

In Vivo Tissue Distribution and Elimination of DUR-928, a First in Class Therapeutic for Treatment of Hepatic and Renal Disease

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INTRODUCTION

DUR-928 [5-cholesten-3 β ,25-diol 3-sulfate (25HC3S)] is a recently discovered endogenous sulfated oxysterol that has been shown to be an intracellular regulatory molecule in lipid metabolism, inflammatory responses, cell survival, and tissue regeneration. This first-in-class molecule is being developed for the treatment of hepatic and renal diseases.

MATERIALS & METHODS

The absorption, distribution, metabolism, and excretion (ADME) of (4-¹⁴C)-DUR-928-derived radioactivity were studied in rats. The plasma pharmacokinetics (PK), the routes of elimination and excretion, mass balance, tissue distribution, and tissue PK were determined using quantitative whole body autoradiography methods in male Sprague-Dawley (N=19) and male Long-Evans (N=9) rats following a single intravenous bolus dose of (4-¹⁴C)-DUR-928 at 10 mg/kg. Blood samples were collected for PK up to 72 hours post-dose. Urine and feces were collected through 168 hours (h) post-dose. Following blood collection, animals were euthanized by CO₂ inhalation and carcasses frozen for processing.

CONFLICT OF INTEREST DISCLOSURE

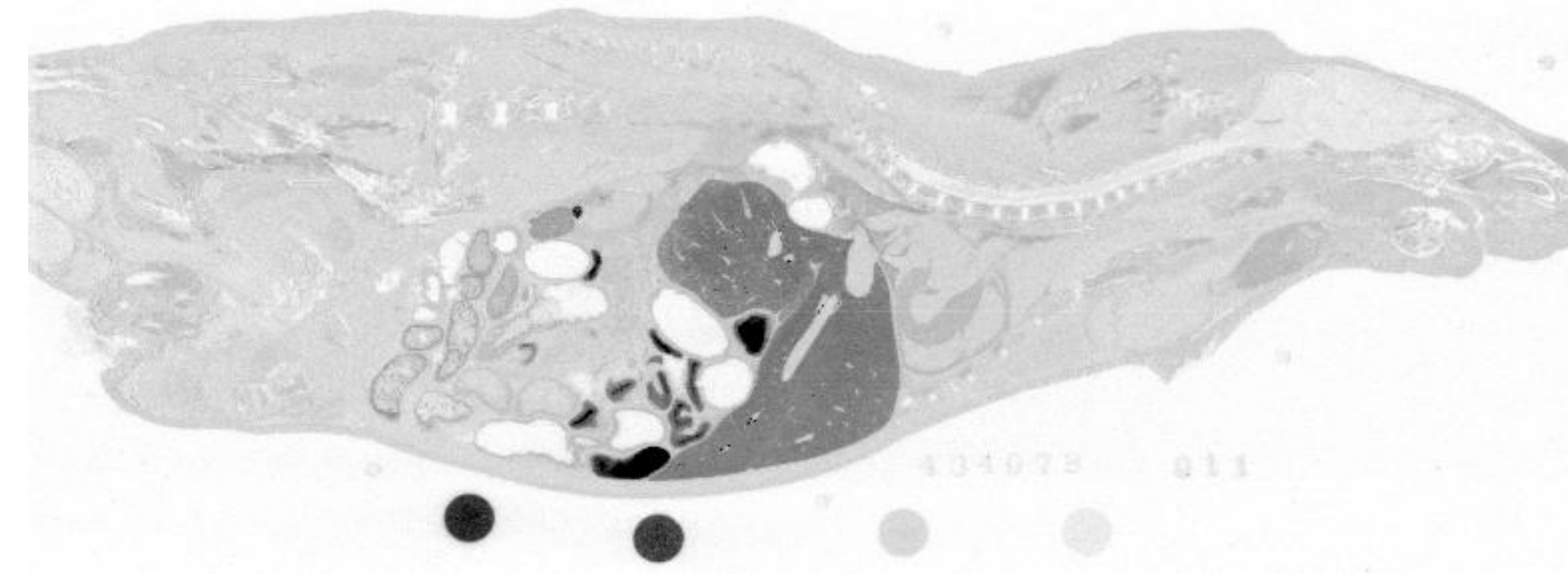
- The authors are employees of DURECT Corporation and may hold company stock/options.
- This presentation includes discussion of an investigational drug product in phase 2 development.

RESULTS

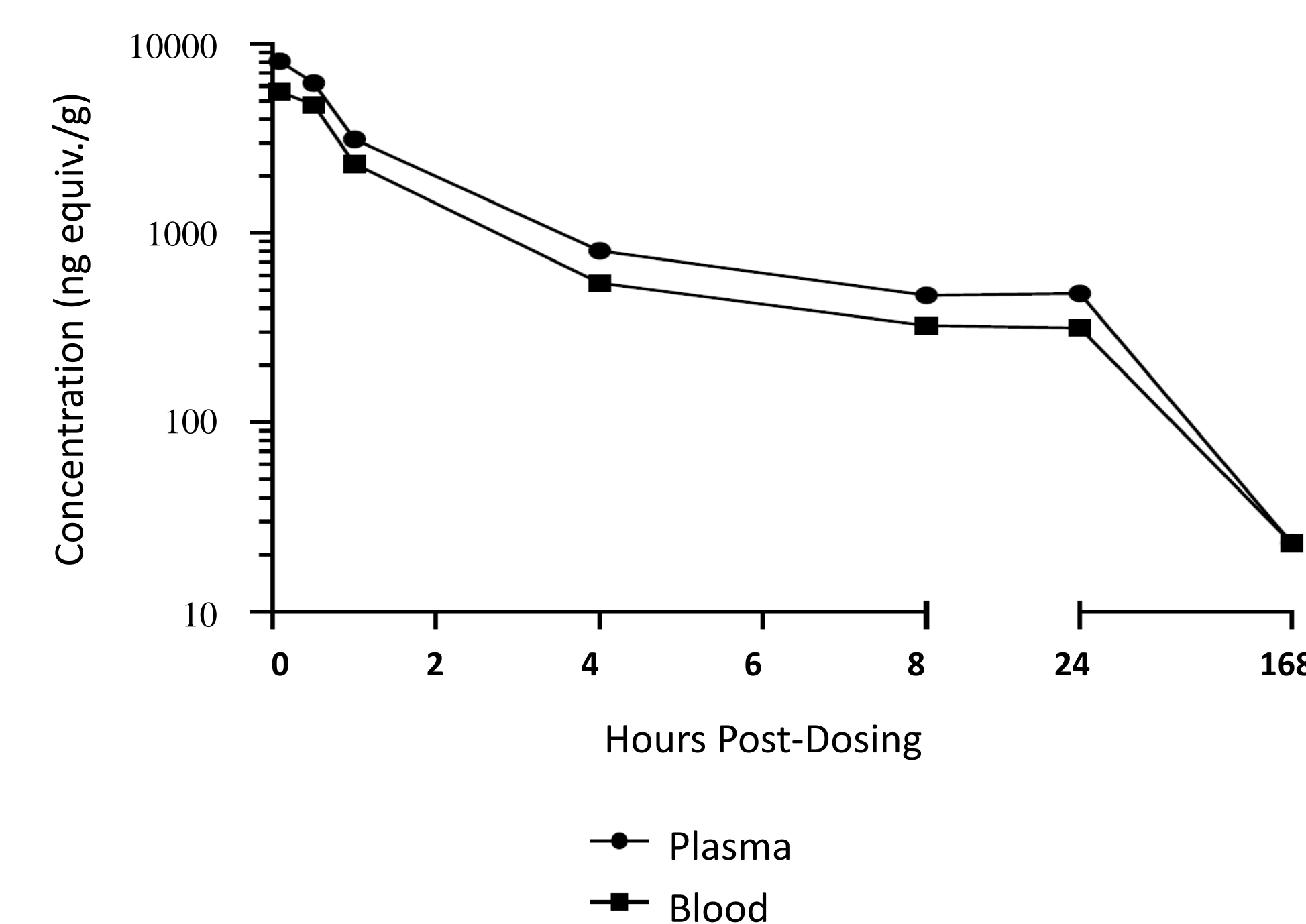
Pharmacokinetic Parameters of DUR-928 Equivalents in Plasma and Selected Tissues of Male Sprague-Dawley Rats Following an Intravenous Dose of 4-¹⁴C-DUR-928 at 10 mg/kg

Tissue	C _{max} (ng.equiv./g)	T _{max} (h)	T _{1/2} (h)	AUC _{last} (ng.equiv.h/g)	Tissue/Plasma AUC Ratio
Plasma	12,400	0.083	26.6	27,900	1.00
Kidney	44,000	0.083	11.1	73,700	2.32
Liver	87,900	0.083	48.4	364,000	11.4
Small Intestine (wall)	19,800	0.5	91.0	241,000	7.58

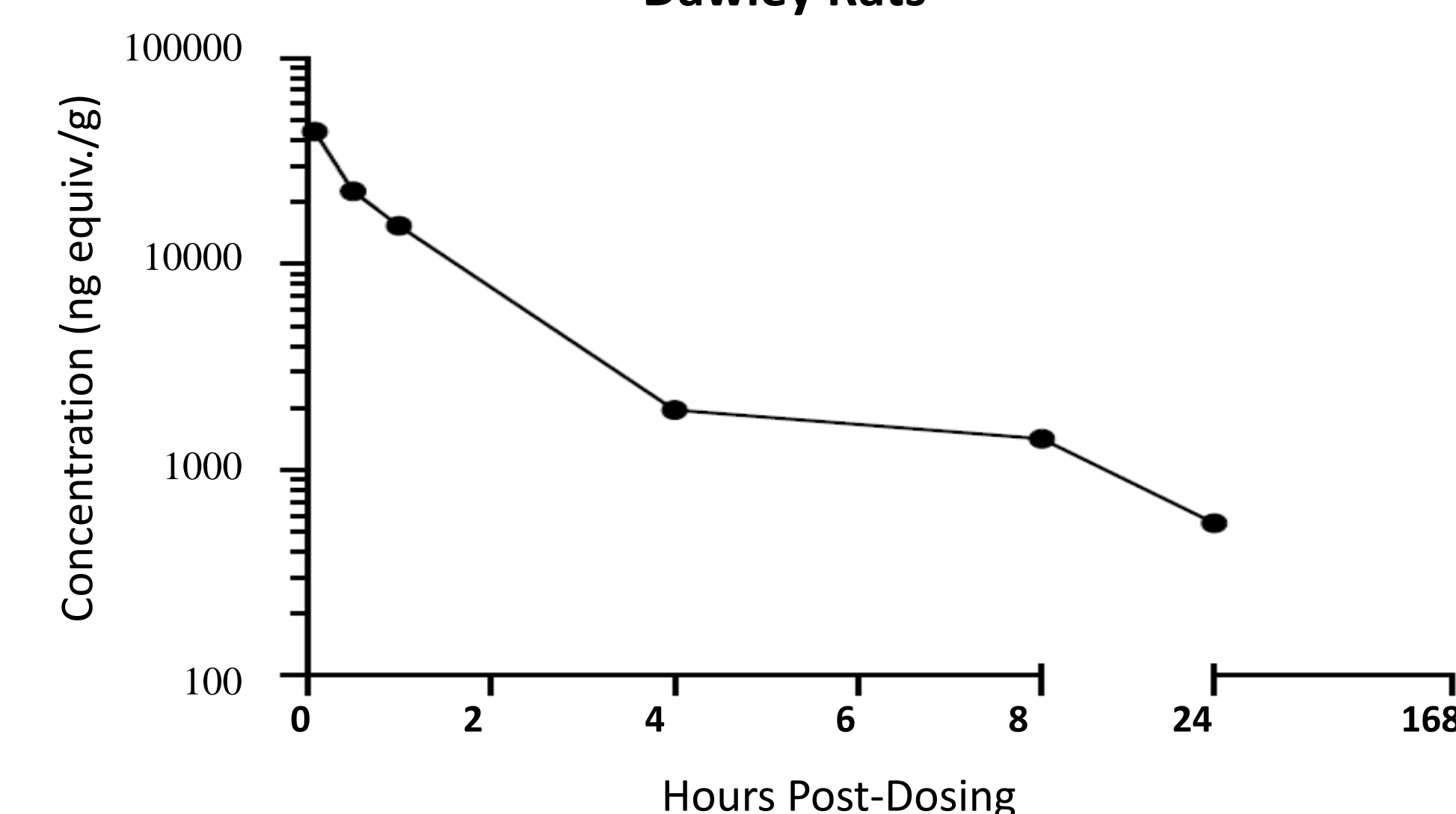
Whole Body Autoradioluminogram Showing Tissue Distribution of Radioactivity at 0.5 Hours following an Intravenous Dose of [4-¹⁴C]-DUR-928 to a Sprague Dawley Rat at 10 mg/kg



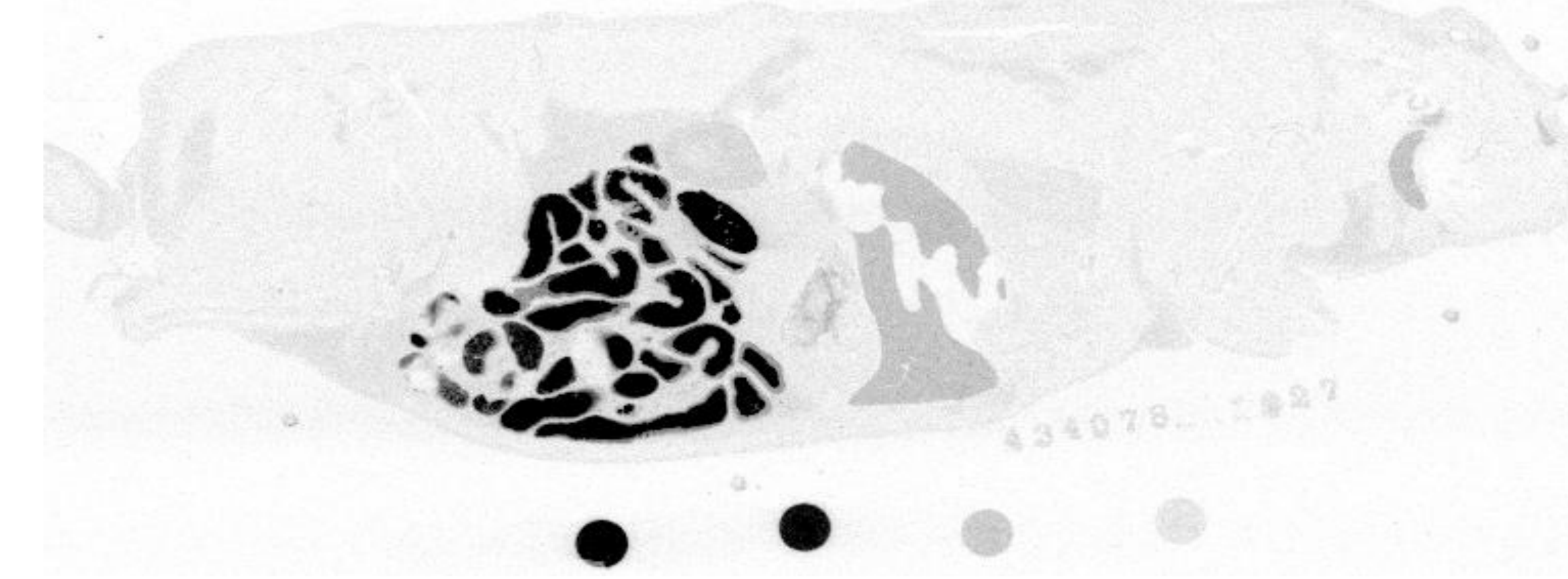
Mean Concentration of DUR-928 Equivalents in Rat Whole Blood and Plasma following an Intravenous Dose of [4-¹⁴C]-DUR-928 at 10 mg/kg



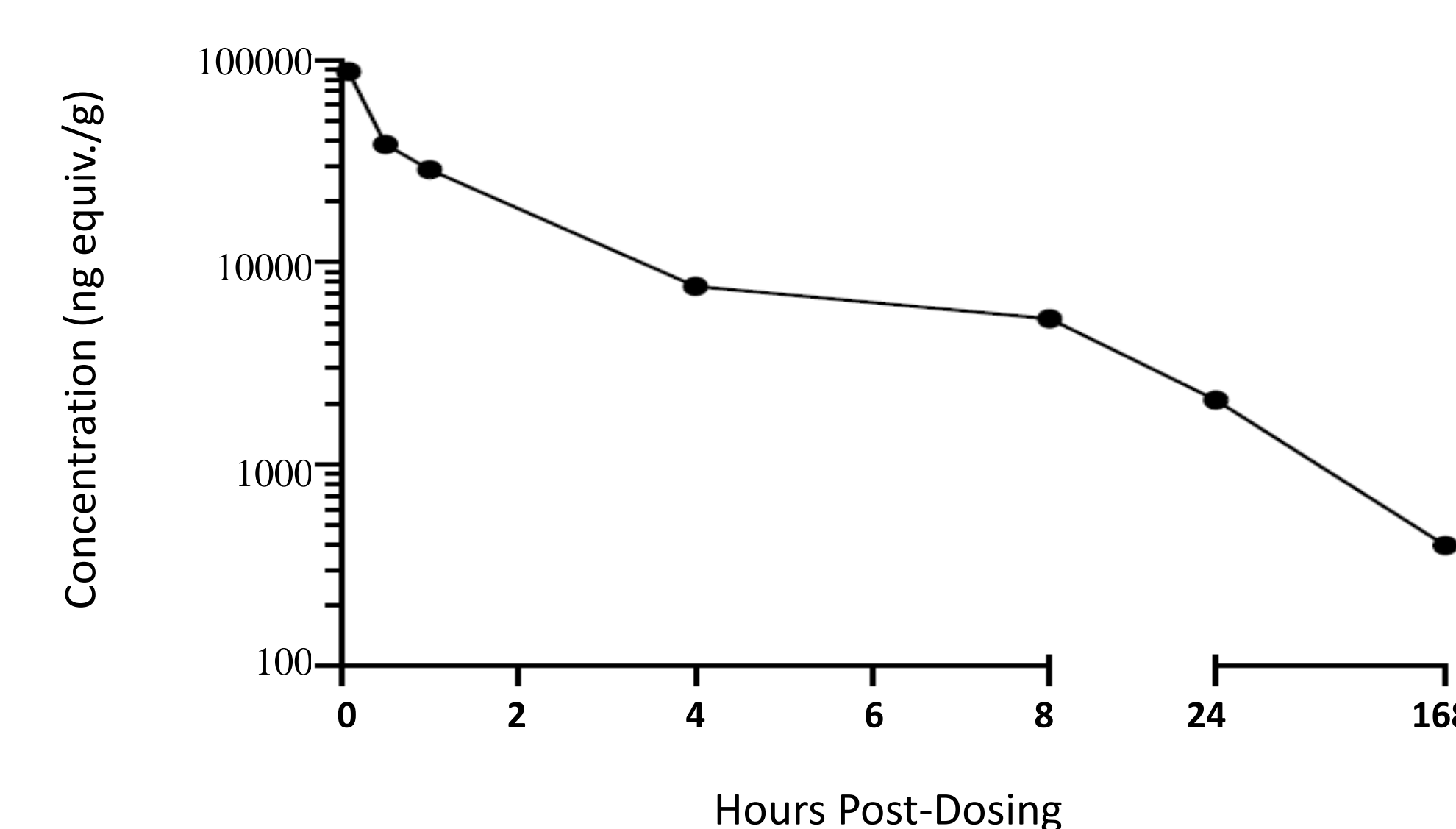
Concentration of DUR-928 Equivalents in Kidney following a Single Intravenous Dose of [4-¹⁴C]-DUR-928 at 10 mg/kg to Male Sprague Dawley Rats



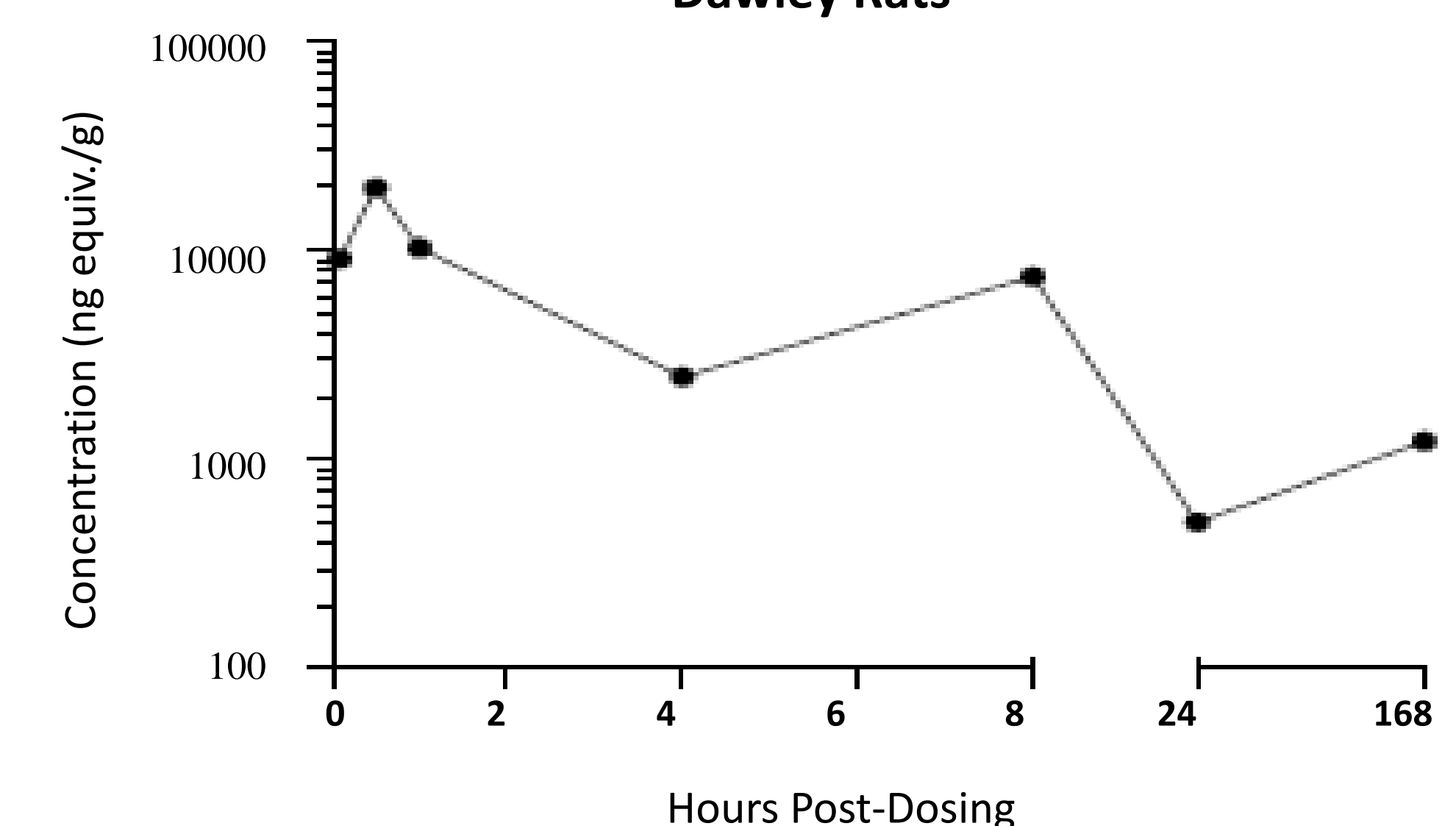
Whole Body Autoradioluminogram Showing Tissue Distribution of Radioactivity at 8 Hours following an Intravenous Dose of [4-¹⁴C]-DUR-928 to a Sprague Dawley Rat at 10 mg/kg



Concentration of DUR-928 Equivalents in Liver following a Single Intravenous Dose of [4-¹⁴C]-DUR-928 at 10 mg/kg to Male Sprague Dawley Rats



Concentration of DUR-928 Equivalents in Small Intestine (Wall) following a Single Intravenous Dose of [4-¹⁴C]-DUR-928 at 10 mg/kg to Male Sprague Dawley Rats



SUMMARY

- 100.2% of the administered dose was recovered in urine, feces, and cage rinse over the 168 hour collection period.
- DUR-928 and/or its metabolites were broadly distributed and detected by quantitative whole body autoradiography in all tissues except the eye (lens).
- 83% of the recovered radioactivity was in feces indicating that biliary excretion is the primary route of excretion in rats, with 84% of the dose recovered in the first 48 hours.
- Liver and small intestine wall had the highest AUCs for DUR-928-derived radioactivity relative to plasma.
- Notable exposures were measured in the kidney.
- DUR-928-derived radioactivity was below quantitation limit in most tissues by 168 hours postdose.

CONCLUSIONS

The current ADME study results highlight the preferential uptake of DUR-928 in selected target organs and support the continued development of DUR-928 for organ injury and disease involving the liver and kidney.

ACKNOWLEDGEMENTS

DURECT wishes to thank the ADME/DMPK department at Charles River Laboratories in Ashland, OH for generating the data contained in this poster. The authors also thank Myriam Theeuwes, MeeJ Kim and Karen Isobe for their contributions to this poster.