

Experiment Number: K61541B

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
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 3)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	298	828	7386
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Experiment Number: K61541B

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
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 5)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	365	1921	5330
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Experiment Number: K61541B

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
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 10)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	372	1608	4728
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Experiment Number: K61541B

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
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day3)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	1017	1283	2652
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Experiment Number: K61541B

Route: Dosed Feed

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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
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 5)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC _{0-T} (ng/mL*hr)	881	1242	3984
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Experiment Number: K61541B

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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
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 10)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	1421	1749	3954
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Experiment Number: K61541B

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
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 3)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC _{0-T} (ng/mL*hr)	403	1099	7492
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Experiment Number: K61541B

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
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 5)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	414	2217	6024
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Experiment Number: K61541B

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
Burroughs Wellcome Co.

Female

Treatment Group (ppm)

(Day 10)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	464	1829	5214
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Experiment Number: K61541B

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
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 3)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC _{0-T} (ng/mL*hr)	12908	20644	44494
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Experiment Number: K61541B

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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
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 5)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	14590	20300	54790
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Experiment Number: K61541B

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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
Burroughs Wellcome Co.

Female

Treatment Group (ppm)

(Day 10)

400 Dosed Feed Plasma^a

800 Dosed Feed Plasma^a

1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	27654	45288	103412
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Experiment Number: K61541B

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine Phosphate/ **Analyte:** Codeine

CAS Number: 52-28-8

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 3)

400 Dosed Feed Plasma^a 1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	243	4243
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Experiment Number: K61541B

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine Phosphate/ **Analyte:** Codeine

CAS Number: 52-28-8

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 5)

400 Dosed Feed Plasma^a 1600 Dosed Feed Plasma^a

AUC _{0-T} (ng/mL*hr)	270	3474
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Experiment Number: K61541B

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine Phosphate/ **Analyte:** Codeine

CAS Number: 52-28-8

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 10)

400 Dosed Feed Plasma^a 1600 Dosed Feed Plasma^a

AUC _{0-T} (ng/mL*hr)	221	4286
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Experiment Number: K61541B

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine Phosphate/ **Analyte:** Morphine

CAS Number: 52-28-8

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day3)

400 Dosed Feed Plasma^a 1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	925	5192
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Experiment Number: K61541B

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine Phosphate/ **Analyte:** Morphine

CAS Number: 52-28-8

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 5)

400 Dosed Feed Plasma^a 1600 Dosed Feed Plasma^a

AUC _{0-T} (ng/mL*hr)	895	3864
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Experiment Number: K61541B

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

Compound: Codeine Phosphate/ **Analyte:** Morphine

CAS Number: 52-28-8

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 10)

400 Dosed Feed Plasma^a 1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	1124	5218
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Experiment Number: K61541B

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

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

CAS Number: 52-28-8

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 3)

400 Dosed Feed Plasma^a 1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	310	4510
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Experiment Number: K61541B

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

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

CAS Number: 52-28-8

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 5)

400 Dosed Feed Plasma^a 1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	305	3856
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Experiment Number: K61541B

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

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

CAS Number: 52-28-8

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burroughs Wellcome Co.

Female

Treatment Group (ppm)

(Day 10)

400 Dosed Feed Plasma^a 1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	328	4582
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Experiment Number: K61541B

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

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

CAS Number: 52-28-8

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 3)

400 Dosed Feed Plasma^a 1600 Dosed Feed Plasma^a

AUC _{0-T} (ng/mL*hr)	15300	51414
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Experiment Number: K61541B

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

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

CAS Number: 52-28-8

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burroughs Wellcome Co.

Male

Treatment Group (ppm)

(Day 5)

400 Dosed Feed Plasma^a 1600 Dosed Feed Plasma^a

AUC_0-T (ng/mL*hr)	14972	52362
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Experiment Number: K61541B

Route: Dosed Feed

Species/Strain: Rats/F344

Toxicokinetics Data Summary

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

CAS Number: 52-28-8

Request Date: 7/11/2023

Request Time: 10:03:16

Lab: Microbiological Assoc, Inc
Burroughs Wellcome Co.

Female

Treatment Group (ppm)

(Day 10)

400 Dosed Feed Plasma^a 1600 Dosed Feed Plasma^a

AUC _{0-T} (ng/mL*hr)	27400	106904
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Experiment Number: K61541B

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
Burroughs Wellcome Co.

LEGEND

MODELING METHOD & BEST FIT MODEL

^aAUC values calculated using trapezoidal rule

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}

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Approximate area under the curve (AUC) values over the 20-hour blood sampling period were determined by the trapezoidal rule. Neither plasma concentrations nor AUC values were normalized for the differences in base equivalent content of the 400- and 1600-ppm codeine phosphate doses (295 and 1180 ppm base) and the 400-, 800- and 1600-ppm directly administered doses of codeine base. 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.

Experiment Number: K61541B

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
Burroughs Wellcome Co.

TK PARAMETERS PROTOCOL (cont'd)

TK_DOSED FEED PLASMA

400 ppm, 800 ppm, 1600 ppm Male and Female

Codeine base or codeine phosphate was administered in the feed (NIH-31) to male Fisher 344 rats ad libitum. The rats received 400, 800 and 1600 ppm of codeine base or 400 and 1600 ppm codeine phosphate in the diet for up to 10 days. Blood samples were taken on study days 3, 5 and 10 from subgroups of 3 rats from each drug-treated group at each of 6 timepoints beginning at noon and continuing until 8 AM the next morning. Plasma was analyzed for total (unconjugated plus conjugated) morphine concentrations by radioimmunoassay. Only area under the curve (AUC) values were calculated.