

Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Codeine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Male

Treatment Group (ppm)

(Day 7)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC _{0-T} (ng/mL*hr)	350 ± 30	1566 ± 117	4894 ± 336
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Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Male

Treatment Group (ppm)

(Day 21)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	143 ± 21	635 ± 49	2668 ± 236
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Experiment Number: K61541C

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Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Male

Treatment Group (ppm)

(Day 90)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	224 ± 26	1237 ± 118	1681 ± 136
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Experiment Number: K61541C
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Toxicokinetics Data Summary
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Request Time: 10:03:16
Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Female

Treatment Group (ppm)

(Day 7)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	572 ± 41	1633 ± 90	4820 ± 292
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Experiment Number: K61541C

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Toxicokinetics Data Summary

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CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Female

Treatment Group (ppm)

(Day 21)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	368 ± 24	1319 ± 77	3631 ± 353
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Experiment Number: K61541C
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Species/Strain: Rats/F344

Toxicokinetics Data Summary
Compound: Codeine / **Analyte:** Codeine
CAS Number: 76-57-3

Request Date: 7/11/2023
Request Time: 10:03:16
Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Female

Treatment Group (ppm)

(Day 90)

400 Dosed Feed Plasma^{b,c}

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^{b,d}

AUC_0-T (ng/mL*hr)	394 ± 29	985 ± 65	3350 ± 391
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Total Codeine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Male

Treatment Group (ppm)

(Day7)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC _{0-T} (ng/mL*hr)	358 ± 33	1567 ± 120	4958 ± 387
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / Analyte: Total Codeine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Male

Treatment Group (ppm)

(Day 21)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	175 ± 37	632 ± 46	2689 ± 234
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Total Codeine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Male

Treatment Group (ppm)

(Day 90)

400 Dosed Feed Plasma^{b,e}

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^{b,f}

AUC_0-T (ng/mL*hr)	289 ± 26	1492 ± 144	3042 ± 150
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Total Codeine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Female

Treatment Group (ppm)

(Day 7)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC _{0-T} (ng/mL*hr)	581 ± 35	1676 ± 104	4870 ± 270
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Total Codeine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Female

Treatment Group (ppm)

(Day 21)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	395 ± 26	1380 ± 84	3727 ± 380
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Total Codeine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Male

Treatment Group (ppm)

(Day 90)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	639 ± 48	1547 ± 101	3876 ± 395
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Male

Treatment Group (ppm)

(Day 7)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma

AUC _{0-T} (ng/mL*hr)	427 ± 17	1018 ± 32	2069 ± 155
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Male

Treatment Group (ppm)

(Day 21)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	472 ± 15	676 ± 22	1429 ± 135
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Male

Treatment Group (ppm)

Day 90)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	368 ± 18	764 ± 30	1449 ± 35
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Female

Treatment Group (ppm)

(Day 7)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	382 ± 8	867 ± 76	1447 ± 97
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Experiment Number: K61541C

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Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Female

Treatment Group (ppm)

(Day 21)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	394 ± 16	840 ± 36	1508 ± 105
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / Analyte: Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Female

Treatment Group (ppm)

(Day 90)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	275 ± 25	609 ± 27	1079 ± 89
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Total Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Male

Treatment Group (ppm)

(Day 7)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC _{0-T} (ng/mL*hr)	3752 ± 296	13728 ± 1427	24970 ± 1357
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Total Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Male

Treatment Group (ppm)

(Day 21)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	3422 ± 122	3944 ± 180	15692 ± 1883
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Total Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Male

Treatment Group (ppm)

(Day 90)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	3206 ± 368	7050 ± 491	13102 ± 1195
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / Analyte: Total Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Female

Treatment Group (ppm)

(Day 7)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^{a,g}

AUC _{0-T} (ng/mL*hr)	3638 ± 143	18236 ± 1014	22506 ± 1325
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Total Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Female

Treatment Group (ppm)

(Day 21)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	2900 ± 87	3778 ± 238	13944 ± 1362
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine / **Analyte:** Total Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

Female

Treatment Group (ppm)

(Day 90)

400 Dosed Feed Plasma^b

800 Dosed Feed Plasma^b

1600 Dosed Feed Plasma^b

AUC _{0-T} (ng/mL*hr)	5084 ± 514	12002 ± 470	24254 ± 1647
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Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine

Analyte: Codeine/Total Codeine/Morphine/Total Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

LEGEND

MODELING METHOD & BEST FIT MODEL

^aAUC values calculated using trapezoidal rule, Yuan JH. 1993. Modeling blood/plasma concentrations in dosed feed and dosed drinking water toxicology studies. Toxicol. Appl. Pharmacol. 119, 131-141. No parameters shown.

^bAUC values calculated using trapezoidal rule

EXCEPTIONS

^cdiscrepancy-The original report give AUC value as 1002. Manuscript value is shown.

^ddiscrepancy-The original report give AUC value as 2742. Manuscript value is shown.

^ediscrepancy-The original report give AUC value as 1203. Manuscript value is shown.

^fdiscrepancy-The original report give AUC value as 3312. Manuscript value is shown.

^gdiscrepancy-The original report give AUC value as 25506. Manuscript value is shown.

ANALYTE

Codeine

Total Codeine

Morphine

Total Morphine

TK PARAMETERS

AUC_{0-T} = Area under the plasma concentration versus time curve, AUC, from time t_i (initial) to t_f (final), AUC_{last}

Experiment Number: K61541C

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine

Analyte: Codeine/Total Codeine/Morphine/Total Morphine

CAS Number: 76-57-3

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burrows Wellcome Company

TK PARAMETERS PROTOCOL

TK_DOSED FEED PLASMA

ANALYSIS METHOD

Approximate area under the curve (AUC) values over the 12-hour blood sampling period (dark cycle period) were determined by the trapezoidal rule. Unconjugated and total (unconjugated plus conjugated) concentrations of codeine and its metabolite, morphine, were determined in all plasma samples by separate radioimmunoassays for codeine or morphine, respectively. Determination of total levels involved assay after hydrolysis by a beta-glucuronidase preparation. See citation for description of a model that fits plasma concentrations to a dosed feed model that treats a dosed feed study as a series of consecutive gavage studies, with variable doses repeated at a small time interval such as 0.5 hours. Fit for Day 7 shown in Yuan J et al. 1994. Drug Metab. Dispos. Jan-Feb 22(1), 14-20. Model used for Day 7 was that from Yuan JH. 1993. Modeling blood/plasma concentrations in dosed feed and dosed drinking water toxicology studies. Toxicol. Appl. Pharmacol. 119, 131-141.

400 ppm, 800 ppm, 1600 ppm

In order to elucidate the disposition of codeine and/or some of its metabolites in the dose ranges studied in the full toxicology study (2-year dosed feed rat and mouse study (C61541C) TR455), plasma concentrations of these compounds were determined on three days during the first 90 days of the study in a special toxicokinetic study. Codeine base was administered in the feed (NIH-07) to male and female Fisher 344 rats ad libitum. The rats received 400, 800 and 1600 ppm of codeine base in the diet for up to 90 days. Blood samples were taken on study days 7, 21 and 90 from 5 rats from each treated group at each of 4 timepoints (0, 4, 8, and 12 hours) over the 12-hour dark cycle. Plasma was analyzed for unconjugated codeine, total codeine (unconjugated plus conjugated), unconjugated morphine, and total morphine (unconjugated plus conjugated) concentrations by radioimmunoassay. Only area under the curve (AUC) values were calculated. The animals were dosed and blood collected at one laboratory and the plasma samples shipped to a different laboratory for analysis. Start date is the date the original protocol was signed. Codeine intake in mg/day/kg body weight for the 400, 800, and 1600 ppm doses was 34.0, 69.1, 133.9 (males) and 35.6, 68.6, and 130.2 (females) for Day 7, respectively, 31.7, 64.0, and 135.1 (males) and 32.4, 63.5, and 137.2 (females) for Day 21, respectively, and 23.0, 44.3, 95.8 (males) and 24.1, 48.6, 110.0 (females) for Day 90, respectively. A second report has the 6 month and 12 month data for the full 2-year special study. Bioavailability for codeine on Day 7 was estimated as 10, 24, and 25 percent for 400, 800, and 1600 ppm dosed animals, respectively. Bioavailability of morphine from codeine diet in male rats was estimated to be 15, 20, and 20 percent for 400, 800, 1600 ppm dose groups, respectively.
