	010M	011M	012M	Mean	SD
Adrenal glands	0.010	0.005	0.005	0.007	0.003
Bladder	0.001	0.000	0.000	0.001	0.000
Brain	0.027	0.009	0.006	0.014	0.011
Eyes	0.001	0.001	0.000	0.001	0.000
Heart	0.031	0.043	0.033	0.036	0.007
Injection site	5.231	59.191	24.168	29.530	27.377
Kidneys	0.141	0.101	0.058	0.100	0.041
Large intestine	0.062	0.258	0.123	0.147	0.100
Liver	13.675	6.428	7.436	9.180	3.926
Lung	0.079	0.141	0.069	0.096	0.039
Pancreas	0.003	0.008	0.006	0.006	0.003
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.002	0.001	0.001	0.001	0.001
Salivary glands	0.005	0.003	0.003	0.004	0.001
Small intestine	0.234	0.614	0.356	0.401	0.194
Spinal cord	0.001	0.001	0.001	0.001	0.000
Spleen	0.177	0.530	0.167	0.291	0.207
Stomach	0.007	0.035	0.043	0.028	0.019
Testes	0.048	0.017	0.012	0.026	0.019
Thymus	0.003	0.005	0.003	0.003	0.001
Thyroid	0.001	0.000	0.001	0.001	0.000

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**Appendix 8 Individual Male Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 8 hours Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han
 Rats**

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	013M	014M	015M	Mean	SD
Adrenal glands	0.025	0.021	0.080	0.042	0.033
Bladder	0.002	0.001	0.001	0.001	0.001
Brain	0.012	0.009	0.014	0.012	0.003
Eyes	0.002	0.001	0.002	0.002	0.001
Heart	0.058	0.035	0.081	0.058	0.023
Injection site	8.806	17.803	0.313	8.974	8.746
Kidneys	0.134	0.073	0.091	0.099	0.031
Large intestine	0.511	0.398	0.634	0.514	0.118
Liver	11.864	16.293	24.504	17.553	6.414
Lung	0.192	0.129	0.197	0.172	0.038
Pancreas	0.005	0.006	0.012	0.007	0.004
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.002	0.001	0.003	0.002	0.001
Salivary glands	0.004	0.003	0.008	0.005	0.003
Small intestine	0.585	0.529	0.633	0.582	0.052
Spinal cord	0.002	0.001	0.002	0.002	0.000
Spleen	0.560	0.369	0.848	0.592	0.241
Stomach	0.021	0.019	0.288	0.109	0.155
Testes	0.031	0.036	0.038	0.035	0.004
Thymus	0.002	0.004	0.007	0.004	0.002
Thyroid	0.001	0.001	0.001	0.001	0.000

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**Appendix 8 Individual Male Recovery Data
 (continued)**

Recovery of Total Radioactivity in Tissues 24 hours Following Single Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han Rats

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	016M	017M	018M	Mean	SD
Adrenal glands	0.137	0.095	0.106	0.113	0.022
Bladder	0.003	0.002	0.001	0.002	0.001
Brain	0.012	0.015	0.019	0.015	0.003
Eyes	0.004	0.002	0.004	0.003	0.001
Heart	0.038	0.052	0.051	0.047	0.008
Injection site	3.590	15.406	29.435	16.144	12.938
Kidneys	0.107	0.104	0.165	0.125	0.034
Large intestine	1.668	0.752	0.996	1.139	0.475
Liver	22.736	26.544	20.865	23.382	2.894
Lung	0.170	0.160	0.226	0.185	0.036
Pancreas	0.010	0.016	0.012	0.013	0.003
Pituitary gland	0.000	0.000	0.000	0.000	0.000
Prostate	0.003	0.004	0.004	0.004	0.000
Salivary glands	0.011	0.010	0.011	0.010	0.001
Small intestine	1.194	0.896	1.321	1.137	0.218
Spinal cord	0.002	0.001	0.002	0.002	0.001
Spleen	1.003	1.590	1.111	1.234	0.312
Stomach	0.066	0.099	0.065	0.077	0.019
Testes	0.070	0.056	0.075	0.067	0.010
Thymus	0.007	0.009	0.007	0.008	0.002
Thyroid	0.001	0.001	0.001	0.001	0.000

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**Appendix 8 Individual Male Recovery Data
 (continued)**

**Recovery of Total Radioactivity in Tissues 48 hours Following Single
 Intramuscular Administration of [³H]-08-A01-C01 to Male Wistar Han
 Rats**

Target Dose Level: 100 µg mRNA/Animal; 2.57 mg Total Lipid/Animal

Results expressed as % administered dose

Sample	019M	020M	Mean
Adrenal glands	0.155	0.112	0.134
Bladder	0.002	0.002	0.002
Brain	0.034	0.012	0.023
Eyes	0.002	0.003	0.002
Heart	0.030	0.031	0.030
Injection site	2.978	10.414	6.696
Kidneys	0.063	0.076	0.070
Large intestine	1.070	0.719	0.894
Liver	17.436	16.159	16.797
Lung	0.071	0.132	0.102
Pancreas	0.007	0.006	0.006
Pituitary gland	0.000	0.000	0.000
Prostate	0.003	0.002	0.003
Salivary glands	0.008	0.009	0.008
Small intestine	0.790	1.021	0.905
Spinal cord	0.002	0.002	0.002
Spleen	0.886	0.649	0.768
Stomach	0.044	0.047	0.046
Testes	0.064	0.054	0.059
Thymus	0.006	0.005	0.006
Thyroid	0.001	0.001	0.001

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