Biologically Based Prediction of Lactational and Early Post-Weaning Dosimetry

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ABSTRACT

Reproductive/developmental risk assessments for chemicals involve exposures during multiple life stages, but largely focus on the mother's exposure dose. Data on early life stage exposures, particularly for environmental chemicals, tend to be limited. Poorly characterized dosimetry during the lactational and early post-weaning periods is a substantial source of uncertainty in the extrapolation of rodent toxicity findings to humans. In the present study, a biologically based pharmacokinetic (BBPK) modeling approach, which is essentially predictive theoretical compartmental modeling incorporating realistic biological changes, was used to predict dosimetry in the young for chemicals with a range of characteristics. The model addressed the varied dosing methods used in multigenerational toxicological studies, including gavage, constant diet, and adjusted dietary exposures. Biological changes during lactation and early post-weaning periods in the mother and offspring were incorporated in the model including body weight changes in the mother and the growing offspring, maternal food consumption increases during lactation, changes in milk intake as offspring grow, high food consumption rates by the young after weaning, and changes in elimination capacity in the young. Post-natal exposure from various classes of chemicals was estimated and the impact of changing half-life, the milk to maternal plasma concentration ratio, and volume of distribution was evaluated. The present modeling showed that various exposure patterns during early postnatal periods are possible depending on the dosing method for the dam and biological and chemical factors that can affect pharmacokinetics in the dam and pup. The model developed in this study will contribute to better interpretation of reproductive and developmental studies by providing information to help to design pharmacokinetic studies for the early life period. Consequently, this study will contribute to reducing current uncertainties in extrapolation of animal data to humans by providing a means to make initial estimates of early life stage exposure in rats. (Supported by EPA-NRC #CR82879001. This abstract may not represent official EPA policy.)

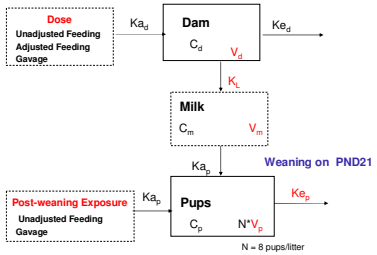
OBJECTIVE

To predict lactational and early post-weaning dosimetry according to

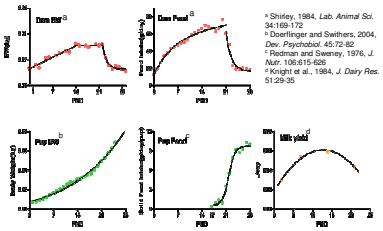
- Different dosing approaches in toxicity studies
  - **Gavage**: constant mg/kg/day to dam
  - **Diet or drinking water:** ***Unadjusted*** constant ppm
    Up to 3-fold increased mg/day during lactation
  - **Diet:** ***Adjusted*** ppm during lactation
    ~constant mg/day during lactation to dam
- Different chemical properties
  - **Half life**
  - **Milk: dam's blood partition coefficient**
  - **Volume of distribution**

METHOD

BBPK Model Structure



Biological Data Incorporated



[a] Shirley, 1984, *Lab. Animal Sci.* 34:169-172
[b] Doerflinger and Swithers, 2004, *Dev. Psychobiol.* 45:72-82
[c] Redman and Sweney, 1976, *J. Nutr.* 106:615-626
[d] Knight et al., 1984, *J. Dairy Res.* 51:29-35

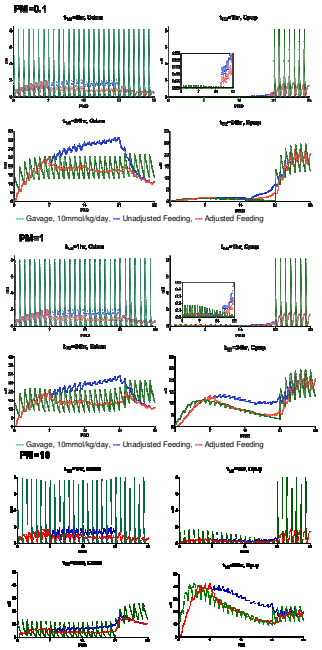
Chemical properties modeled

- Volume of distribution the same in the dam and pup
  Vd = Vp = 0.7 L/kg
- Half-life (Elimination rate constant)
  - the same in the dam and pup (no developmental changes in elimination capacity, already at adult level at birth)
  Kep = Ked = 0.7hr^{-1} or 0.03hr^{-1}
  - postnatal changes in the pup
  Ked = 0.7hr^{-1} or 0.03hr^{-1}
  Kep = R*Ked, where R=1*PND/(7+PND)
- Milk to blood partition coefficient
  - constant throughout lactation
  PM = 0.1, 1, or 10
- Lactational transfer of parent chemical only
- Absorption same in the dam and pup
  Kap = Kad = 2 hr^{-1}

RESULT

Predicted concentration in the dam and pup

with varying milk partition



--- Gavage, 10mmol/kg/day, — Unadjusted Feeding, — Adjusted Feeding

Chemical was mixed in food to produce ~10mmol/kg/day based on first week's food consumption,
Vd=Vp=0.7 L/kg
Kep=Ked

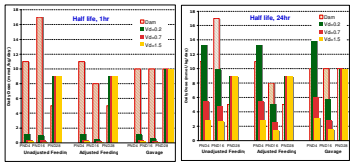
Simulated Cmax and AUC with postnatal development of elimination

Half life *	1hr		Cmax			AUC		
Dosing Mode	PND	Dam	Pup1[a]	Pup2[b]		Dam	Pup1	Pup2
Unadjusted Feeding	4	1.6	0.05	0.13		21	0.8	2.2
	16	2.1	0.03	0.04		35	0.6	0.9
	28	0.6	1.4	1.7		10	19	24
Adjusted Feeding	4	1.6	0.05	0.13		21	0.8	2.2
	16	1	0.02	0.02		17	0.3	0.5
	28	0.6	1.4	1.7		10	19	24
Gavage	4	8	0.2	0.3		20	0.8	2.1
	16	8	0.1	0.1		20	0.4	0.5
	28	8	8	9		20	20	26
Half life	24hr		Cmax			AUC		
Dosing Mode	PND	Dam	Pup1	Pup2		Dam	Pup1	Pup2
Unadjusted Feeding	4	16	9	15		327	182	280
	16	25	10	15		588	249	366
	28	12	20	25		259	432	535
Adjusted Feeding	4	16	9	15		327	182	280
	16	14	6	9		312	145	220
	28	12	20	25		255	431	532
Gavage	4	22	11	19		362	245	422
	16	21	6	9		339	146	221
	28	26	25	29		478	446	548

[a] Pup1 shows values simulated without modeling developmental increase in renal function
[b] Pup2 shows values simulated with modeling renal function development.
* Dam's half life
Pm=1, Vd=Vp=0.7L/kg

Prediction of Daily dose

with varying volume of distribution



Pm = 1
Kep=Ked

Benchmarking the model to 2,4-D data[a]

μg/ml / 15mg/kg	Cdam	Cmilk	Cpup
Sturtz et al.	26 ± 4	29 ± 3	6.3 ± 1.7
Simulation: Adjusted feeding No changes in $t_{1/2}$ during development	≈ 9	≈ 10	≈ 1.4
Simulation: Adjusted feeding Changes in $t_{1/2}$ during development	≈ 9	≈ 10	≈ 2.0

[a] 2,4-dichlorophenoxyacetic acid, Sturtz et al. 2006, Food Chem. Toxicol. 44:8-16 Recirculation between the dam and pups was modeled.
Pharmacokinetic parameters for 2,4-D were adapted from Timchack, 2004, Toxicol. 200:1-19

SUMMARY

Predicted lactational exposure of pups

- Various patterns were predicted depending on the pharmacokinetic properties of the dam.
- Greater differences between the dam and pups with shorter half life, lower milk secretion, and larger volume of distribution in the dam (lower exposure in the pups)
- Approaching or exceeding maternal levels for longer half-life compounds, especially with higher milk:plasma partition coefficient and smaller volume of distribution.
- The gavage and adjusted diet are more similar to each other than the unadjusted diet, except for peak concentrations for short half life compounds.
- Higher when pup elimination capacity was modeled to increase with age compared to the value predicted without modeling such age-dependent change.

Predicted post-weaning exposure of pups

- Higher than lactational exposure with pharmacokinetic factors in the dam such as shorter half life, lower milk secretion, and larger volume of distribution which also cause greater differences between the dam and pups during lactation
- Same as dam's exposure for gavage dosing
- Higher than dam's exposure for diet dosing

CONCLUSION

❑ Various exposure patterns during early postnatal periods are possible depending on the mode of exposure to the dam and biological/chemical factors that can affect pharmacokinetics in the dam and pup.

❑ The current model appears to capable of predicting early postnatal dosimetry at reasonable levels using limited pharmacokinetic information about the dam with biological information about the dam and the pups.

❑BBPK model can be used to design limited pharmacokinetic studies for the early life period to improve interpretation of reproductive and developmental studies.

❑ This work will contribute to reducing current uncertainties in extrapolation of animal data to humans by providing a means to make initial estimates of early life stage exposure in rats.

Acknowledgments

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