Time-to-event (TTE) modelling in drug safety evaluation: a case study

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sensitivity/specificity analysis conducted as part of the TTE model assessment. For your info, those stat measures were calculated based on the number of match and mismatch between the observed toxicity (0/1) and the simulated ones from the TTE model (1000 replicates).

Introduction

The descriptive approach for defining the no-observed-adverse-effect level (NOAEL) is known to have several limitations with its concept, determination and application[1-4]. As an alternative to the NOAEL approach, benchmark dose has been proposed in the environmental safety[1-3] but to the author knowledge, there is no other published example of model-based approach for NOAEL determination. Glatard et al. have been working on a Logit model for a test compound but it is still under review by the journal of Toxicology and Applied Pharmacology.

Objectives

- To apply a TTE approach to the same toxicity real case data as Glatard et al.
- To compare the TTE and the Logit approaches

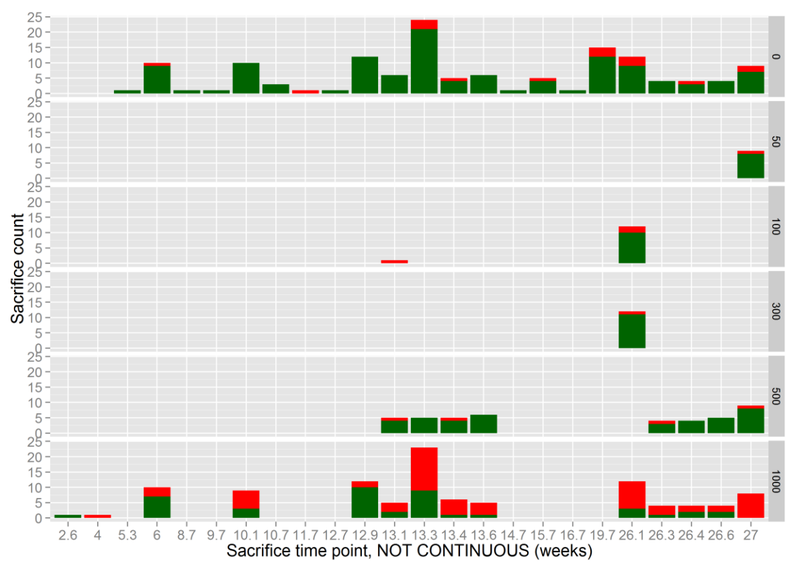
Data

- Seven studies conducted at various doses, durations and sample size to determine NOAEL values and to guide FTIH (**Table 1**)
- Histopathology toxicity data collected from each animal once, at the time of sacrifice (n = number of rats assessed by histopathology)
- Binary outcome presence/absence of histopathology toxicity (not the severity) indicative of a toxicity event (**Fig 1**)

Table 1: Toxicology data

Study	Dose (mg/kg/day)	Duration (weeks)	n per dose & duration
1	0, 1000	13	12
2	0, 100, 300, 1000	26	12
3	0	13, 26	23, 12
	100	13	1
	500	13, 26	21, 13
	1000	13, 26	21, 12
4	0, 50, 500	26	9
	1000	4, 26	1, 8
5	0, 1000	13	18
6	0	5-20	30
7	0	6, 10	10
	1000	2.6, 6, 10	1, 10, 9

Fig 1: Sacrifice counts over time stratified by dose levels. Absence of toxicity & presence of toxicity



Methods

- Model building using the survival package in R[5] (**Fig 2**)
- Covariate test using the forward backward selection, based on AIC, BIC, LRT
- Model evaluation using VPC[6] and a sensitivity/specificity analysis looking at the number of match (0-0 & 1-1) & mismatch (0-1 & 1-0) between observations & simulations per group of time and dose

Fig 2: Extract of R scripts for the TTE analysis

- Creation of a survival object with interval-censored data

```
> surv_object = Surv(data$time_i, data$time_e, type="interval2")
```

ID	DOSE	TIME	DVALL	time_i	time_e
60	500	13.57143	0	13.57143	NA
89	1000	26.42857	1	0.00000	26.42857
114	0	12.85714	0	12.85714	NA
191	50	27.00000	1	0.00000	27.00000
301	0	6.00000	1	0.00000	6.00000

Where "TIME" is the sacrifice time point, "DVALL" is the absence (0) or presence (1) of toxicity, "time_i" and "time_e" are the lower & upper bound of the interval censored. Note that to avoid error with survival regression in R, 1e-14 has been used instead of 0.

- Generation of Kaplan-Meier estimator and data fitting

```
> KM.fit = survfit(surv_object ~ dose, type="kaplan-meier",
error="greenwood")
> fit = survreg(surv_object ~ dose, dist="distribution_name")
```

Where "distribution_name" can be Exponential, Weibull, Logistic, Extreme, t, Gaussian, Rayleigh, Log logistic and Log-normal

TTE Model

- Time dependent hazard model with a Weibull distribution and dose as significant covariate (multiplicative effect on hazard)
- Model performance to detect toxicity:
  - True positives of 21%, True negatives of 66%
  - False positives of 6.6%, False negatives of 6.2%
  - Sensitivity of 77% , Specificity of 90%

$$h(t) = \frac{shape}{scale} \times \left(\frac{t}{scale}\right)^{(shape-1)} \qquad S(t) = exp\left(-\left(\frac{t}{scale}\right)^{shape}\right)$$

$$scale\ (DOSE) = scale_0 \times \exp\left(\beta_{DOSE}\right)^{DOSE}$$

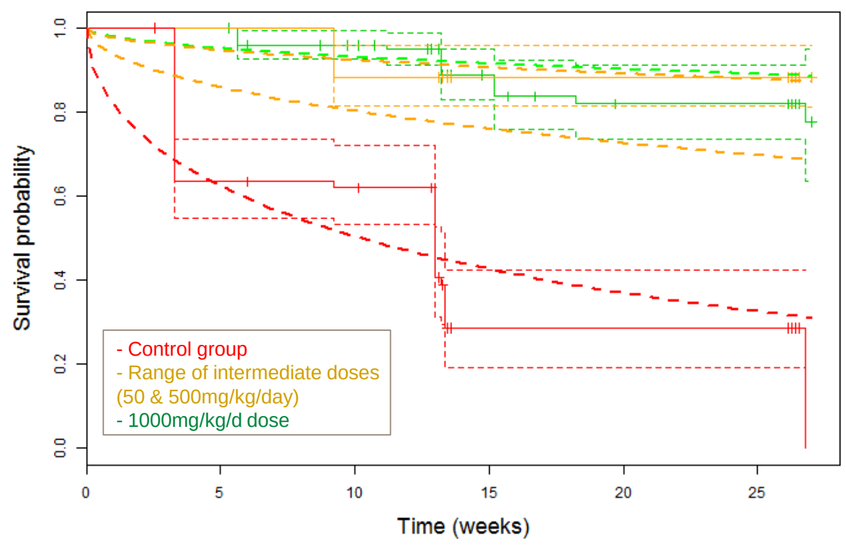
Where h(t) and S(t) are the hazard and the survival functions, t the time and DOSE the dose level

Table 2: Parameter estimates

Parameters	Value	SE	RSE	Transformation
A	7.22	1.98	27.4%	A = ln($scale_0$)
B	0.61	0.46	74.1%	B = ln(1/shape)
b_{DOSE}	-0.0042	0.0019	47%	

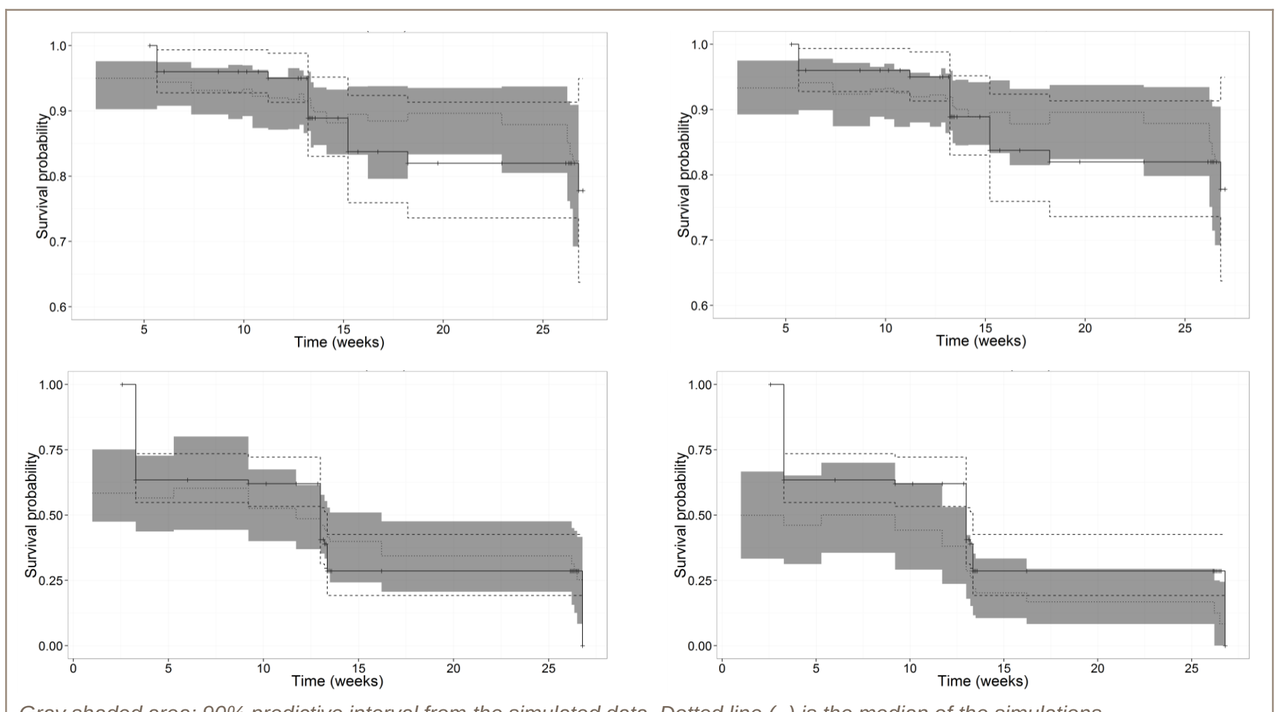
shape = 0.54
$scale_0$ = 1366 weeks for the control arm
$scale_{1000}$ = 20 weeks for a dose of 1000 mg/kg/day

Fig 3: Survival predictions (---) vs. KM plots (—) with 95%CI (···)



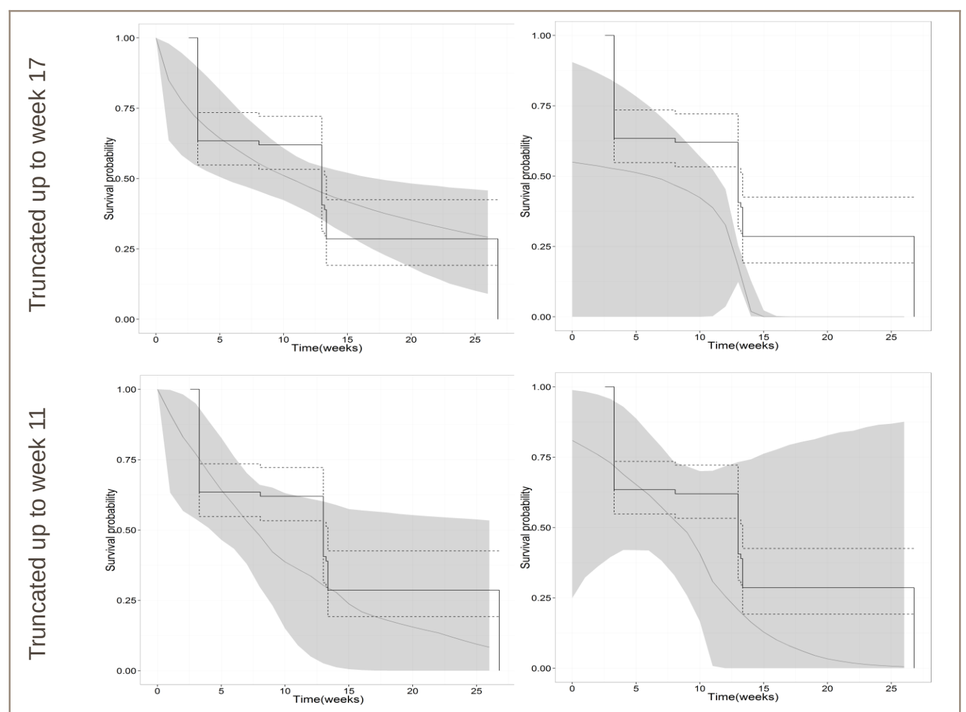
TTE versus Logit[4]

Fig 4: Comparison in data description: VPC with 1000 replicates (left: TTE, right: Logit, top: control group, bottom: 1000 mg/kg/day)



Gray shaded area: 90% predictive interval from the simulated data. Dotted line (···) is the median of the simulations. The continuous black line (—) and black dotted lines (---) are the observed KM and its 90% CI

Fig 5: Comparison in data extrapolation using truncated versions of the original dataset, example with 1000mg/kg/day (left: TTE, right: Logit)



Model predictions (90% CI from bootstrap with 1000 replicates) in gray KM observations (90% CI) in black

Conclusion

We have developed a time dependent hazard model with a Weibull distribution to characterise an irreversible histopathology toxicity. The diagnostic showed a satisfactory fit of the data, despite the high degree of censoring. The comparison with the Logit model shows comparable performance in describing the data with a slight underestimation of survival by the Logit model. The TTE model was found to be more robust in extrapolating survival beyond the observation range. This would suggest to use the TTE approach as a first choice for any model-based application. However, further investigations are needed to explore the domain of application of this kind of approach in drug safety assessment.

References

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