**Experiment Number:** S0361
**Route:** IV, Gavage
**Species/Strain:** Mouse/B6C3F1

**Toxicokinetics Data Summary**
**Compound:** Pentachloroanisole/ **Analyte:** Pentachloroanisole
C**AS Number:** 1825-21-4

**Request Date:** 7/11/2023
**Request Time:** 10:03:16
**Lab:** NIEHS_Midwest Research Institute

**Male**

| | Treatment Group (mg/kg) | | | |
|---|---|---|---|---|
| | **10 IV Plasma[a,d]** | **10 Gavage Plasma[b,d]** | **20 Gavage Plasma[b,d]** | **40 Gavage Plasma[b,d]** |
| Cmax (ug/mL) | | 0.06 ± 0.007 | 0.22 ± 0.17 | 0.44 ± 0.03 |
| AUC_0-T (ug/mL/hr) | 1.26 ± 0.24 | 0.41 ± 0.04 | 1.19 ± 0.06 | 4.62 ± 0.37 |
| F (percent) | | 33 ± 7 | 48 ± 9 | 95 ± 20 |

**Experiment Number:** S0361
**Route:** IV, Gavage
**Species/Strain:** Mouse/B6C3F1

**Toxicokinetics Data Summary**
**Compound:** Pentachloroanisole/ **Analyte:** Pentachloroanisole
C**AS Number:** 1825-21-4

**Request Date:** 7/11/2023
**Request Time:** 10:03:16
**Lab:** NIEHS_Midwest Research Institute

**Female**

| | Treatment Group (mg/kg) | | | |
|---|---|---|---|---|
| | **10 IV Plasma[a,d]** | **10 Gavage Plasma[b,d]** | **20 Gavage Plasma[b,d]** | **40 Gavage Plasma[b,d]** |
| Cmax (ug/mL) | | 0.049 ± 0.0012 | 0.13 ± 0.03 | 0.35 ± 0.08 |
| AUC_0-T (ug/mL/hr) | 1.10 ± 0.23 | 0.38 ± 0.15 | 0.77 ± 0.11 | 3.58 ± 0.33 |
| F (percent) | | 35 ± 15 | 35 ± 9 | 71 ± 15 |

**Experiment Number:** S0361
**Route**: IV, Gavage
**Species/Strain:** Mouse/B6C3F1

**Toxicokinetics Data Summary**
**Compound:** Pentachloroanisole/ **Analyte:** Pentachlorophenol
C**AS Number:** 1825-21-4

**Request Date:** 7/11/2023
**Request Time:** 10:03:16
**Lab:** NIEHS_Midwest Research Institute

**Male**

| | Treatment Group (mg/kg) | | | |
|---|---|---|---|---|
| | **10 IV Plasma[a,d]** | **10 Gavage Plasma[c,d]** | **20 Gavage Plasma[c,d]** | **40 Gavage Plasma[c,d]** |
| Cmax (ug/mL) | 26.85 ± 0.851 | 28.8 ± 0.74 | 40.3 ± 3.4 | 103 ± 7.6 |
| AUC_0-T (ug/mL/hr) | 412 ± 16 | 560 ± 19 | 984 ± 66 | 1752 ± 111 |

**Experiment Number:** S0361
**Route:** IV, Gavage
**Species/Strain:** Mouse/B6C3F1

**Toxicokinetics Data Summary**
**Compound:** Pentachloroanisole/ **Analyte:** Pentachlorophenol
C**AS Number:** 1825-21-4

**Request Date:** 7/11/2023
**Request Time:** 10:03:16
**Lab:** NIEHS_Midwest Research Institute

**Female**

| | Treatment Group (mg/kg) | | | |
|---|---|---|---|---|
| | **10 IV Plasma[a,d]** | **10 Gavage Plasma[c,d]** | **20 Gavage Plasma[c,d]** | **40 Gavage Plasma[c,d]** |
| Cmax (ug/mL) | 31.62 ± 1.9 | 34.2 ± 2.5 | 62.9 ± 2.5 | 115 ± 1.5 |
| AUC_0-T (ug/mL/hr) | 468 ± 21 | 551 ± 24 | 1001 ± 29 | 1759 ± 34 |

LEGEND

MODELING SOFTWARE

NONLIN

MODELING METHOD & BEST FIT MODEL

[a]NONLIN, Two-compartmental model with first-order elimination. AUC estimated using the trapezoidal rule with an endpoint correction based on the estimated elimination half-life.

[b]NONLIN, open one-compartmental model. AUC estimated using the trapezoidal rule with an endpoint correction based on the estimated elimination half-life.

[c]NONLIN, open one-compartmental model. AUC estimated using the trapezoidal rule with an endpoint correction based on the estimated elimination half-life. No intravenous data for PCP in mice so bioavailability not calculated.

EXCEPTIONS

Cmax = Observed or Predicted Maximum plasma (or tissue) concentration
AUC_0-T = Area under the plasma concentration versus time curve, AUC, from time ti (initial) to tf (final), AUClast
F = Bioavailability, absolute bioavailability

ANALYTE

Pentachloroanisole
Pentachlorophenol

TK PARAMETERS

[d]Cmax and F variation is standard deviation not standard error. Endpoint correction using terminal half-life of 5 hours for male and female rats.(sic should be mice)

TK Parameters (cont'd)

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Pentachloroanisole (PCA) samples were analyzed by gas chromatography using electron capture detection with aldrin in hexane as the internal standard. The PCA limit of detection was 0.025 ug/mL for iv and less than 0.9 ug/mL for the gavage studies.

TK_INTRAVENOUS PLASMA

10 mg/kg Male and Female

These toxicokinetic values were listed in the TR 414 Appendix H. NONLIN (Metzer et al. 1974. A package of computer programs for pharmacokinetic modeling. Biometrics 30, 562-563) was used to evaluate the concentration versus time curves. Initial values used in the NONLIN program were estimated by a curve stripping method. The area under the plasma curve (AUC) were estimated for all dose groups using the trapezoidal rule with an endpoint correction based on the estimated terminal elimination half-life. The standard error of the area under the concentration versus time curve was calculated based on the standard error of plasma concentrations at each time point using Microsoft Excel (Microsoft Corporation, Redmond, WA). Bioavailability of pentachloroanisole (PCA) was estimated, based on the ratio of the AUC values of PCA obtained in gavage study to those AUC values of PCA obtained in the intravenous study. Linear regression analysis was performed using KaleidaGraph (Synergy Software, Reading PA, USA). Raw data for the pentachlorophenol (PCA) 5 mg/kg intravenous injection is not shown (no report with data available unless it is the 5 mg/kg intravenous dose shown in the Pentachlorophenol S0328 toxicokinetic study (AUC values were 314 S.D. 14 and 295 S.D. 34 ug*h/mL for male and female rats)). However the calculated AUCs for that study are similar but not identical to the values listed in the TR which are 440 and 365 ug/ml/hr for male and female rat AUC values. The paper indicates the AUC values for the PCP 5 mg/kg administration were 322 SEM 9 and 298 SEM 25 ug*h/mL for male and female rats. The TR values were used to calculate the bioavailability in rats for the PCP metabolite shown here. Mice were not administered PCP in this study so there are no AUC values for the PCP metabolite for mice. The TR 414 text lists for the intravenous studies the calculated clearance of 6.07 and 5.61 L/kg*hour for male and female rats, respectively, and 8.45 and 10.2 L/kg*hr for male and female mice, respectively.

TK PARAMETERS PROTOCOL (cont'd)

TK_INTRAVENOUS PLASMA (cont'd)

10 mg/kg Male and Female (cont'd)

The calculated volume of the central compartment was approximately 2.41 and 2.01 L/kg for male and female rats, respectively and 2.05 and 4.5 l/kg for male and female mice, respectively. The terminal elimination half-life of PCA in rats and mice were approximately 1.2 and 1.0 hours whereas for PCP in both rats and mice terminal half-life was estimated at approximately 8 hours. For gavage administered animals the terminal half-life of PCP in both rats and mice was estimated to be 5 to 9 hours. Start date listed here is the date samples were received by the analysis laboratory.

TK_GAVAGE PLASMA

10 mg/kg, 20 mg/kg, 40 mg/kg Male and Female

These toxicokinetic values were listed in the TR 414 Appendix H. NONLIN (Metzer et al. 1974. A package of computer programs for pharmacokinetic modeling. Biometrics 30, 562-563) was used to evaluate the concentration versus time curves. Initial values used in the NONLIN program were estimated by a curve stripping method. The area under the plasma curve (AUC) were estimated for all dose groups using the trapezoidal rule with an endpoint correction based on the estimated terminal elimination half-life. The standard error of the area under the concentration versus time curve was calculated based on the standard error of plasma concentrations at each time point using Microsoft Excel (Microsoft Corporation, Redmond, WA). Bioavailability of pentachloroanisole (PCA) was estimated, based on the ratio of the AUC values of PCA obtained in gavage study to those AUC values of PCA obtained in the intravenous study. Linear regression analysis was performed using KaleidaGraph (Synergy Software, Reading PA, USA). Raw data for the pentachlorophenol (PCA) 5 mg/kg intravenous injection is not shown (no report with data available unless it is the 5 mg/kg intravenous dose shown in the Pentachlorophenol S0328 toxicokinetic study (AUC values were 314 S.D. 14 and 295 S.D. 34 ug*h/mL for male and female rats)). However the calculated AUCs for that study are similar but not identical to the values listed in the TR which are 440 and 365 ug/ml/hr for male and female rat AUC values. The paper indicates the AUC values for the PCP 5 mg/kg administration were 322 SEM 9 and 298 SEM 25 ug*h/mL for male and female rats. The TR values were used to calculate the bioavailability in rats for the PCP metabolite shown here.

TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA (cont'd)

10 mg/kg, 20 mg/kg, 40 mg/kg Male and Female (cont'd)

Mice were not administered PCP in this study so there are no AUC values for the PCP metabolite for mice. The TR 414 text lists for the intravenous studies the calculated clearance of 6.07 and 5.61 L/kg*hour for male and female rats, respectively, and 8.45 and 10.2 L/kg*hr for male and female mice, respectively. The calculated volume of the central compartment was approximately 2.41 and 2.01 L/kg for male and female rats, respectively and 2.05 and 4.5 l/kg for male and female mice, respectively. The terminal elimination half-life of PCA in rats and mice were approximately 1.2 and 1.0 hours whereas for PCP in both rats and mice terminal half-life was estimated at approximately 8 hours. For gavage administered animals the terminal half-life of PCP in both rats and mice was estimated to be 5 to 9 hours. Start date listed here is the date samples were received by the analysis laboratory.

TK Parameters (cont'd)

TK PARAMETERS PROTOCOL

ANALYSIS METHOD

Pentachlorophenol (PCP) samples were analyzed by high performance liquid chromatography (HPLC) with ultraviolet absorbance (229 nm) using octanophenone as the internal standard. The PCP minimum detection limit (MDL) was 0.37 ug mL and minimum level of quantitation (MLQ) was 1 ug/mL.

TK_INTRAVENOUS PLASMA

10 mg/kg Male and Female

These toxicokinetic values were listed in the TR 414 Appendix H. NONLIN (Metzer et al. 1974. A package of computer programs for pharmacokinetic modeling. Biometrics 30, 562-563) was used to evaluate the concentration versus time curves. Initial values used in the NONLIN program were estimated by a curve stripping method. The area under the plasma curve (AUC) were estimated for all dose groups using the trapezoidal rule with an endpoint correction based on the estimated terminal elimination half-life. The standard error of the area under the concentration versus time curve was calculated based on the standard error of plasma concentrations at each time point using Microsoft Excel (Microsoft Corporation, Redmond, WA). Bioavailability of pentachloroanisole (PCA) was estimated, based on the ratio of the AUC values of PCA obtained in gavage study to those AUC values of PCA obtained in the intravenous study. Linear regression analysis was performed using KaleidaGraph (Synergy Software, Reading PA, USA). Raw data for the pentachlorophenol (PCA) 5 mg/kg intravenous injection is not shown (no report with data available unless it is the 5 mg/kg intravenous dose shown in the Pentachlorophenol S0328 toxicokinetic study (AUC values were 314 S.D. 14 and 295 S.D. 34 ug*h/mL for male and female rats)). However the calculated AUCs for that study are similar but not identical to the values listed in the TR which are 440 and 365 ug/ml/hr for male and female rat AUC values. The paper indicates the AUC values for the PCP 5 mg/kg administration were 322 SEM 9 and 298 SEM 25 ug*h/mL for male and female rats. The TR values were used to calculate the bioavailability in rats for the PCP metabolite shown here. Mice were not administered PCP in this study so there are no AUC values for the PCP metabolite for mice. The TR 414 text lists for the intravenous studies the calculated clearance of 6.07 and 5.61 L/kg*hour for male and female rats, respectively, and 8.45 and 10.2 L/kg*hr for male and female mice, respectively. The calculated volume of the central compartment was approximately 2.41 and 2.01 L/kg for male and female rats, respectively and 2.05 and 4.5 l/kg for male and female mice, respectively. The terminal elimination half-life of PCA in rats and mice were approximately 1.2 and 1.0 hours whereas for PCP in both rats and mice terminal half-life was estimated at approximately 8 hours. For gavage administered animals the terminal half-life of PCP in both rats and mice was estimated to be 5 to 9 hours. Start date listed here is the date samples were received by the analysis laboratory.

TK Parameters (cont'd)

TK PARAMETERS PROTOCOL (cont'd)

TK_GAVAGE PLASMA

10 mg/kg, 20 mg/kg, 40 mg/kg Male and Female

These toxicokinetic values were listed in the TR 414 Appendix H. NONLIN (Metzer et al. 1974. A package of computer programs for pharmacokinetic modeling. Biometrics 30, 562-563) was used to evaluate the concentration versus time curves. Initial values used in the NONLIN program were estimated by a curve stripping method. The area under the plasma curve (AUC) were estimated for all dose groups using the trapezoidal rule with an endpoint correction based on the estimated terminal elimination half-life. The standard error of the area under the concentration versus time curve was calculated based on the standard error of plasma concentrations at each time point using Microsoft Excel (Microsoft Corporation, Redmond, WA). Bioavailability of pentachloroanisole (PCA) was estimated, based on the ratio of the AUC values of PCA obtained in gavage study to those AUC values of PCA obtained in the intravenous study. Linear regression analysis was performed using KaleidaGraph (Synergy Software, Reading PA, USA). Raw data for the pentachlorophenol (PCA) 5 mg/kg intravenous injection is not shown (no report with data available unless it is the 5 mg/kg intravenous dose shown in the Pentachlorophenol S0328 toxicokinetic study (AUC values were 314 S.D. 14 and 295 S.D. 34 ug*h/mL for male and female rats)). However the calculated AUCs for that study are similar but not identical to the values listed in the TR which are 440 and 365 ug/ml/hr for male and female rat AUC values. The paper indicates the AUC values for the PCP 5 mg/kg administration were 322 SEM 9 and 298 SEM 25 ug*h/mL for male and female rats. The TR values were used to calculate the bioavailability in rats for the PCP metabolite shown here. Mice were not administered PCP in this study so there are no AUC values for the PCP metabolite for mice. The TR 414 text lists for the intravenous studies the calculated clearance of 6.07 and 5.61 L/kg*hour for male and female rats, respectively, and 8.45 and 10.2 L/kg*hr for male and female mice, respectively. The calculated volume of the central compartment was approximately 2.41 and 2.01 L/kg for male and female rats, respectively and 2.05 and 4.5 l/kg for male and female mice, respectively. The terminal elimination half-life of PCA in rats and mice were approximately 1.2 and 1.0 hours whereas for PCP in both rats and mice terminal half-life was estimated at approximately 8 hours. For gavage administered animals the terminal half-life of PCP in both rats and mice was estimated to be 5 to 9 hours. Start date listed here is the date samples were received by the analysis laboratory.