The Value of Priors and Prior Uncertainty in Clinical Trial Simulation: Case Study with Actinomycin-D in Children with Cancer

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Outline

- Trial Simulation for Pediatrics
  - Setting, Value, Regulatory
  - Basic Approach
- Actinomycin-D
  - Background and Objectives for Clinical Evaluation
  - Prior Information
- Model Elements
  - I/O (PK) Model
  - PD Model
  - Outcomes (Design) Model
- Proposal for Assigning Uncertainty
  - Valuation of Priors
- Current Status:

Trial Simulation for Pediatric Research

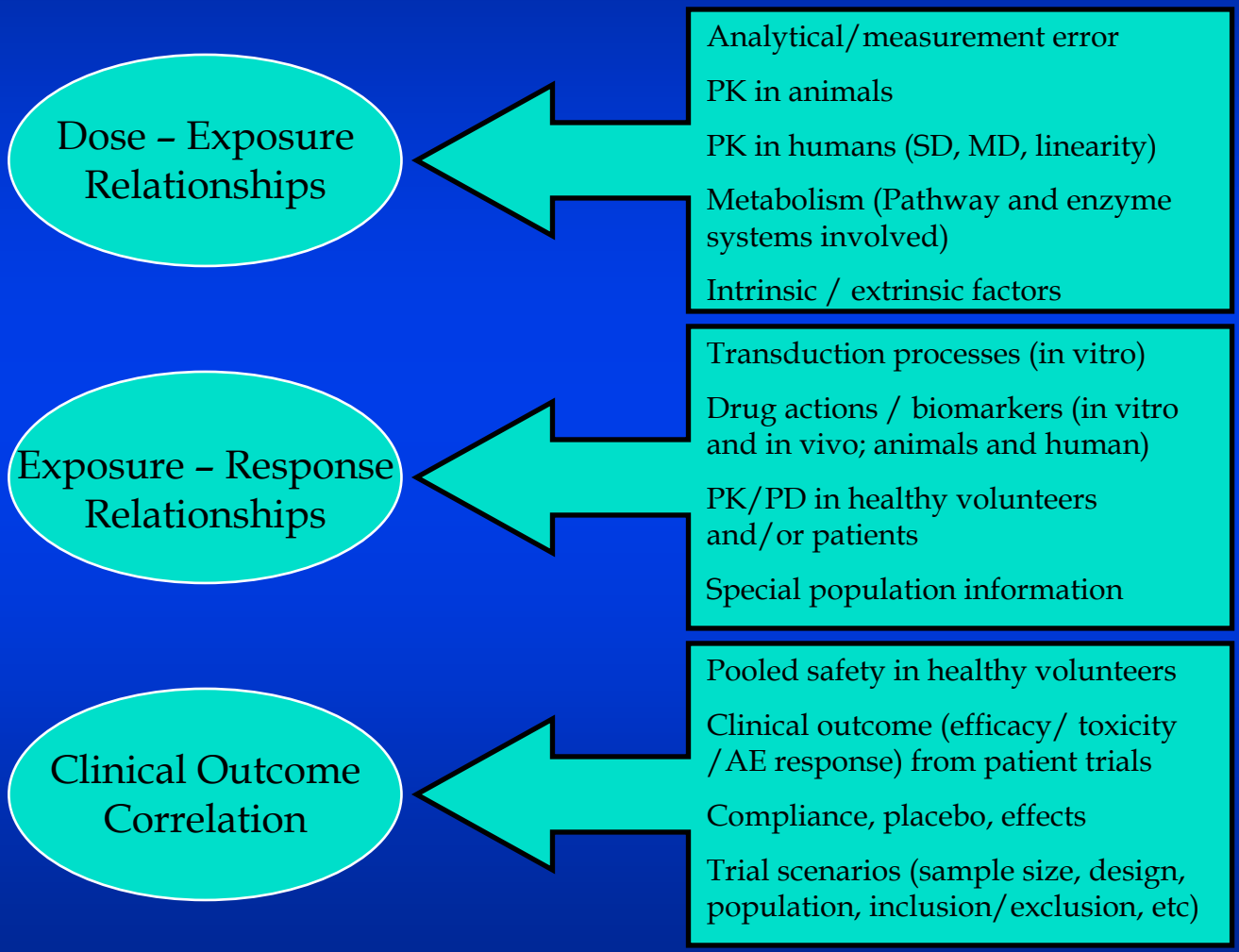
- 75% prescription drugs in children "off-label"
- Usage not described in package insert
- Approved indications
- Adequate controlled studies
- Consequences of off label usage
  - Benefit
  - No effect
  - Harm

Trial Simulation for Pediatric Research

- Unapproved is not improper
- Decision based on safety/efficacy data
- Medical literature vs Regulatory Community
- "Best medical judgment"

Trial Simulation

Assembling prior information



Actinomycin-D

Clinical Rationale for Study

- Actinomycin-D (AMD) is an antineoplastic agent.
- Despite its widespread use in pediatric oncology, there is limited knowledge as to its precise mechanism of action, and there is no PK information from which safe and appropriate dosing can be derived.
- In August of 2002, the Children's Oncology Group (COG) suspended 3 active protocols for pediatric rhabdomyosarcoma after 4 chemotherapy-associated deaths from veno-occlusive disease, as characterized by elevated liver enzymes and hyperbilirubinemia, abdominal pain, and weight gain.

Actinomycin-D

Clinical Rationale for Study

- There has been no subsequent evaluation as to the cause of these devastating side effects or correlation between toxicity and drug exposure.
- This has been hindered primarily by the limited pharmacokinetic knowledge of AMD.
- Because AMD is crucial to soft tissue sarcoma therapy, its use as an anti-neoplastic agent must continue and clinical evaluation is vital.

Actinomycin-D

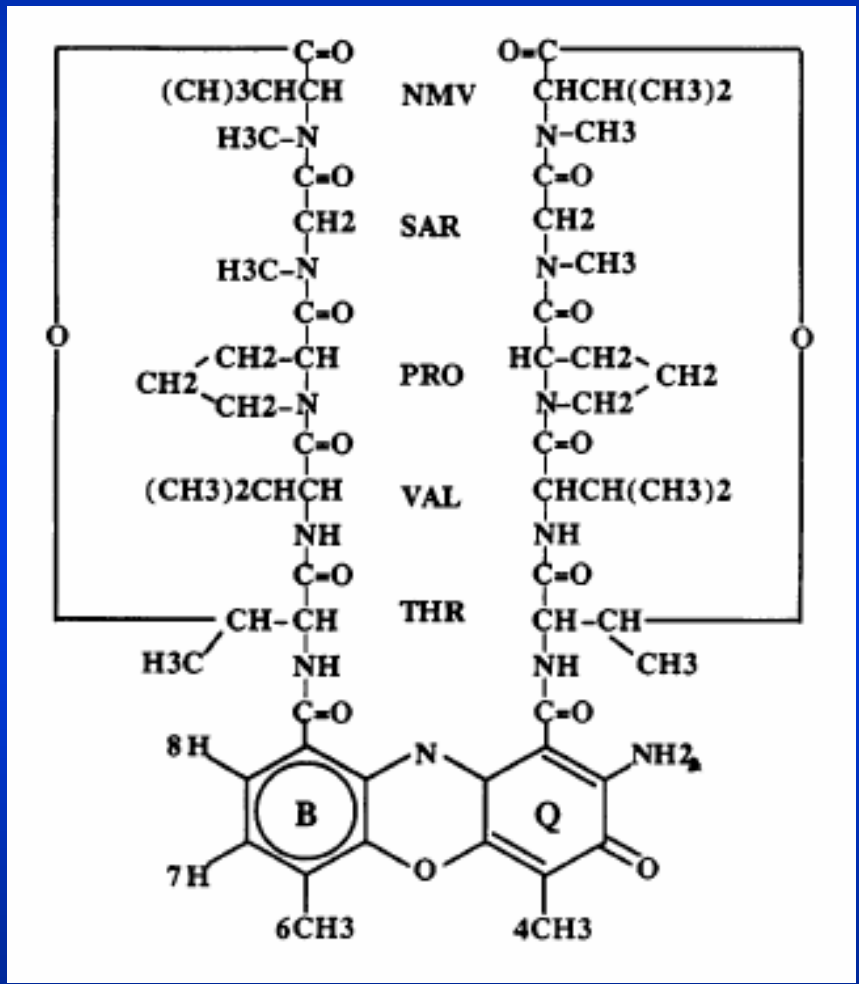
Clinical Setting - Rhabdomyosarcoma study dosing

Age	VCR dose	AMD dose	CPM dose	Adjustments
≥ 3 years	1.5 mg/m² IV Push (max dose 2.0 mg)	0.045 mg/kg one dose (max dose 2.5mg)	2.2 g/ m² IV as 30 minute infusion with IV fluids and MESNA	Omit AMD during radiotherapy
≥ 1 year < 3 years	0.05 mg/kg IV Push (max dose 2.0 mg) If child has turned 3 years old at time of therapy use guidelines in box above (≥ 3 years)	0.045 mg/kg one dose (max dose 2.5mg)	73 mg/kg/dose IV as 30 minute infusion with IV fluids and MESNA If child has turned 3 years old at time of therapy use guidelines in box above (≥ 3 years)	Omit AMD during radiotherapy
< 1 year	0.025 mg/kg IV Push ° If child has turned 1 year old at time of therapy use guidelines in box above (≥ 1 year and < 3 years)	0.025 mg/kg one dose° If child has turned 1 year old at time of therapy use guidelines in box above (≥ 1year and <3 years)	36 mg/kg° IV as 30 minute infusion with IV fluids and MESNA If child has turned 1 year old at time of therapy use guidelines in box above (≥ 1year and <3 years)	Omit AMD during radiotherapy

° For children still less than one year of age by week 12 of protocol, call the Study Chair for recommendations of upward dose adjustment for Vincristine, Actinomycin-D, and Cyclophosphamide.

Actinomycin-D

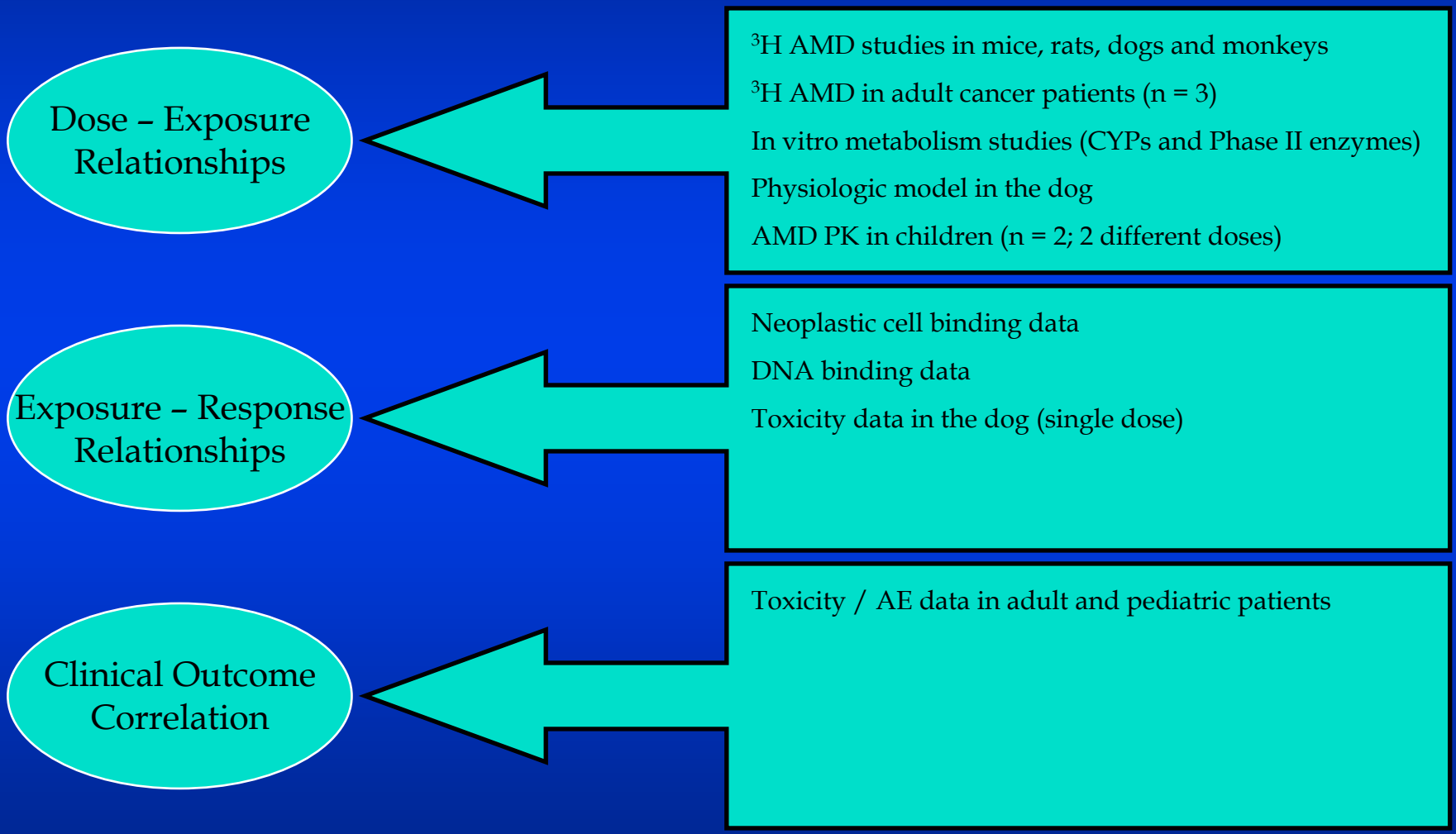
Structure – activity data



- A product of Streptomyces yeast (MW = 1255 Da).
- Cyclic polypeptide-based antibiotic that inhibits RNA synthesis by binding to guanine residues and inhibiting DNA-dependent RNA polymerase (Reich; Cancer Res 1963).
- The earliest report of actinomycins interacting with DNA is from 1960 (Kawamata; Nature 1960).
- Further elucidation into the stereochemistry of AMD and DNA binding was completed in 1972 via co-crystalization and hypothesized a working model for AMD activity (Jain; J. Mol Biol 1972).
- Appears to show preferential binding to neoplastic cells (Heened; Can Res 1973), and resistance appears to be related to inefficient drug transport (reference, use Biedler, 1970).
- In clinical use since 1954 (Farber, Adv Cancer Res; 1956), and has been used against many pediatric soft tissue cancers (Frei; Cancer Chemo Rep 1974), for example Wilms' tumor and rhabdomyosarcoma.

Actinomycin-D

Actual prior information



Actinomycin-D

Prior Knowledge – adult PK data

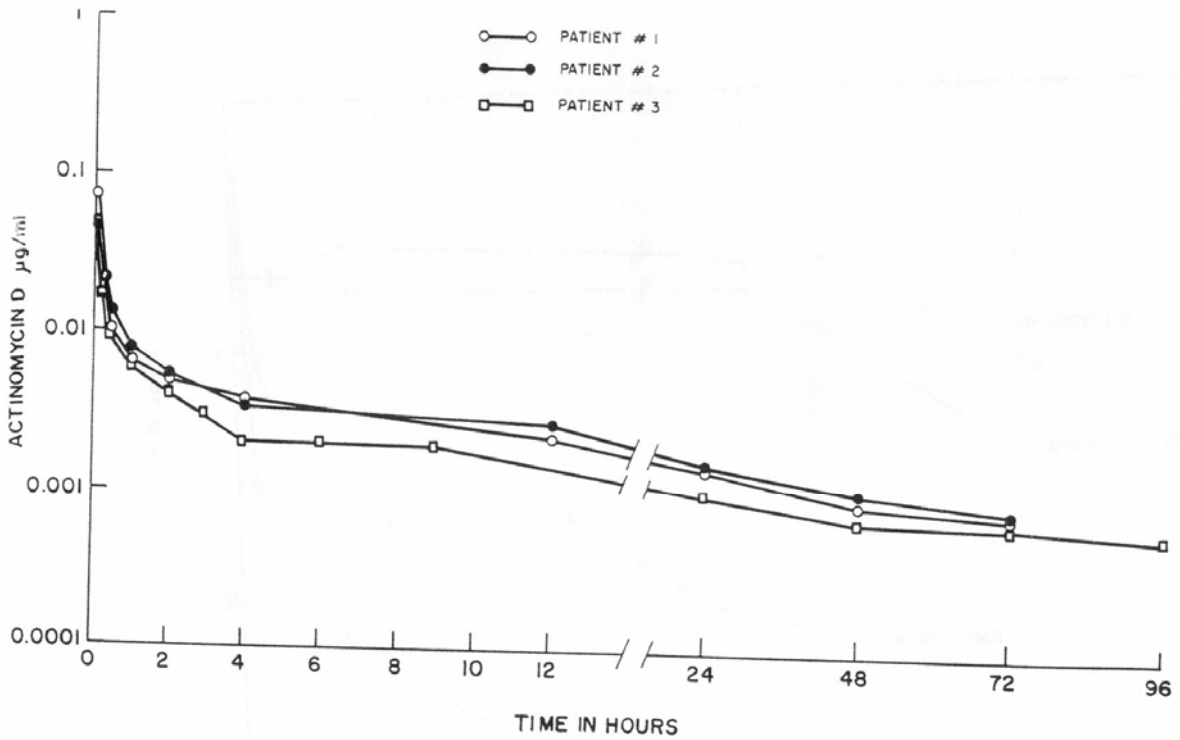


Fig. 1. Plasma disappearance of ^{3}H actinomycin D.

Actinomycin-D

Prior Knowledge – adult cellular disposition data

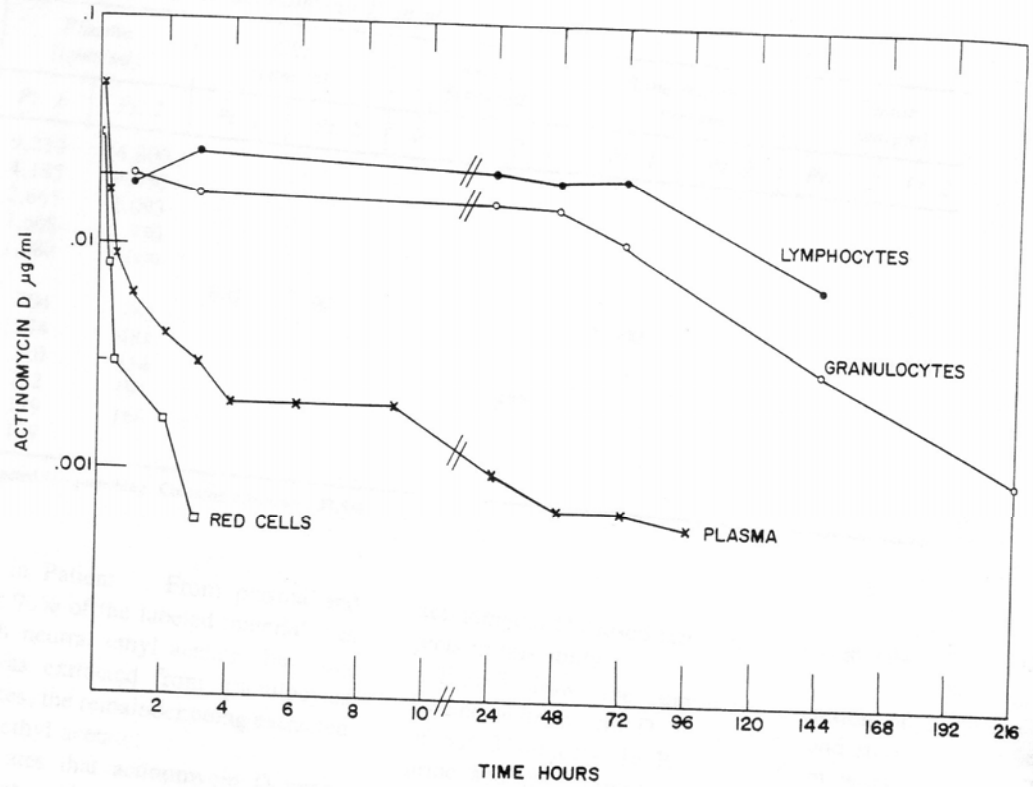
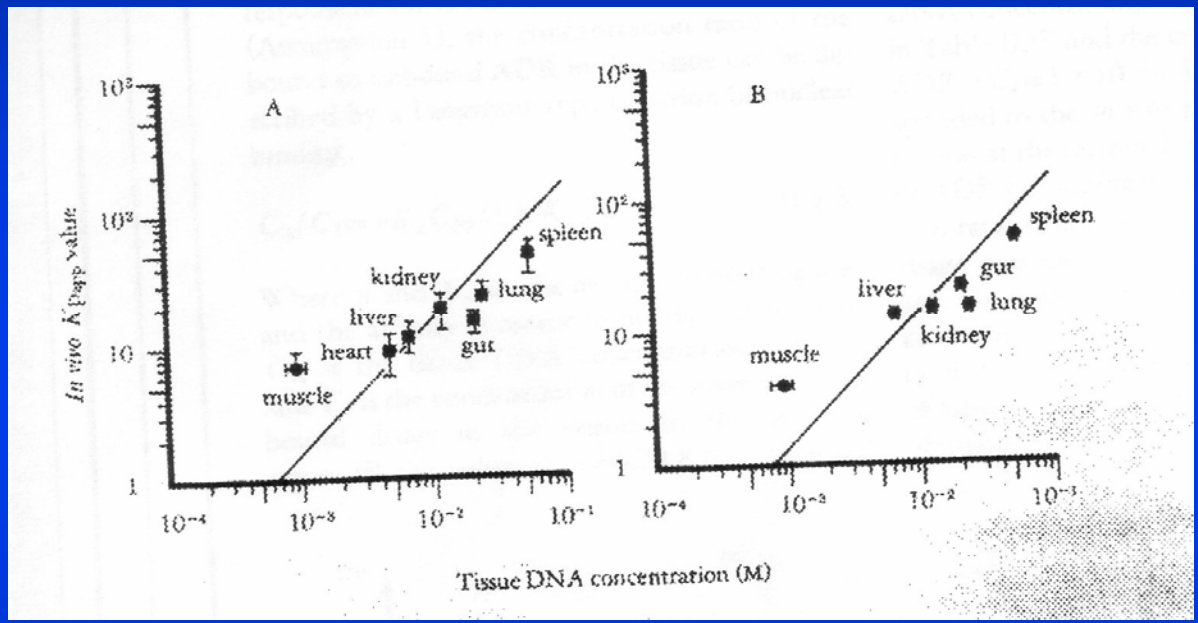


Fig. 2. ^{3}H actinomycin D clearance from the blood.

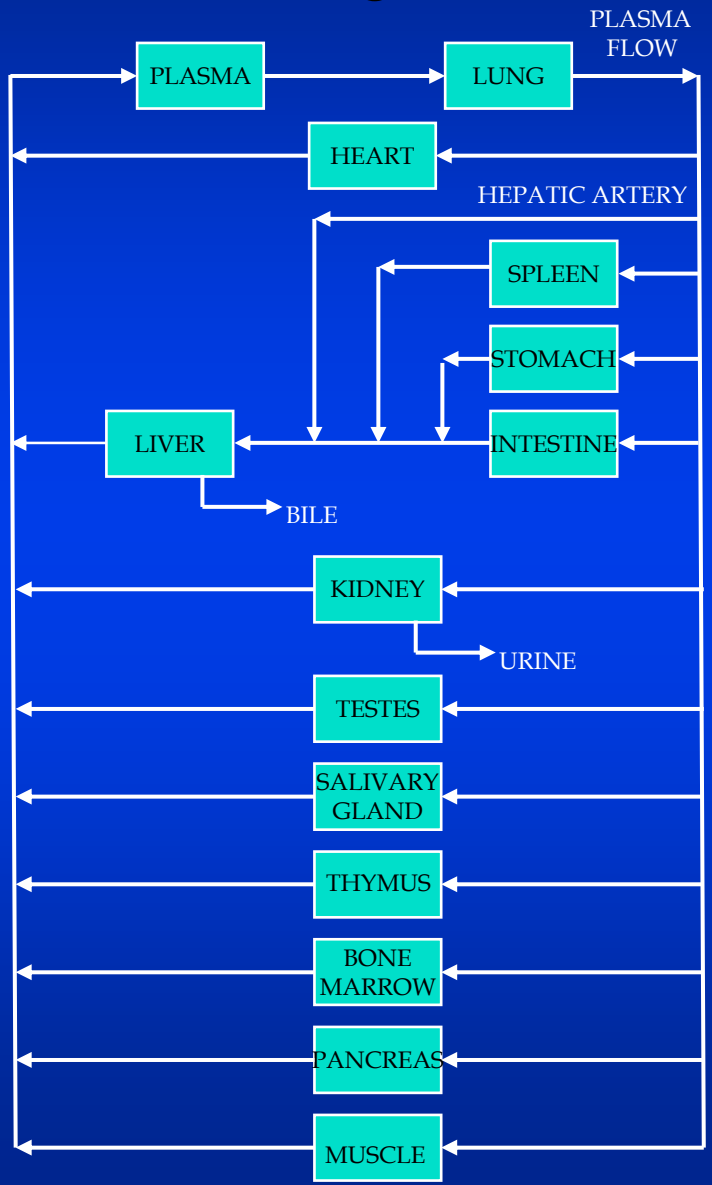
Actinomycin-D

Prior Knowledge – tissue distribution and nuclear binding data



Actinomycin-D

Prior Knowledge – PBPK data in the dog



- Beagle dog, flow-limited PBPK model (Lutz et. al., JPET 200(3): 469-478, 1977)
- Simulations validated against iv doses of 0.6 and 2.7 mg/m^2 (approximately 0.03 and 0.135 mg/kg) based on systemic and tissue exposure of ^{3}H-AMD
- Data (exposures) used to support the model collected at 3 hours and on days 1, 2, 3, 4 and 5
- Simple mass balance relationships for each tissue based on
  - Accumulation = net perfusion – clearance

Actinomycin-D

Prior Knowledge – PK data in the children

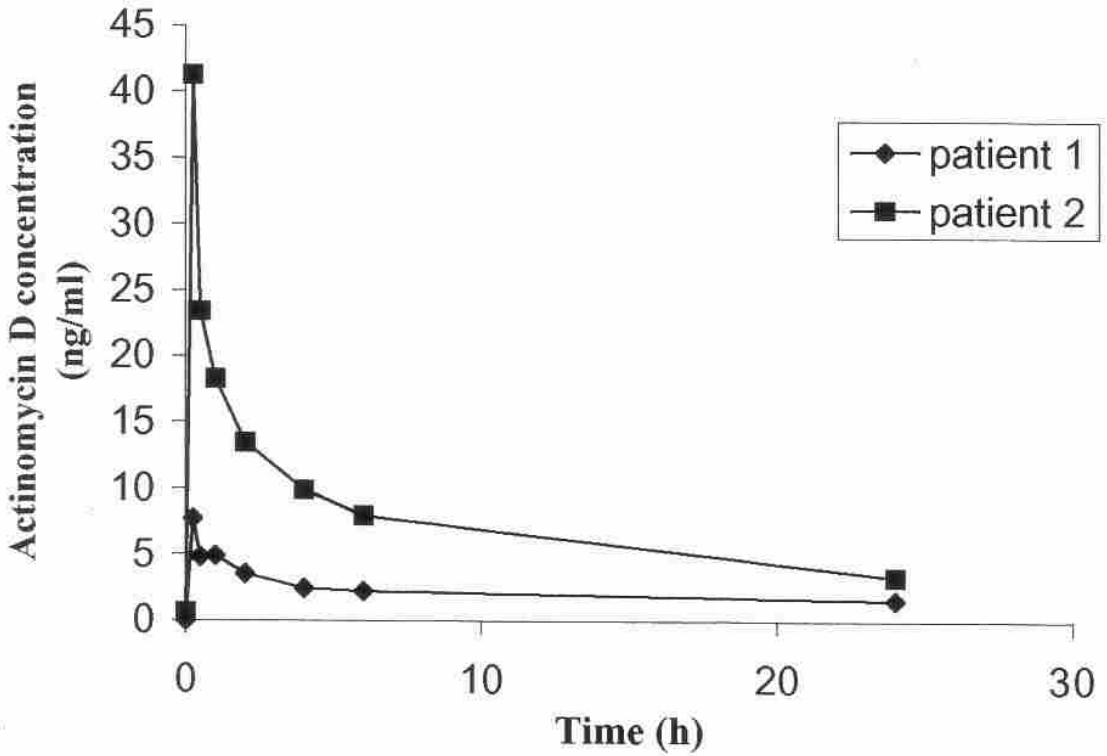


Fig. 3. Plasma pharmacokinetics of actinomycin D following doses of 0.75 mg/m^2 (patient 1) and 1.5 mg/m^2 (patient 2).

- Analytical paper (Veal et. al., 2004)
- Data in 2 patients administered different doses of AMD
- Age and BW not provided

Actinomycin-D

I/O Model: Dose-concentration prediction

- Objective is to predict AMD exposure in pediatric populations
- Propose to build relationships to scale: Dog →Human (adult) and adult→peds
- As there is no reasonable estimate of inter-subject variation, we propose to examine only the uncertainty about the prediction of mean exposure profiles
- Refine PBPK model with proper variance estimates from pilot PK studies

Actinomycin-D

PD Model: Exposure-response prediction

- The pediatric PBPK model will then be used to correlate systemic and target organ exposure with observed toxicity profiles (adult and pediatric clinical trials)
- Create transduction model which predicts intracellular time course and actions (utilize DNA binding, cellular partitioning and cytotoxicity data
- Generate *in vitro* cell kill data with commonly prescribed co-administered agents

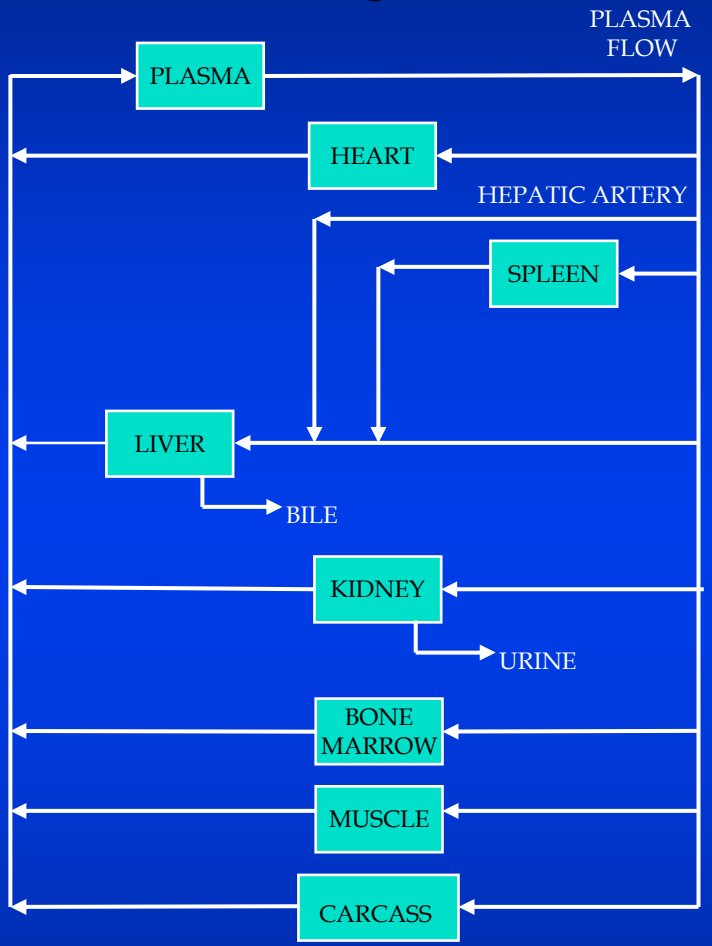
Actinomycin-D

Outcomes Model: Trial Outcome prediction

- Create mean response profile (AE, toxicity) from published studies in which AMD was administered – summary data
- Assemble individual response data from Children's Oncology Group (COG) – individual data
- Examine correlation of adverse effect / tox profile with AMD dose
  - Construct outcome expressions (i.e., logistic model)

Actinomycin-D

Prior Knowledge – PBPK Reduced Model



Criteria for model reduction

- High DNA concentration
- High blood flow
- Organs potentially correlated with toxicity

Methods

- NONMEM v5, Level 1.1
- ADVAN 8 with 8 DEs defined
- 100 Subproblems

Parameter Derivation

- Dog flows and volumes, clearances
  - Lutz et al. *Model for the kinetics of distribution of actinomycin-D in the beagle dog*. JPET, 1977; 200(3): 469-478
- Human flows and volumes, dog variability
  - Brown et al. *Physiological parameter values for physioligically based pharmacokinetic models*. Toxicology and Industrial Health. 1997; 13(4):407-484
- Human clearance values (approx 1/3 biliary, 2/3 renal) derived from modeled data
  - Tattersall et al. *Pharmacokinetics of actinomycin-D in patients with malignant melanoma.* Clin Pharm Ther. 1975; 17(6):701-708
- Carcass R and CV calculated as mean values of all other organs
- CV for partition coefficients and organs without values were assumed to be 0.20

Parameter Derivation

- Clearance in dog
  - Biliary – 774 mL/h
  - Renal – 936 mL/h
- Clearance in humans
  - Biliary – 1362 mL/h
  - Renal – 3729 mL/h
- Parameters in children allometrically scaled from adult parameters

CL=a*WT^0.75 V=c*WT^1 Q=b*WT^0.75

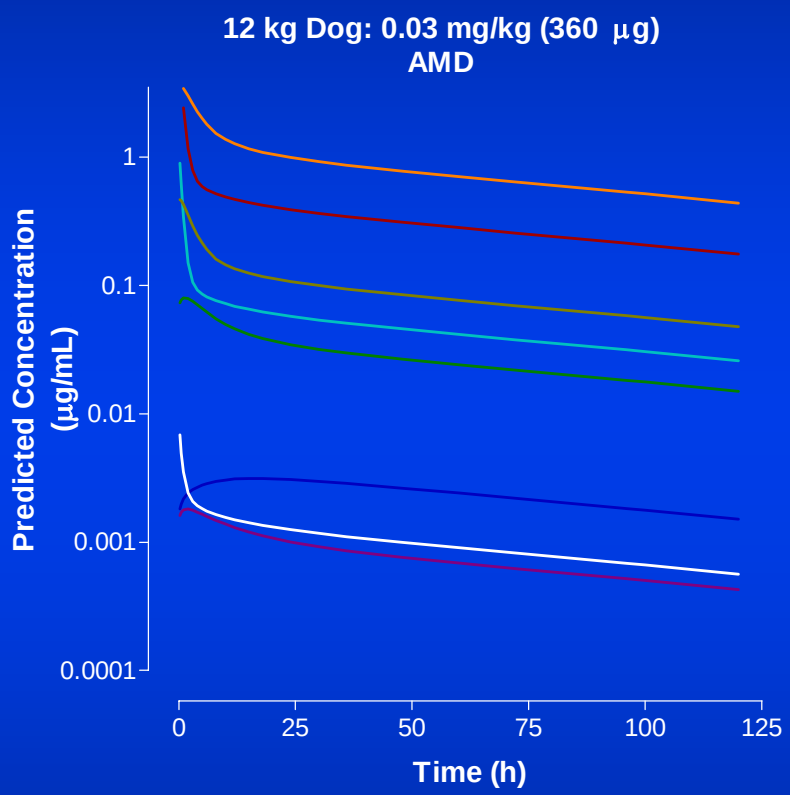
Model Parameters

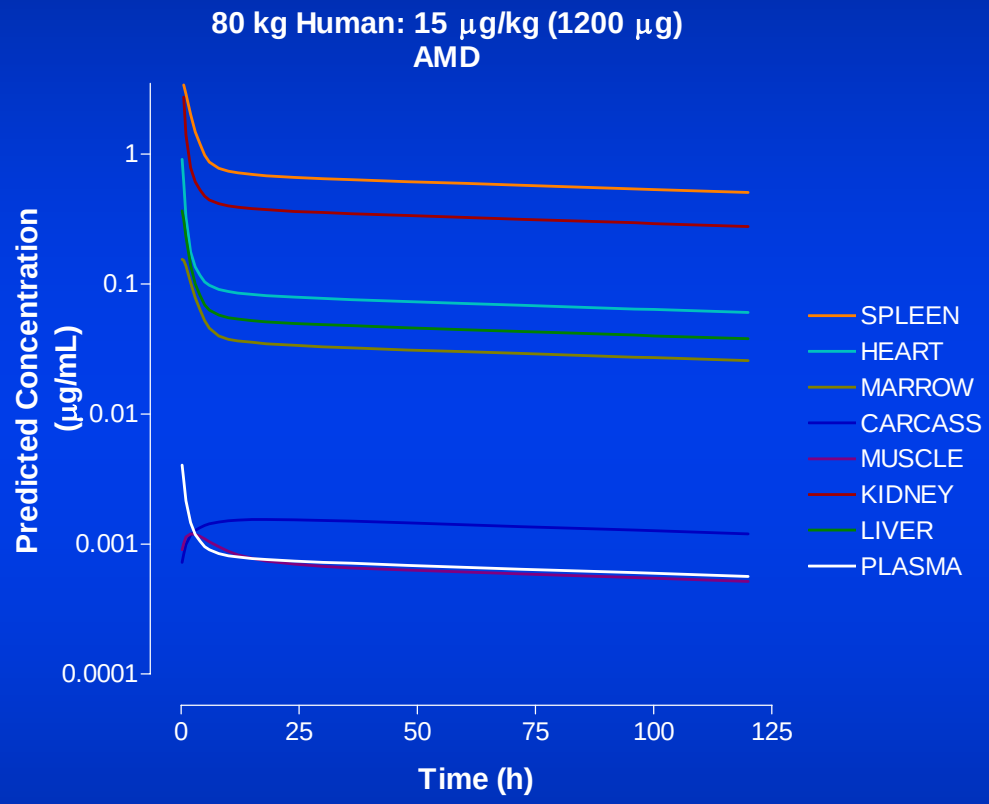
	R	Dog		Adult Human	
		Q (mL/h)	V (mL)	Q (mL/h)	V (mL)
Plasma[a]		30730	500 (0.2)	340200	3400 (0.12)
Liver	30 (0.2)	3600 (0.14)	480 (0.07)	78000 (0.16)	1500 (0.16)
Kidney	45 (0.2)	5400 (0.09)	60 (0.13)	66000 (0.21)	300 (0.21)
Marrow	20 (0.2)	1200 (0.2)	120 (0.2)	27000 (0.16)	1500 (0.16)
Muscle	8 (0.2)	8280 (0.18)	5530 (0.18)	54600 (0.17)	30000 (0.17)
Heart	11 (0.2)	3600 (0.07)	120 (0.08)	15600 (0.14)	350 (0.14)
Spleen	55 (0.2)	810 (0.2)	36 (0.07)	12600 (0.16)	210 (0.16)
Carcass	25 (0.2)	7840 (0.12)	5190 (0.14)	86400 (0.16)	42740 (0.16)

[a] $Q_p = Q_{li} + Q_{ki} + Q_{mr} + Q_{mu} + Q_h + Q_{sp} + Q_c$

Interspecies Exposure Comparison

Mean Profiles





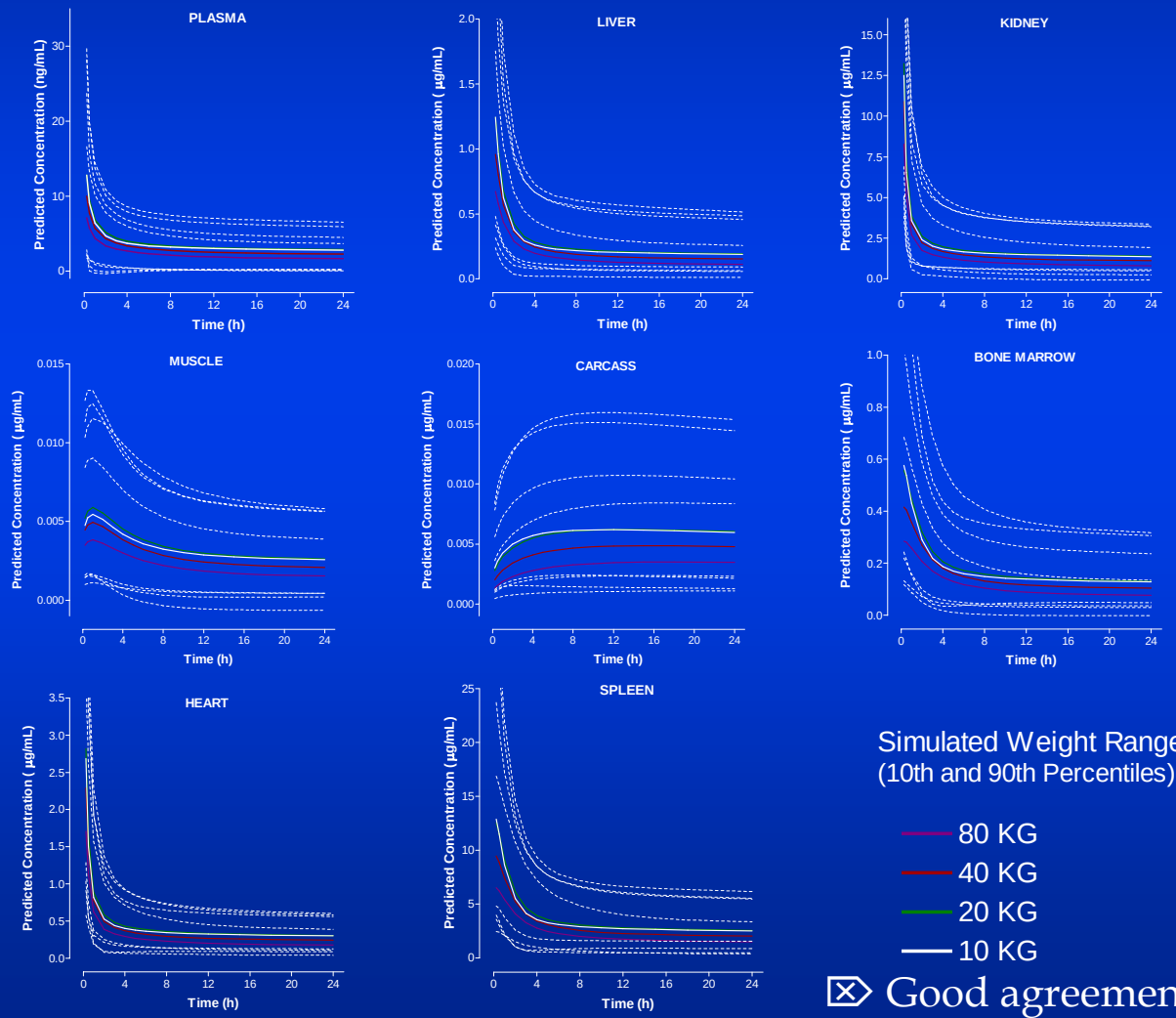
⌦ Good agreement with Lutz et. al.
All tissue exposures

⌦ Good agreement with Tattersall et. al.
Human plasma exposure comparable

Simulated Pediatric Exposure Results

Mean Response (uncertainty on mean only)

Pediatric Exposure Profiles following 1.5 mg/m^2 AMD



⌦ Good agreement with Veal et. al.

Pediatric plasma exposure comparable

Clinical Outcomes

Capturing Response from Pooled Literature Data

- AE/toxicity data pooled from 17 trials with AMD
  - Patient population (cancer type); Wilms tumor, Ewing's disease rhabdomyosarcoma, malignant melanoma, breast, trophoblastic disease, endometrial carcinoma and various mixed cancers
  - Total N = 1289 patients
- Response data coded by event type, dose range, severity and frequency of occurrence (within study)
  - 3 Dose Ranges: 0 – 0.45, 0.46 – 1.35, 1.36 – 2.5 mg/m^2
  - AMD-associated Events: platelet count, hemoglobin and WBC decline, myelosupression, mucositis, nausea/vomiting, LFT elevation, and rash
  - Severity Grades: I – IV

Clinical Outcomes

Capturing Response from Pooled Literature Data - example

Dose Range (mg/m^2)	Event	Severity	Occurrence (n)	Tot_N	Occurrence (%)
0 - 0.45	Dec_Hgb	Gradel/II	20	36	55.6
		GradeIII/IV	78	267	29.2
	Dec_WBC	Gradel/II	10	36	27.8
		GradeIII/IV	7	50	14.0
	Dec_Plts	Gradel/II	7	36	19.4
		GradeIII/IV	219	281	77.9
	Myelosupression Undefined	Gradel/II	84	231	36.4
		GradeIII/IV	84	231	36.4
	Mucositis	All	255	772	33.0
	Nausea/Vomiting	All	106	297	35.7
	Inc_LFTs	Gradel/II	30	576	5.2
		GradeIII/IV	78	862	9.0
	Rash	All	NA	NA	NA

Ongoing and Future Efforts

- Metabolism Studies (ongoing)
  - Liver microsomes: CYP and phase II enzyme evaluation
  - Preliminary results suggest minimal CYP involvement
- Protein binding (ongoing)
  - Adult and pediatric evaluation
- Preliminary (pilot) PK trial in children (n = 8) – ongoing
  - Performance of new analytical method (LC/MS-MS) which detects AMD and vincristine from single injection
  - First estimate of inter-subject variation in PK parameters

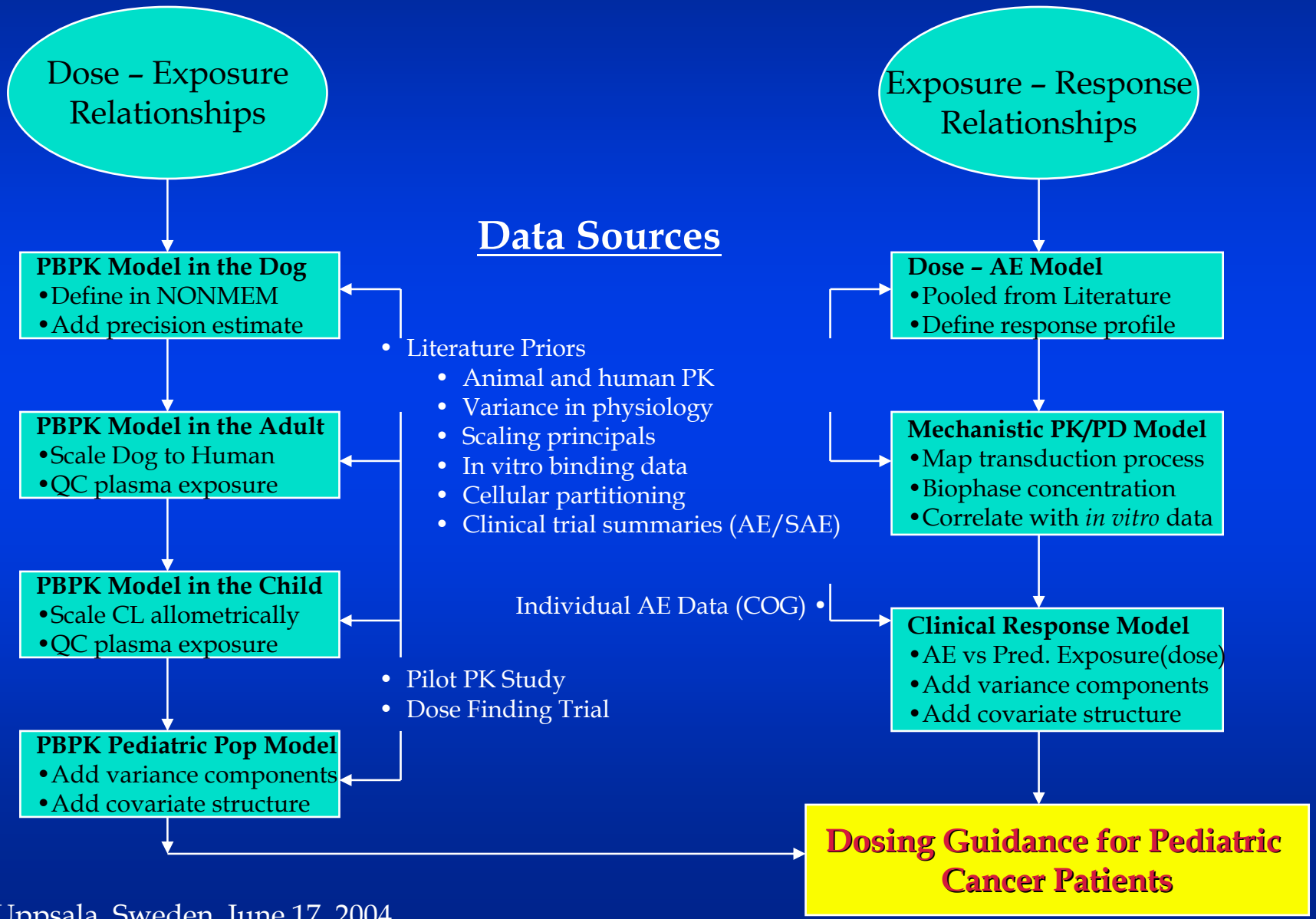
Ongoing and Future Efforts

- Design of pop-PK study to define dosing rule (n = 100 – 150)
  - Collaboration with NCI and possibly UK group
  - As sparse pediatric data are collected, population PK parameters will be estimated using a hierarchical Bayesian model given diffuse priors for those parameters that are well defined by the new data and informative, literature-based priors where necessary to support the model.
- Creation of Transduction Model for AMD intracelluar dynamics – mechanistic PK/PD model
  - Incorporate DNA binding and cellular partitioning
  - Mine clinical data (COG) to explore correlation with blood chemistry and hematologic toxicities (No PK in this DB)

Ongoing and Future Efforts

- Creation of Clinical Response Model for therapeutic window
  - Literature response rates, AE profile
  - Qualify literature response by COG data: stochastic model
- Create Clinical Trial Simulation Model from I/O (PK), PD and Clinical Response expressions

Valuation of Priors



Valuation of Priors

Bayesian Model Hierarchy

4. Uncertainty

3. Population

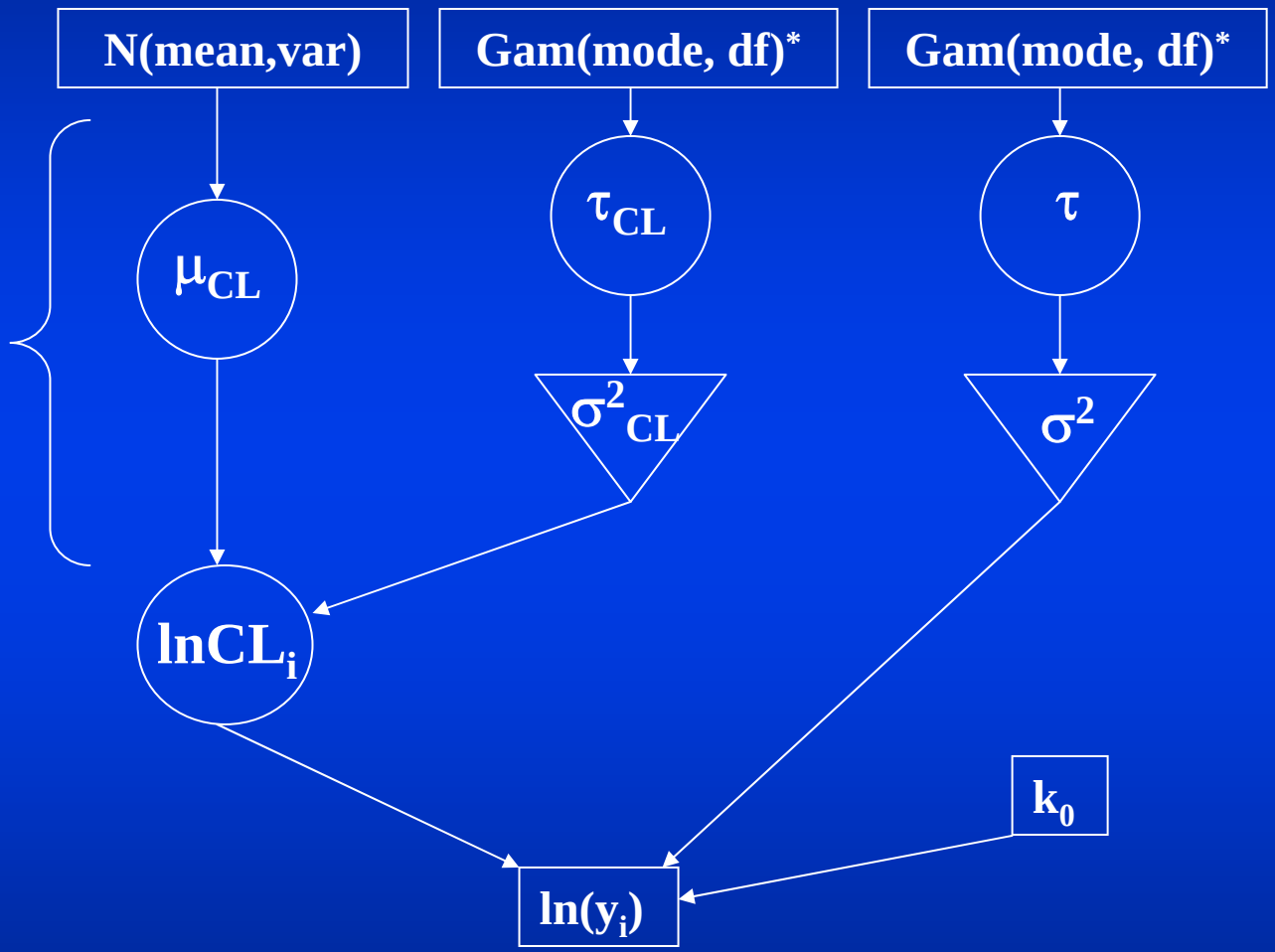
   μ = mean

   τ = 1/var

   σ^2 = var

2. Individual

1. Observation



* **A Wishart distribution is analogous to a Gamma distribution in the multivariate case.**

Conclusions

- Despite the limited available "priors" for modeling Actinomycin-D exposure → response → outcomes, a model for mean exposure in pediatric patients has been created based on allometric scaling of physiologic-based PK originally defined in the dog.
- The PBPK model evolution included QC checks against sparse adult and pediatric systemic exposure (poor man's PPC) – both were acceptable.
- Ongoing and future efforts of the CTS model incorporate mechanistic PK/PD and multivariate (ordinal) AE response modeling.
  - In both cases, variance estimates will eventually be added based on prospective clinical investigation.

Conclusions

- While a mean prediction model may appear to have limited value, it permits the quantitative description of the exposure → response → outcome relationship beyond an empirical "feeling" about the status of a pharmacotherapy.
- The addition of variance to mean models offers a method of exploring parameter sensitivities and the relevant "parameter space."


THE
END