

**A Bayesian dose-escalation procedure for
phase I clinical trials based only on the
assumption of monotonicity**

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1. Introduction

- **Resistance to implementation of formal dose-escalation procedures**
 - *Appropriateness of dose-response models*
 - *Communication of process to clinical investigators*

- **New Bayesian approach**
 - *Simple model assuming only monotonicity*
 - *Model parameters have simple interpretation*
 - *Approach can be applied automatically*
 - *Can be used transparently in decision making process*

2. Bayesian model

- **k doses of drug available for testing: $d_1 < \dots < d_k$**
- **Binary patient outcome Y : 1 = toxicity, 0 = no toxicity**
- **Risks $r_j = P(Y = 1 | d_j)$ $j = 1, \dots, k$**
- **r_j treated as random variables and modelled directly**
- **Assume r_j is equal to one of a grid of h values $a_1 < \dots < a_h$**

Example: *Ferry (1996)*

Trial: Phase I clinical trial of quercetin in terminal cancer (*Cancer Research Campaign, Birmingham*)

Doses: 60, 120, 200, 300, 420, 630, 945, 1400, 1700 mg/m²

Patients: no longer amenable to standard therapies, suffer from a variety of forms of solid tumour

Toxicity: renal toxicity, WHO grade ≥ 2

Objective: find the TD20

Maximum number of cohorts: 18 of size 3

Choice of possible values for risk of toxicity (r_j)

		Interpretation
a_1	0.05	Very safe
a_2	0.1	Safe
a_3	0.2	Ideal
a_4	0.3	Risky
a_5	0.6	Toxic

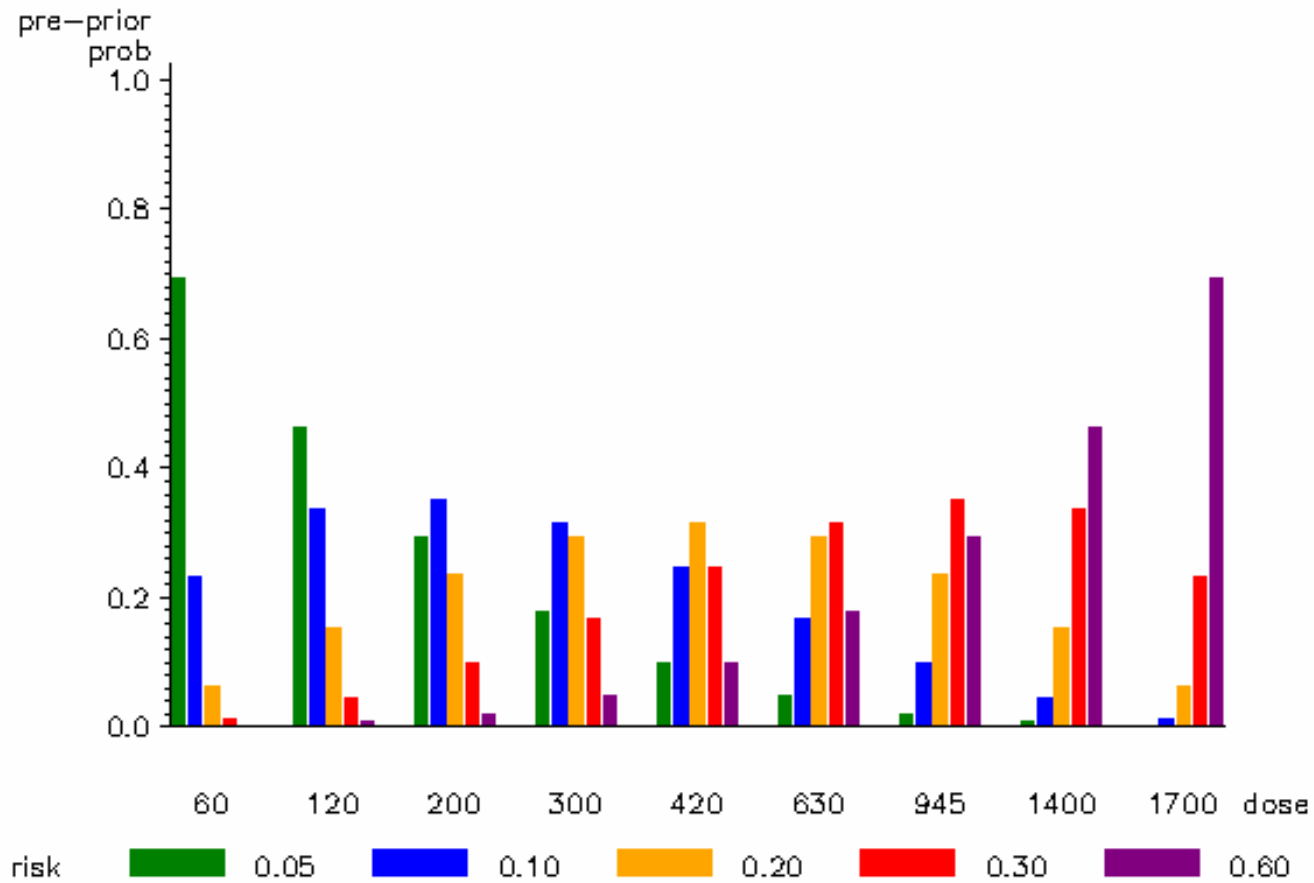
Monotonicity constraint

- Higher doses have a risk of toxicity greater than or equal to that of lower doses

Pre-prior joint distribution of r_1, \dots, r_k

$$\begin{aligned}\pi^0(b_1, \dots, b_k) &= \mathbf{P}(r_1 = b_1, \dots, r_k = b_k) \\ &= c_0 \quad \text{if } b_1 \leq \dots \leq b_k \text{ and} \\ &\quad b_1, \dots, b_k \in \{a_1, \dots, a_h\} \\ &= \mathbf{0} \quad \text{otherwise}\end{aligned}$$

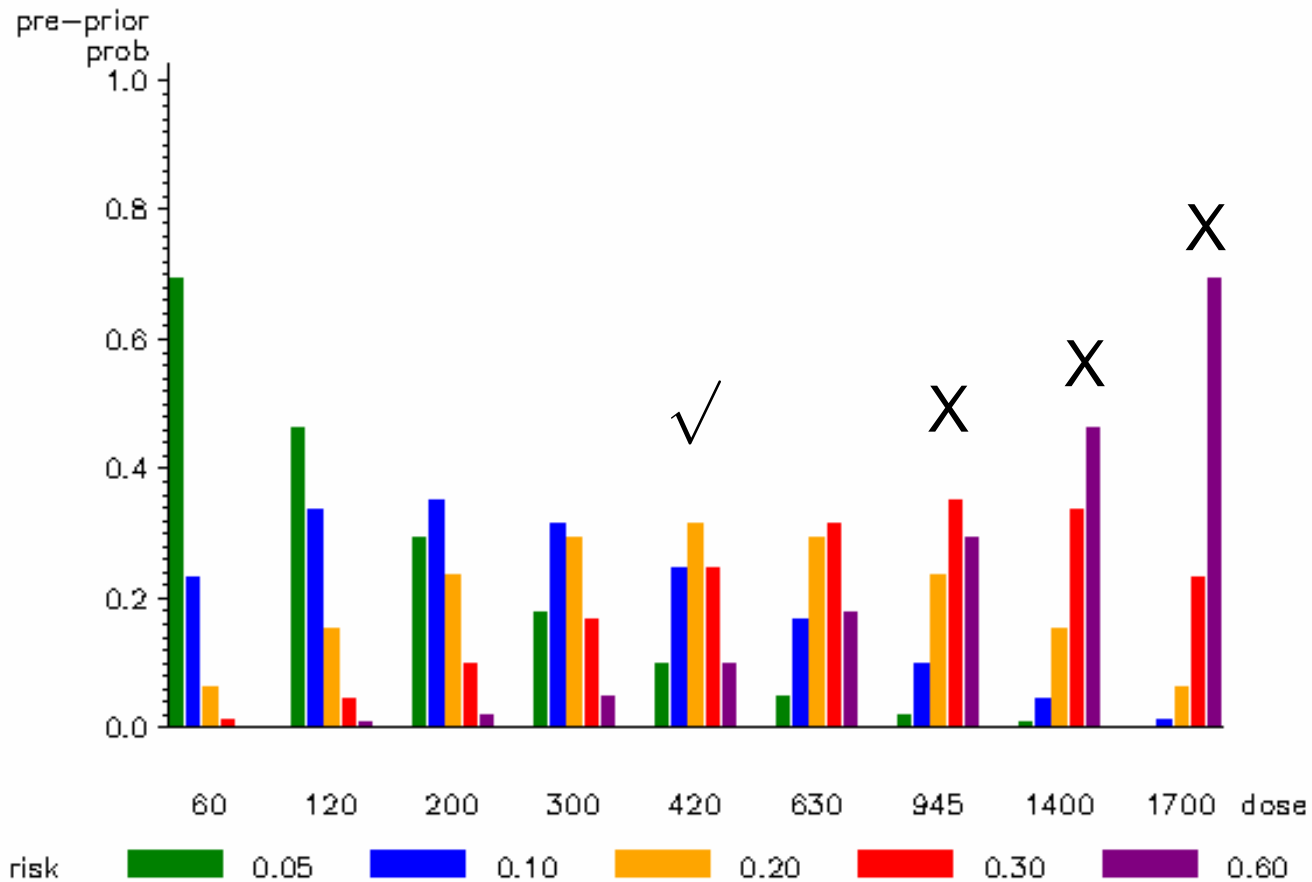
Pre-prior marginal distribution for each dose



3. Criteria for dose escalation

- **A cohort of new patients is ready for treatment**
- **Assume all patients in cohort receive same dose**
- **Criteria for choice of dose may vary from study to study**
- **For Ferry study the criteria might be**
 - *Do not administer dose d_j if $P(r_j = 0.60) \geq 0.20$*
 - *From remaining doses chose d_j that maximises $P(r_j = 0.2)$*

Dose for first cohort based on pre-prior marginal distribution



4. Choice of prior distribution

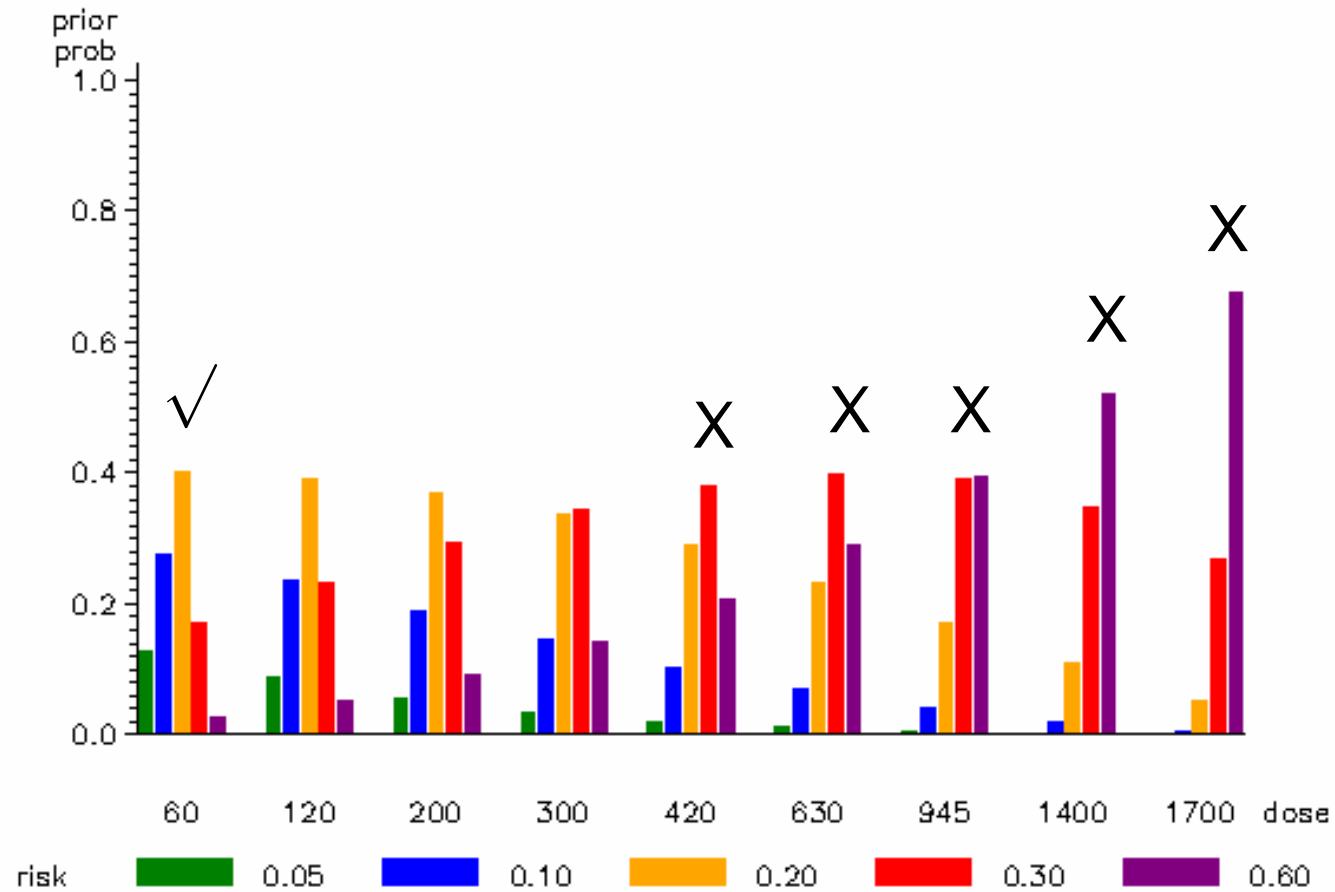
- Starting first cohort at middle dose not usually appropriate
- Usually first cohort receives lowest dose
- Choose a more appropriate prior

$$\pi(b_1, \dots, b_k | \text{data}) \propto c_0 \prod_{j=1}^k r_j^{t_j} (1 - r_j)^{n_j - t_j}$$

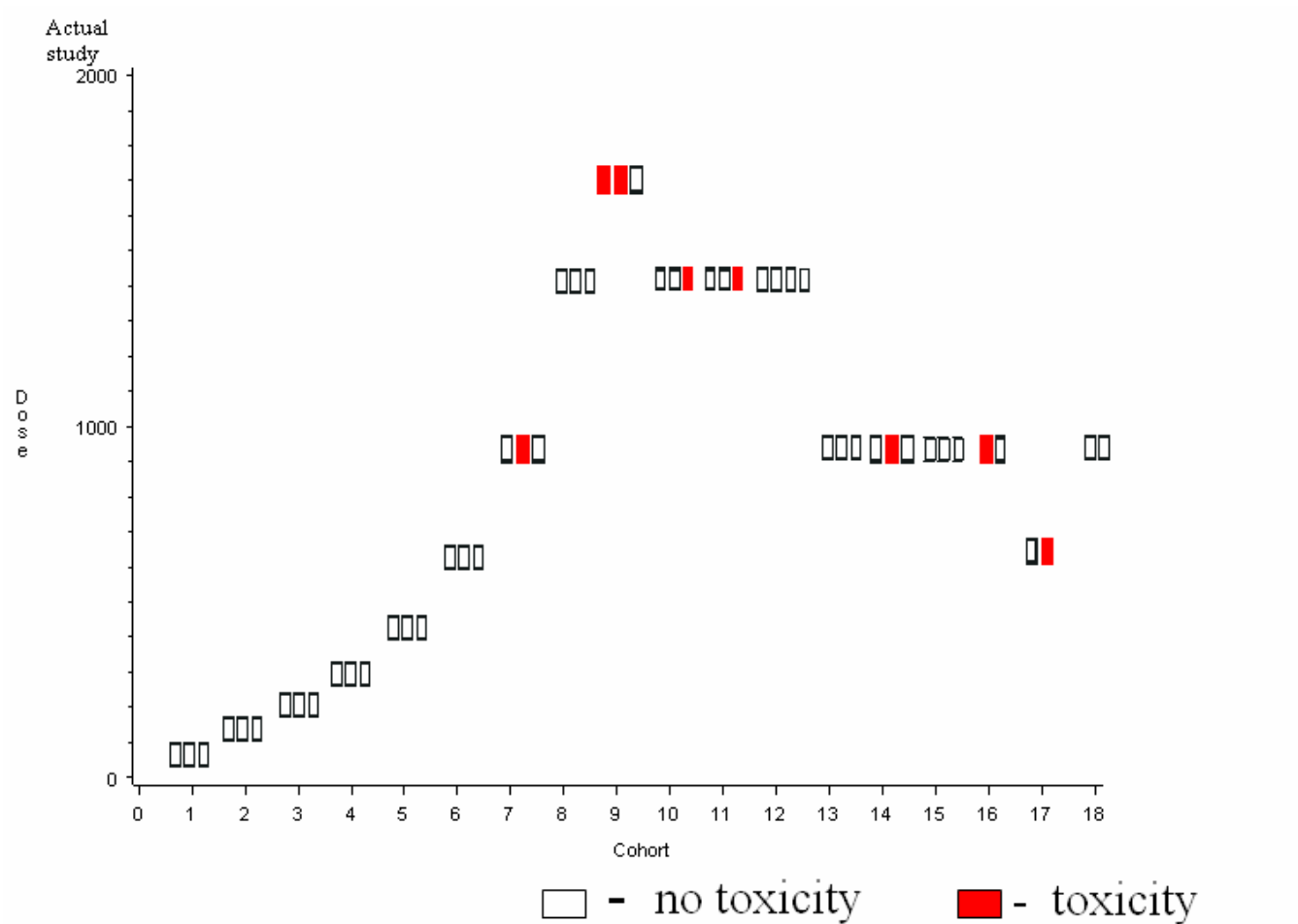
for b_1, \dots, b_k satisfying monotonicity constraint

- For Ferry study
 - *Add 6 subjects at lowest dose, with 3 suffering toxicity*
 - *Add 1 subject at highest dose, with 0 suffering toxicity*

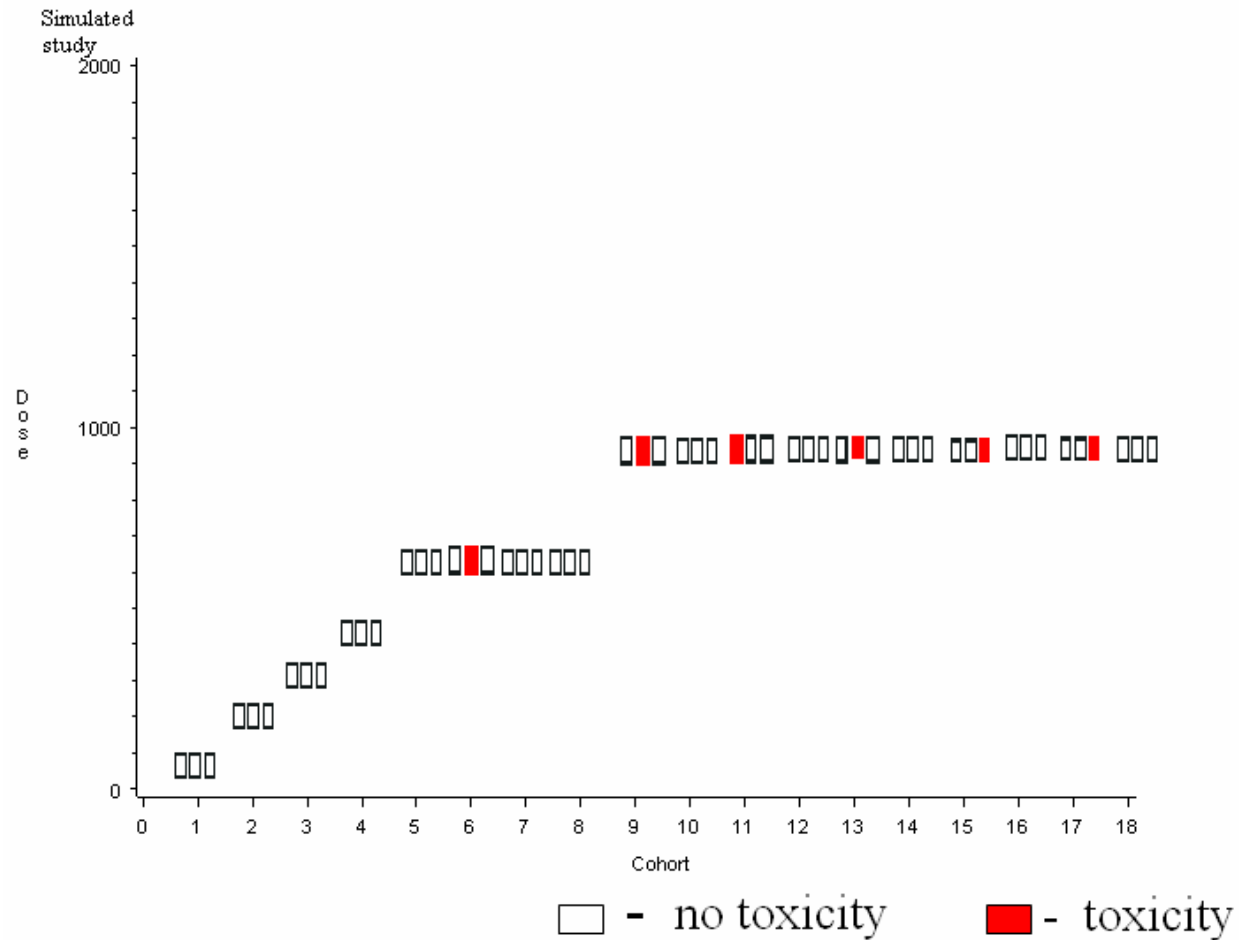
Dose for first cohort based on prior distribution incorporating pseudo data



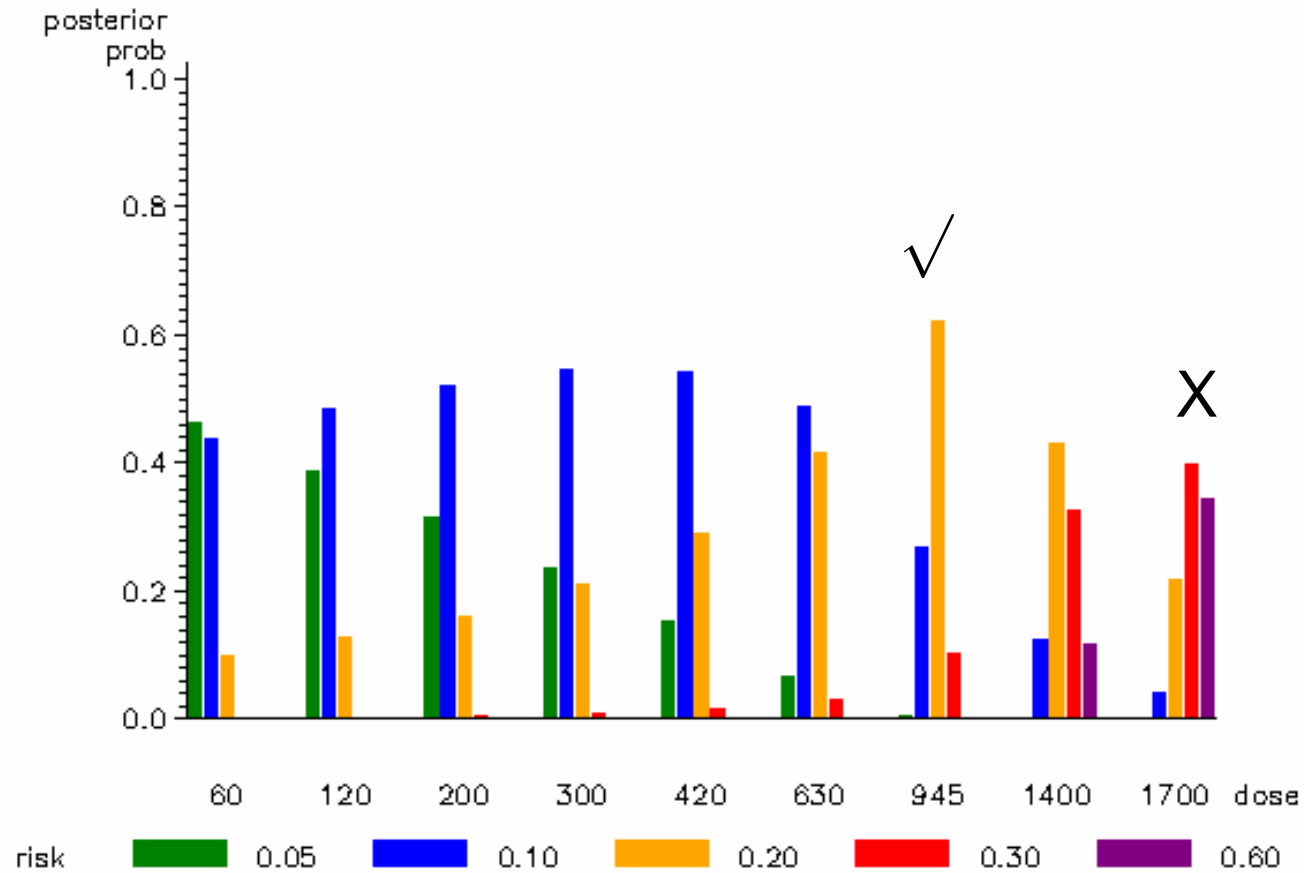
Actual data collected in Ferry study



Simulated study based on Ferry study data



Posterior distribution using simulated study data

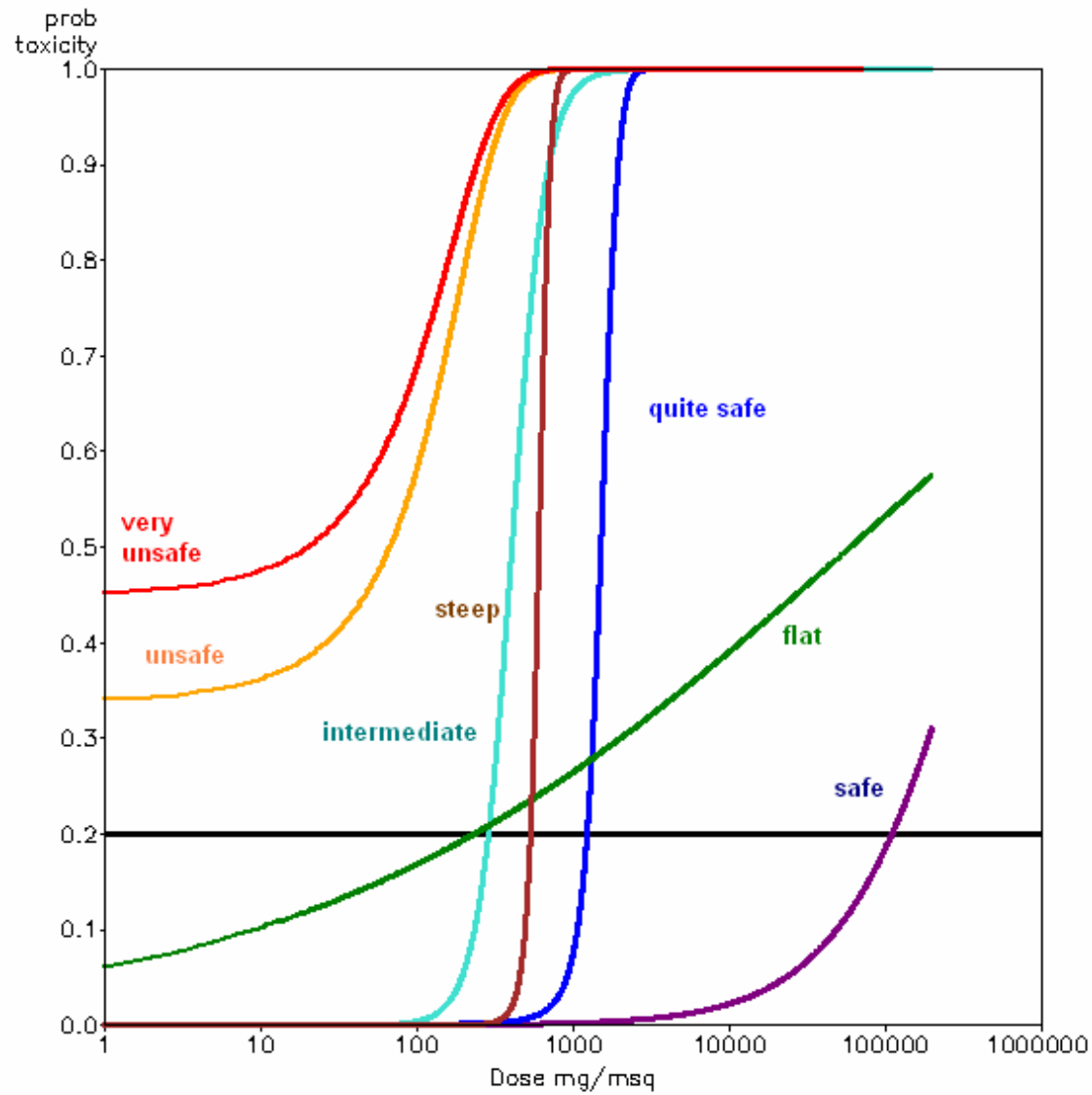


5. Simulation study to evaluate procedure

- **Based on setting in Ferry study**
- **Cohorts of size 3**
- **Maximum of 36 subjects**
- **1000 simulations**

- **Comparison with CRML**
 - *3 subjects given increasing doses until a toxicity observed*
 - *Model $r_j = \alpha_j^a$*
 - *Using skeleton probabilities $\{\alpha_1, \dots, \alpha_k\}$ equal to mean risks from non-informative pre-prior*
0.075, 0.104, 0.139, 0.179, 0.224, 0.278, 0.340, 0.413, 0.499
 - *Next cohort receives d_j which minimises $(\hat{r}_j - 0.2)^2$*

Seven simulation scenarios



Scenario	Rule	Best dose	Number of recommendations (out of 1000)			
			Too low	Correct	Too high	None
Safe	New	1700	55	945	0	0
	CRML	1700	0	1000	0	0
Quite safe	New	945	4	572	424	0
	CRML	945	25	549	426	0
Intermediate	New	300	250	727	23	0
	CRML	300	344	580	76	0
Flat	New	200	451	196	346	7
	CRML	200	367	156	477	0
Steep	New	420	0	939	61	0
	CRML	420	117	523	360	0
Unsafe	New	60	0	821	10	169
	CRML	60	0	981	19	0
Very unsafe	New	60	0	87	0	913
	CRML	60	0	1000	0	0

Scenario	Rule	Best dose	Average number			
			Patients	Toxicities	Risk ≥ 0.3	Risk ≥ 0.6
Safe	New	1700	36	0.07	0	0
	CRML	1700	36	0.08	0	0
Quite safe	New	945	36	3.08	6.03	0.02
	CRML	945	36	5.85	11.36	3.14
Intermediate	New	300	36	6.56	3.22	0.15
	CRML	300	36	7.49	6.45	1.70
Flat	New	200	35.79	6.47	0	0
	CRML	200	36	6.61	0	0
Steep	New	420	36	4.87	6.72	6.72
	CRML	420	36	6.94	9.72	9.72
Unsafe	New	60	31.79	9.92	2.41	1.25
	CRML	60	36	11.18	3.67	0.62
Very unsafe	New	60	13.15	7.06	19.15	0.41
	CRML	60	36	19.12	36.00	0.56

Scenario	Rule	Best dose	Precision error	Minimum possible precision error	True risk selected dose (average)
Safe	New	1700	0.20	0.20	0.00
	CRML	1700	0.20	0.20	0.00
Quite safe	New	945	0.16	0.14	0.19
	CRML	945	0.18	0.14	0.20
Intermediate	New	300	0.10	0.03	0.20
	CRML	300	0.13	0.03	0.20
Flat	New	200	0.03	0.01	0.19
	CRML	200	0.04	0.01	0.20
Steep	New	420	0.20	0.17	0.06
	CRML	420	0.30	0.17	0.25
Unsafe	New	60	0.09	0.09	0.29
	CRML	60	0.09	0.09	0.29
Very unsafe	New	60	0.32	0.32	0.52
	CRML	60	0.32	0.32	0.52

6. Discussion

- **New Bayesian approach requires specification of**
 - *Grid of toxicity risks $\{a_1, \dots, a_h\}$*
 - *Criteria for dose escalation*
 - *Characteristics of prior distribution*

- **The approach**
 - *Provides model parameters with simple interpretation*
 - *Provides probability tables for small grid of toxicity risks*
 - *Can be applied automatically*
 - *Provides guidance to Safety Committee*
 - *Could include Bayesian stopping rules if required*
 - *Has potential for generalisation*