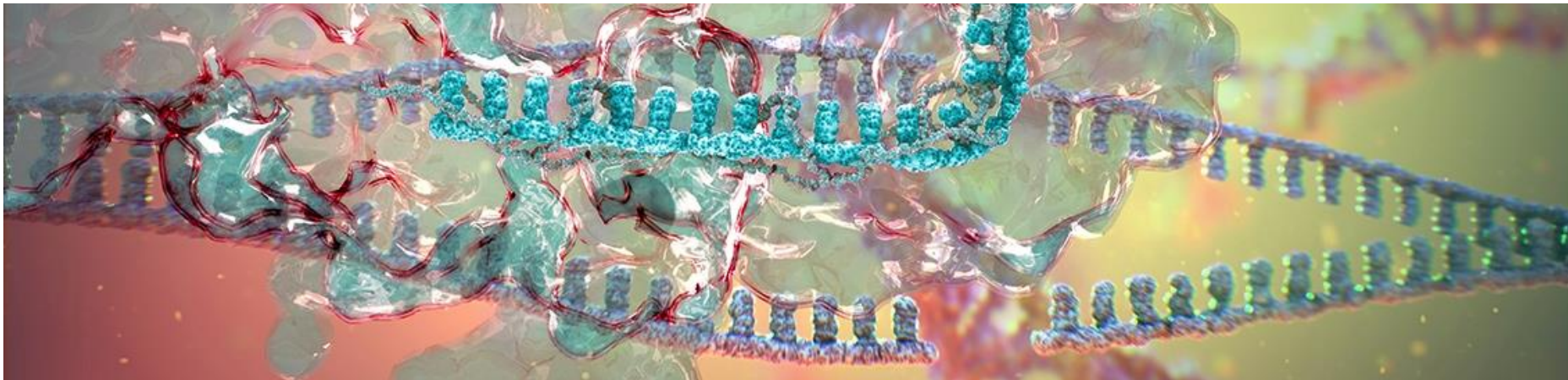


# Determining organ weight toxicity with Bayesian causal models: Improving on the analysis of relative organ weights

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# Background and the research question

- A change in organ weight is a sensitive organ-specific indicator of chemically induced toxicity.
- Does a new drug/biologic/chemical/food additive change organ weight in rodents?



# The problem

- A compound might affect overall body weight (e.g. feeding behaviour, growth rates), and thus indirectly affect organ weight.
- What about multiple comparisons (especially when a null result is a good result)?



# Current practice

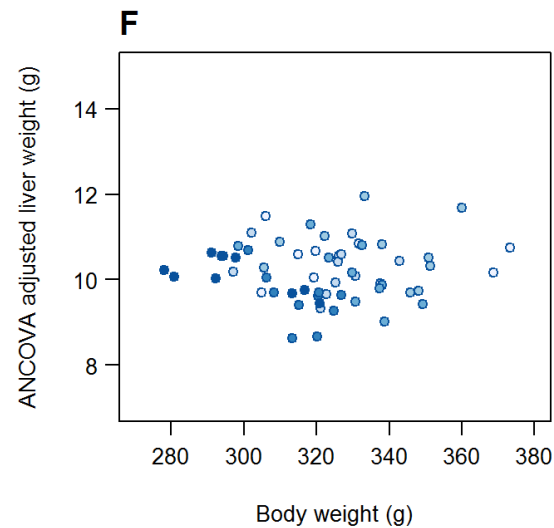
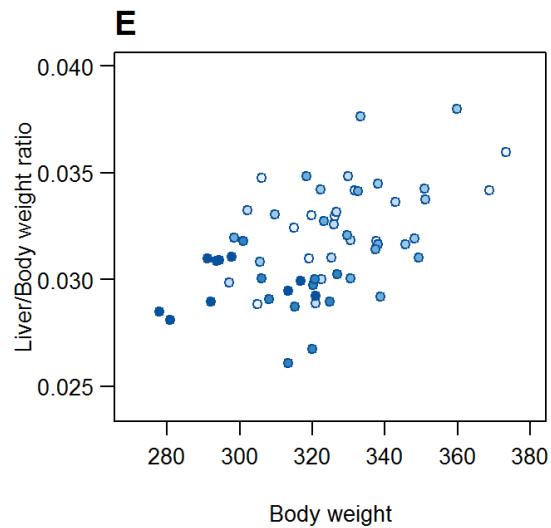
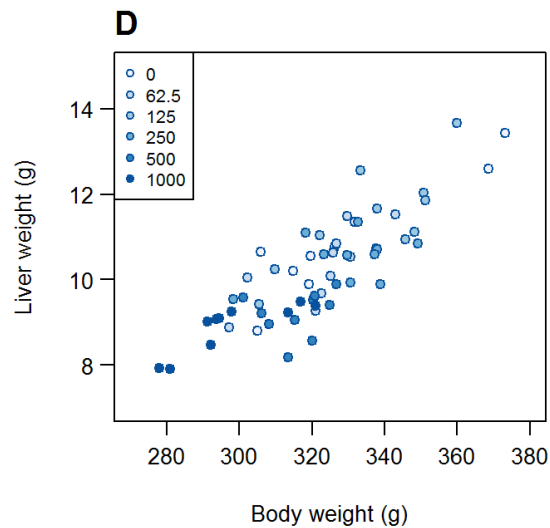
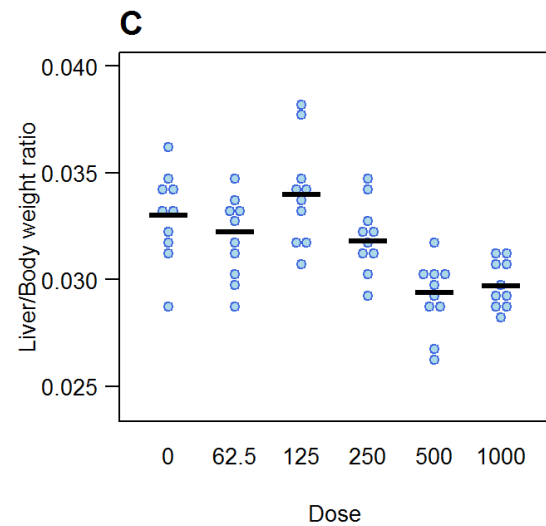
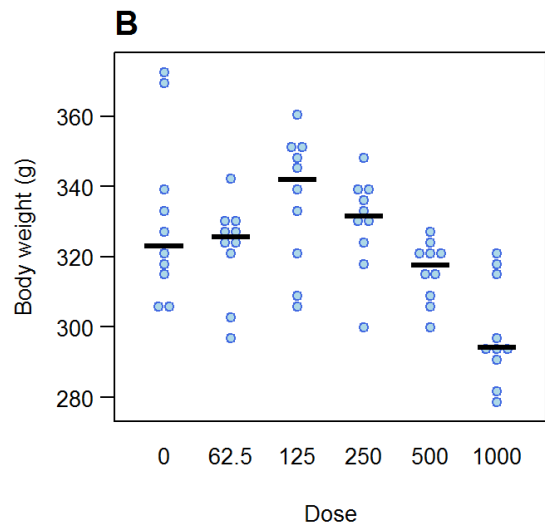
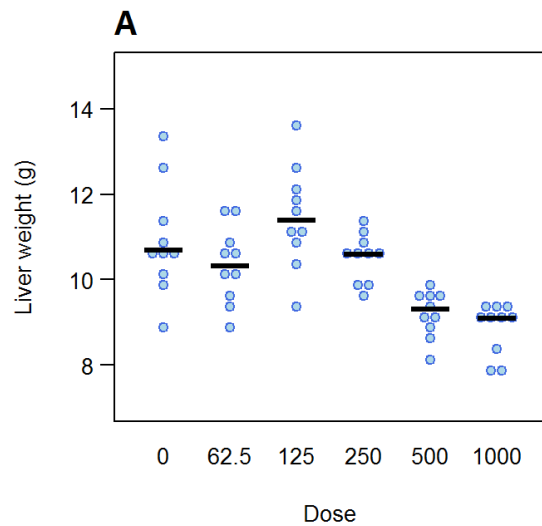
Michael B, *et al. Toxicol Pathol* **35**, 742–750 (2007).

	Pharma	Veterinary	Chemical	Food/ Nutritional	Consumer Products	Europe	Japan	North America	Multinational
Total respondents (%)	91	9	12	3	9	9	24	29	38
Standard list of organs weighed	83	33	50	100	100	33	75	90	92
Customized list of organs weighed	33	67	75	100	33	67	25	20	50
Customize based on:									
Study length	33	33	25	0	0	33	38	20	25
GLP status	17	0	0	0	0	67	13	0	17
Compound activity	70	33	75	100	67	67	63	50	67
Regulatory Guidelines	17	33	50	0	0	67	25	10	17
Species	3	0	0	0	0	0	0	0	0
Efficacy	3	0	0	0	0	0	0	0	0
History of compound	3	0	0	0	0	0	0	0	8
Paired organs weighed together <sup>a</sup>	86	100	100	100	100	100	100	100	100
Paired organs weighed individually	14	0	0	0	0	0	75	0	0
Organs are weighed after fixation	50	67	75	100	67	100	63	67	23
Organs are not weighed after fixation	50	33	25	0	33	0	38	33	77
Calculate organ weight to body weight	100	100	100	100	100	100	100	100	100
Calculate organ weight to brain weight	43	0	25	100	33	0	38	56	46
Do not calculate organ weight to brain weight	57	100	75	0	67	100	63	44	54
Statistical analysis for routine toxicity studies?									
Yes	90	67	100	100	67	100	86	56	92
No	10	33	0	0	33	0	14	33	0
N/A	0	0	0	0	0	0	0	11	8
Statistical analysis for carcinogenicity studies?									
Yes	29	67	100	100	33	33	67	38	15
No	46	33	0	0	33	33	33	50	62
N/A	18	0	0	0	33	33	0	13	23
Comparison to concurrent controls	74	33	50	0	33	67	50	56	100
Comparison to concurrent and historic controls	26	67	50	100	67	33	50	44	0
Pathologist interprets the organ weight data	74	67	75	100	100	0	63	100	82
Pathologist do not interpret the organ weight data	19	33	25	0	0	100	38	0	0

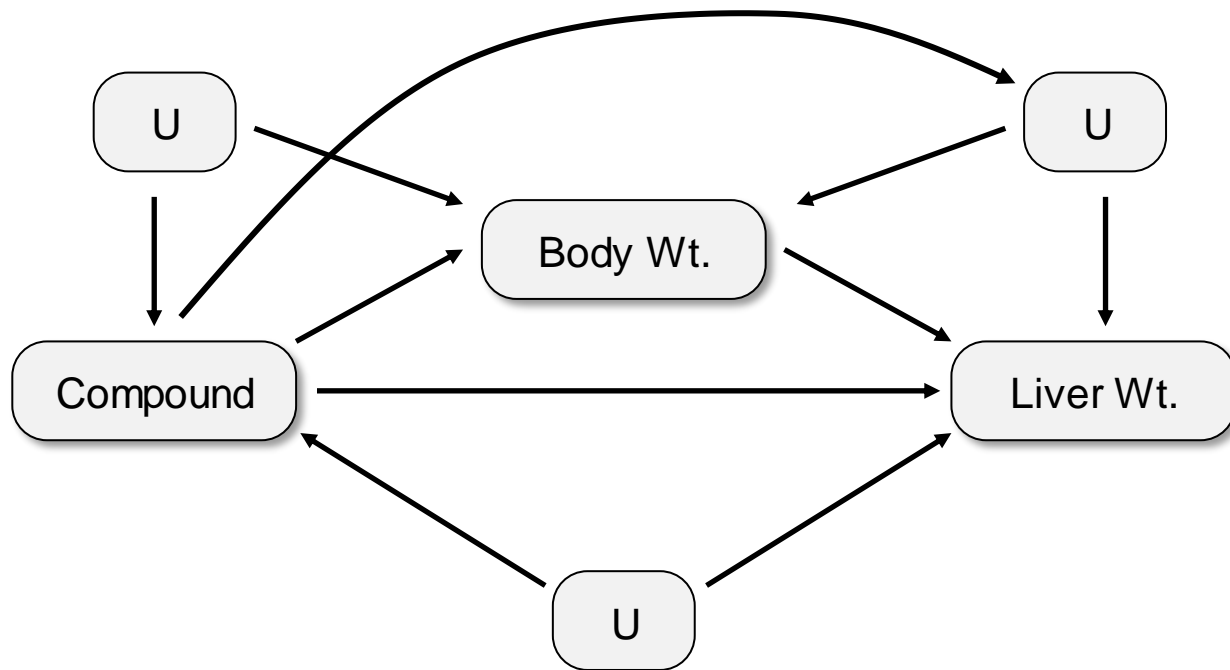
## Current practice

- “Relative organ weight” (organ weight/body weight)
- ANCOVA
- Comment from the survey: **“Respondents believed that statistical analyses did not always enhance the understanding of these effects and could be misleading.”**

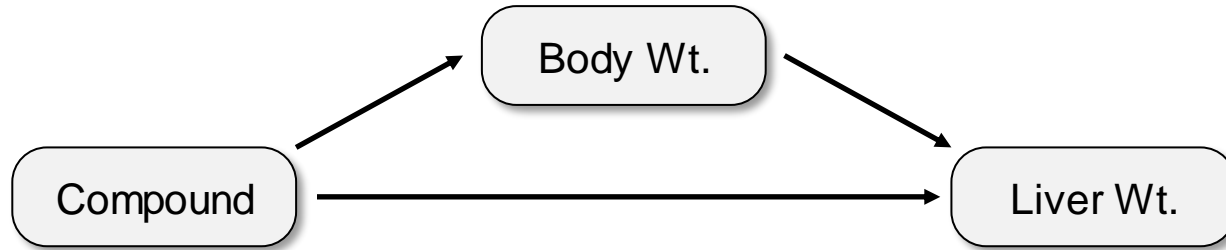




# The causal model



# The query

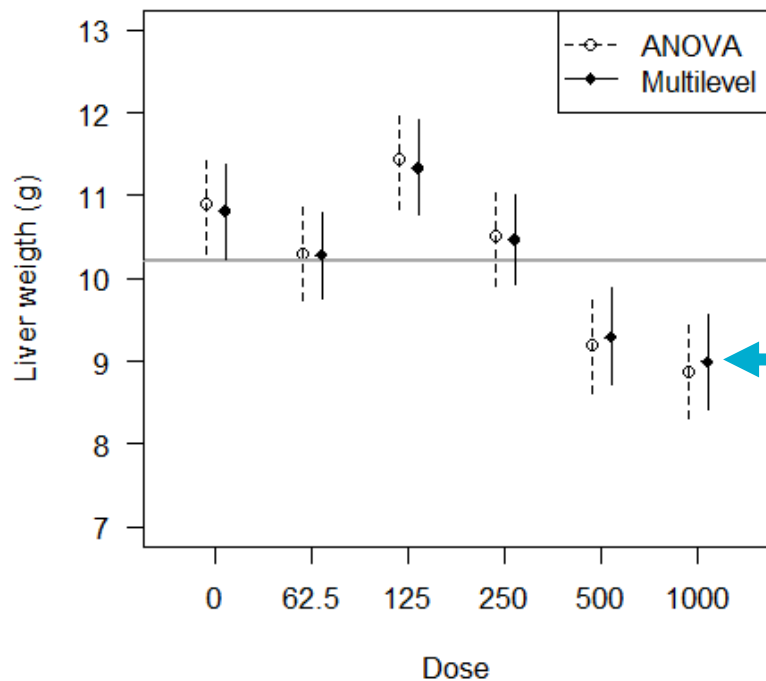
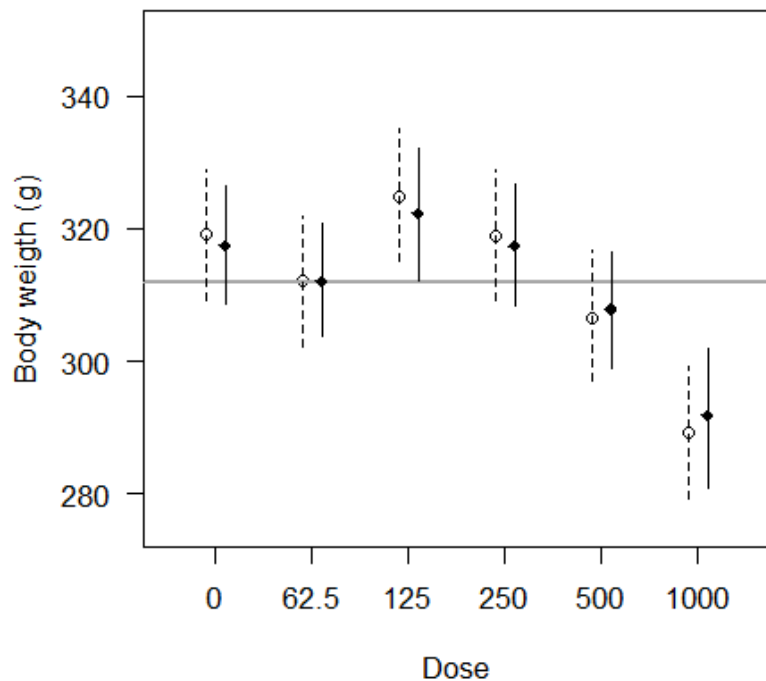


“What is the effect of the compound on liver weight, when fixing each animal’s body weight to what it would have been in the control condition?” (Natural Direct Effect).





# Use multilevel models to control false positives

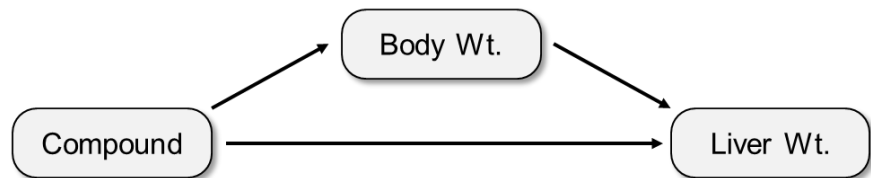


Note the shrinkage towards the overall mean.

Points are posterior means with 95% HPDI



# The model



$$BW_i \sim N(\beta_{j[i]} \text{dose}_j, \sigma_{BW})$$
$$LW_i \sim N(\theta_{j[i]} \text{dose}_j + \alpha BW_i, \sigma_{LW})$$

$$\beta \sim t(3, 0, \sigma_\beta)$$

$$\theta \sim t(3, 0, \sigma_\theta)$$

$$\alpha \sim N(0, 50)$$

$$\sigma_\beta \sim N(0, 50)^+$$

$$\sigma_\theta \sim N(0, 50)^+$$

$$\sigma_{BW} \sim N(0, 50)^+$$

$$\sigma_{LW} \sim N(0, 50)^+$$

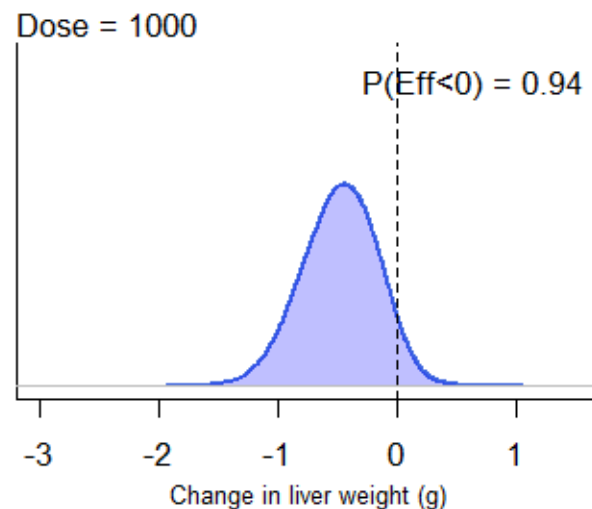
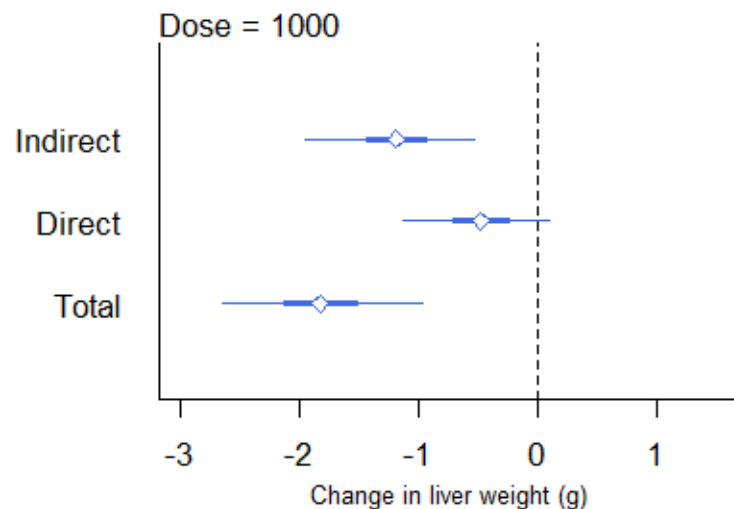
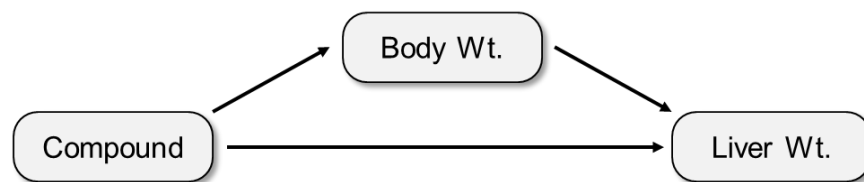
$$DE_j = \theta_1 - \theta_j \quad j = 2, \dots, 6$$

$$IE_j = (\beta_1 - \beta_j)\alpha$$

$$TE_j = DE_j + IE_j$$

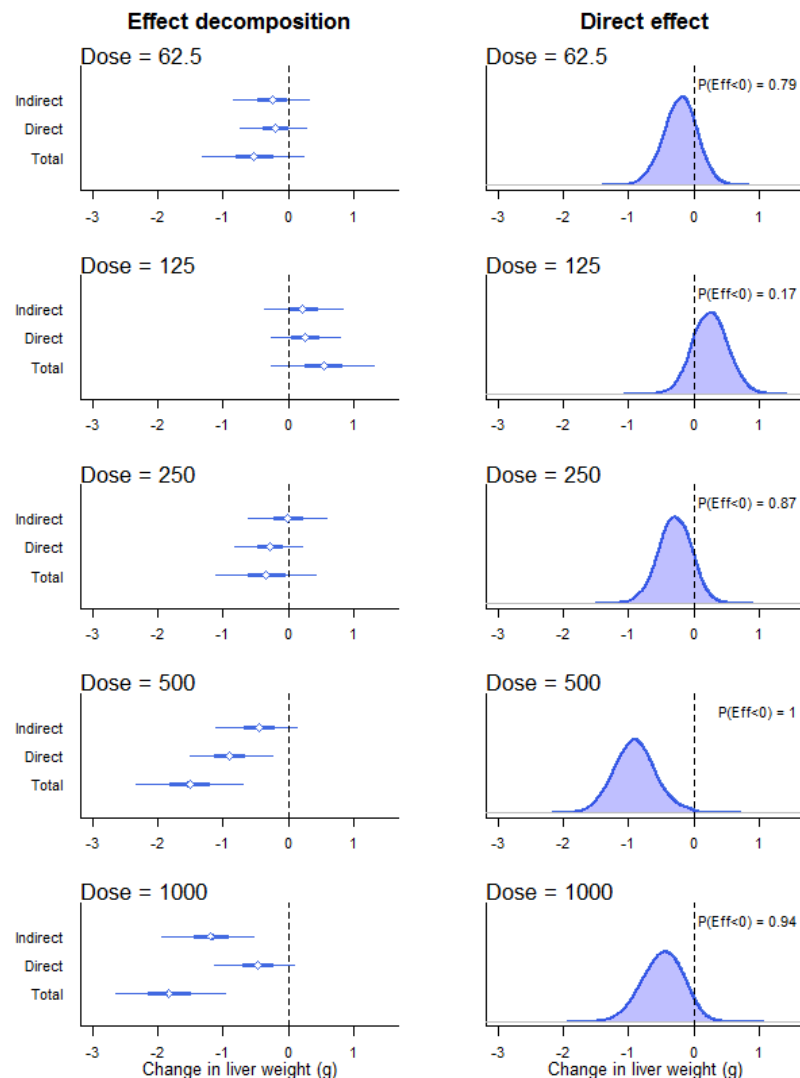


# Results

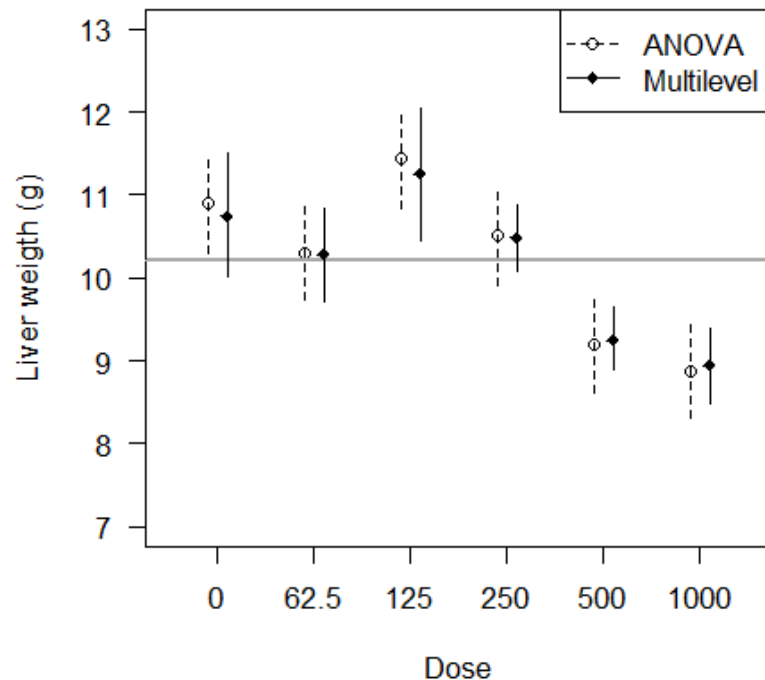
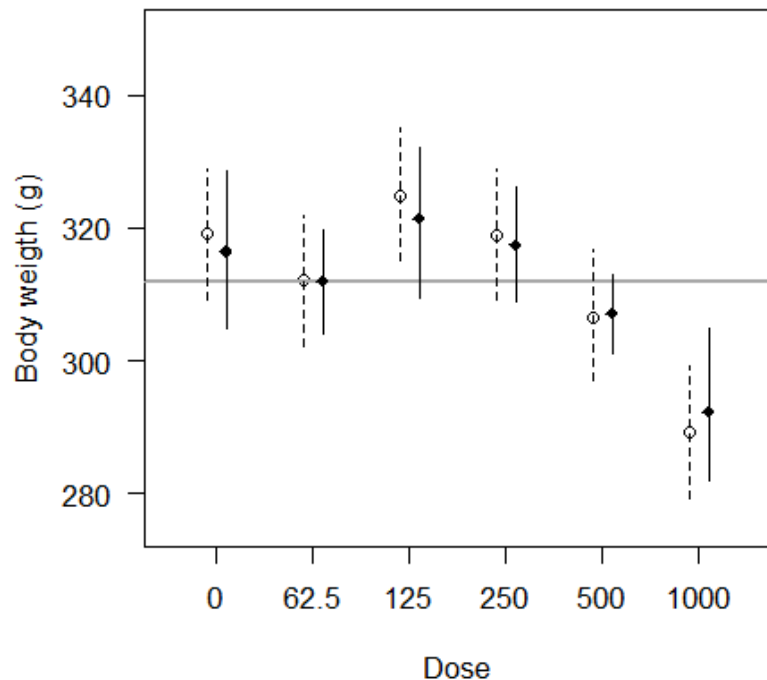


# Results

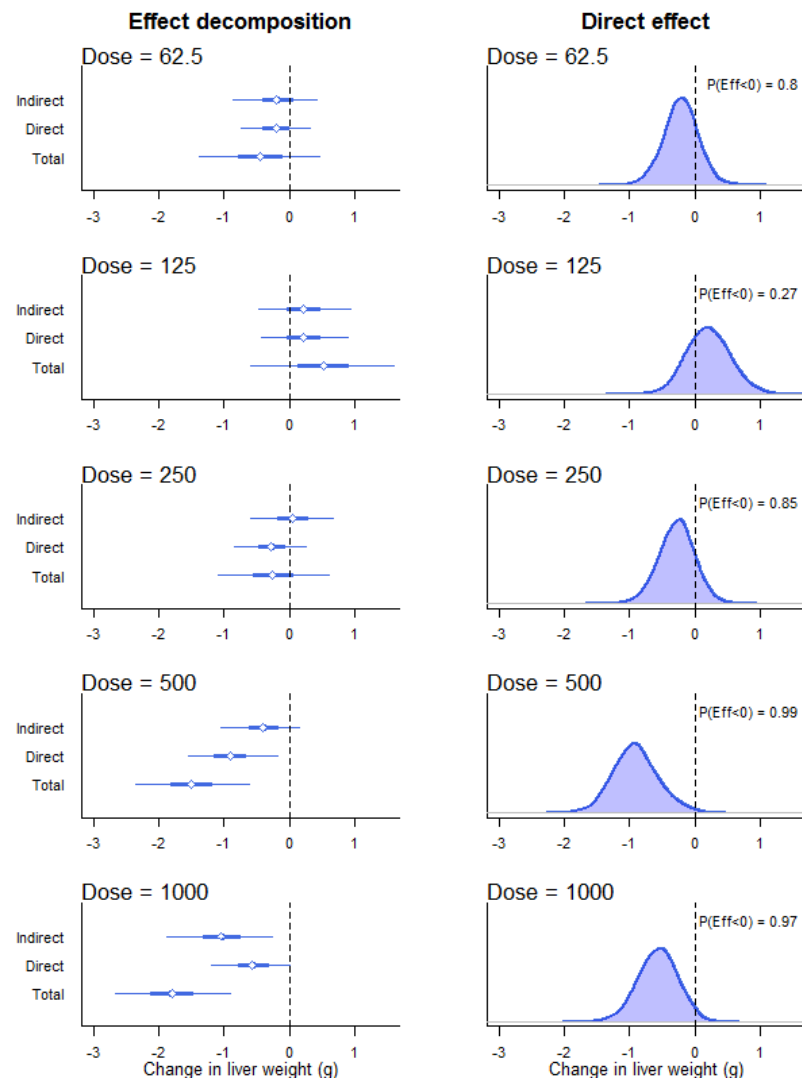
“What is the effect of the compound on liver weight, when fixing each animal’s body weight to what it would have been in the control condition?”



# Allow within-group SDs to vary (with shrinkage)



# Results



## Next steps

1. Reanalyse past AZ data.
2. Get a better understanding of false positive and false negative rates with simulation studies.
3. Develop R Shiny app for safety toxicologists.



# Acknowledgements

Dominic Williams, Drug Safety & Metabolism, AstraZeneca

## References

1. Hothorn LA (2016). *Statistics in Toxicology Using R*. CRC Press. [data set]
2. Michael B, et al., (2007). Evaluation of organ weights for rodent and non-rodent toxicity studies: a review of regulatory guidelines and a survey of current practices. *Toxicol Pathol.* 35(5):742-750.
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**Thank you!**

**Questions?**

