Dose response modelling of staphylococcal enterotoxins using outbreak data: which model, which precision?
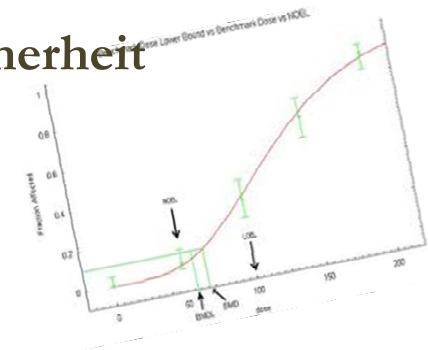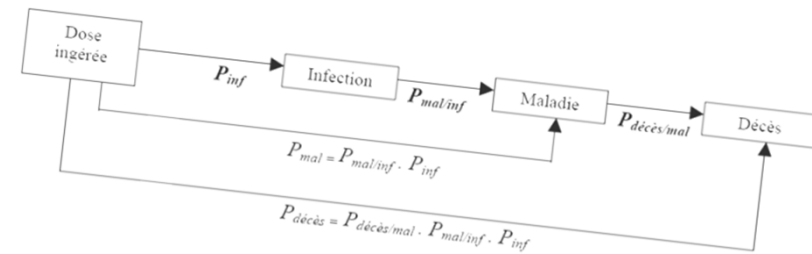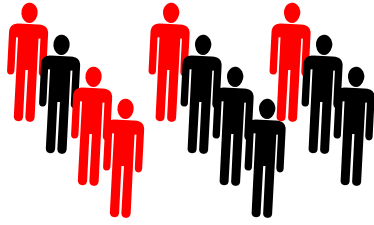
L. Guillier

ANSES FOOD SAFETY LABORATORY
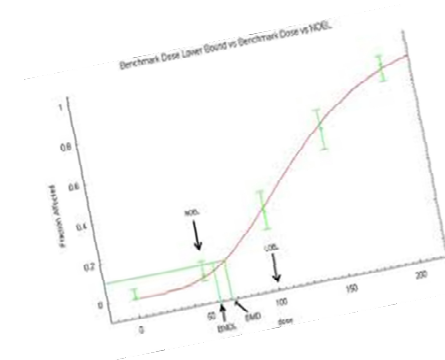
BFR Symposium Zoonosen und Lebensmittelsicherheit
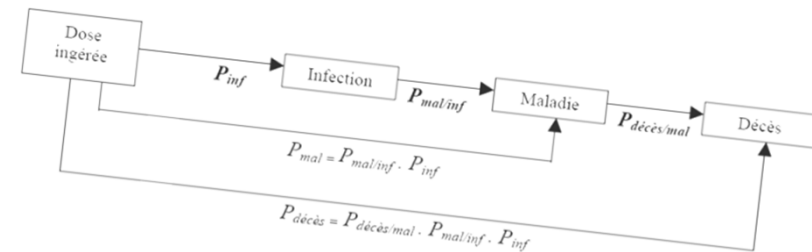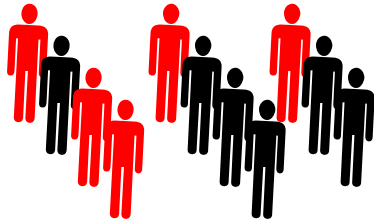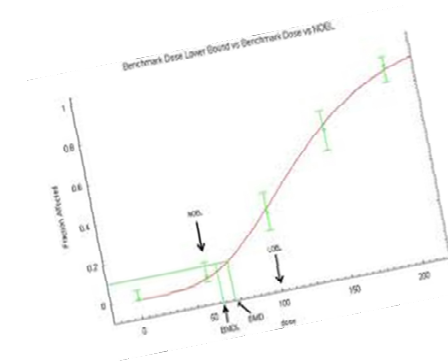**10th and 11th November 2016**

Outline

1. Dose-response modeling

2. Data available and modeling for *Staphylococcus aureus* enterotoxins

3. Conclusion and perspectives

1. Dose-response modeling
2. Data available and modeling for *Staphylococcus aureus* enterotoxins
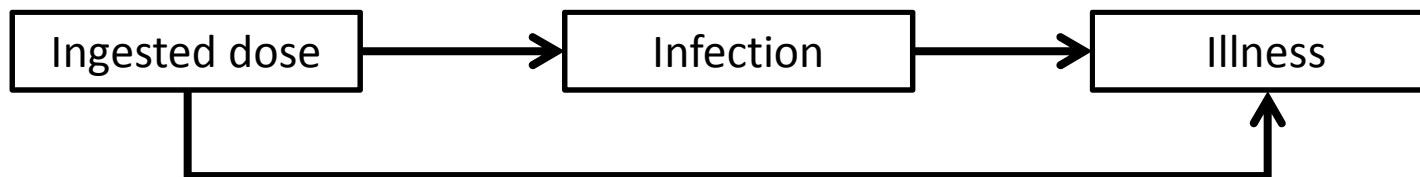3. Conclusions and perspectives

1. Dose-response modeling

- Definition(s)
- Which data ?
- Which models ?

Definition(s)

- Objective of dose-response model:

  To establish a link between exposure to a hazard and the probability of occurrence of an effect

- According to the hazard (toxin, infectious micro-organism): different effects (infection, illness, death, ...) can be of interest

```
┌──────────────┐                                    ┌──────────┐
│ Ingested dose│ ─────────────────────────────────▶ │ Illness  │
└──────────────┘                                    └──────────┘
```

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┌──────────────┐       ┌──────────────┐       ┌──────────┐
│ Ingested dose│ ────▶ │  Infection   │ ────▶ │ Illness  │
└──────────────┘       └──────────────┘       └──────────┘
```

$$P_{ill}=P_{ill/inf}.P_{inf}$$

Definition(s)

- Warning: distinction between dose-effect and dose response!

Effect (intensity) vs Dose; Response (%) vs Dose
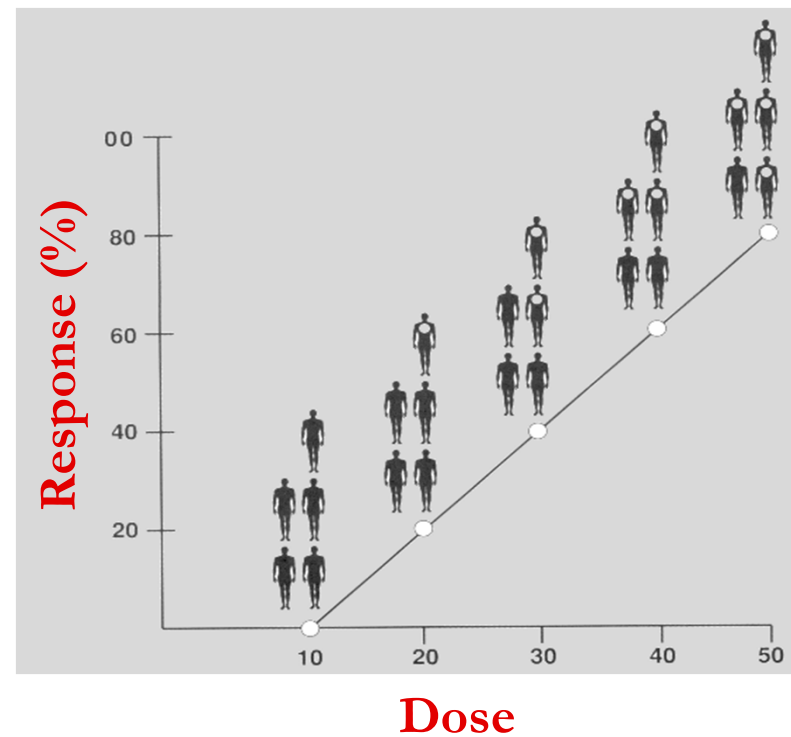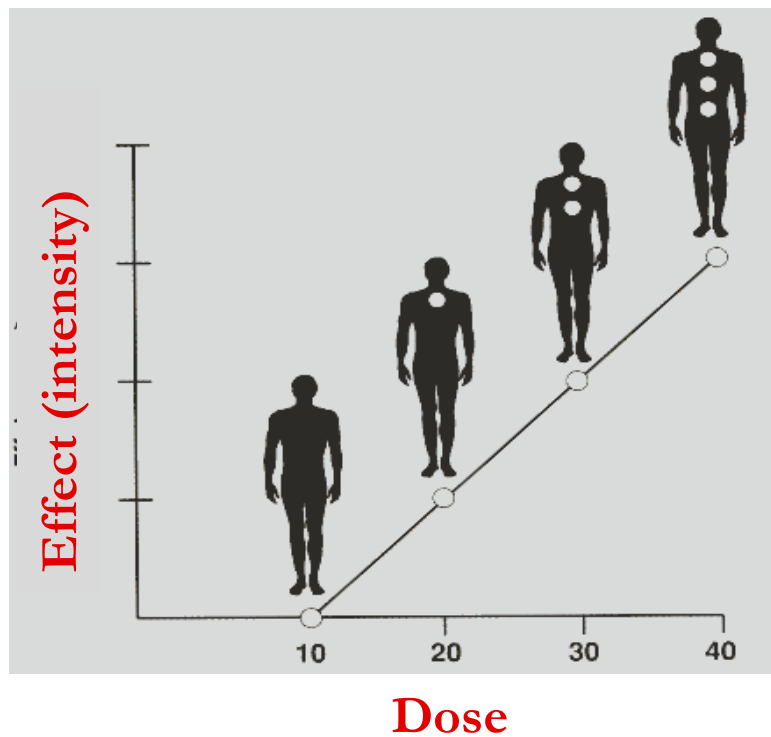
Which data?

- Self experiment (e.g. *Yersinia* Redey, 1974)
- Human volunteers (e.g. 1950s studies for *Clostridium perfringens* and *Salmonella*)
- Animal model (e.g. gerbil for *Listeria monocytogenes*)
- Cell cultures

… ethical problems, relevance of animal models, health status of volunteers

- Alternative: outbreaks
    - *Salmonella* (Teunis et al., 2010)
    - *Trichinella* (Teunis et al., 2012)
    - *Norovirus* (Thébault et al., 2013)
    - *C. perfringens* (Jaloustre, 2013)
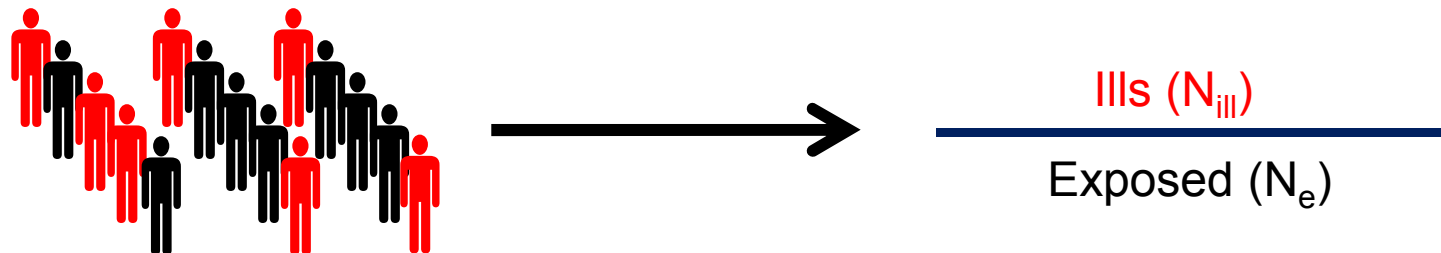   - …
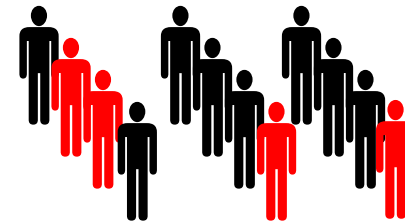
Which data?

- Data needed to be collected during the investigation
  - Effect

  - Observed attack rate $P_{ill} = N_{ill}/N_e$

$$\frac{\text{IIIs } (N_{ill})}{\text{Exposed } (N_e)}$$

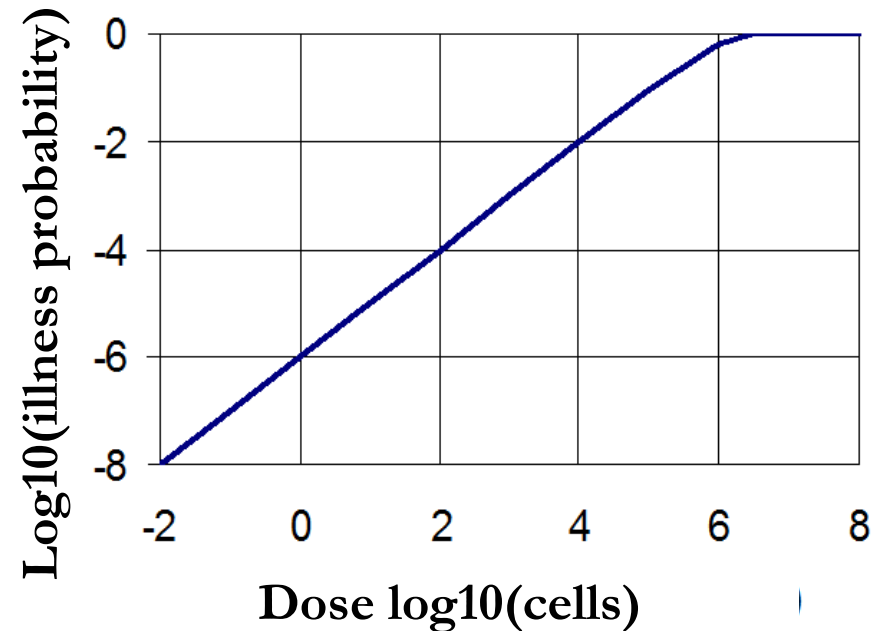 - Ingested dose = Hazard concentration x food intake

- To establish a dose response model: several outbreaks

Models used for infectious organism

- Hypothesis
  - Each ingested cell can trigger infection
  - Cells act independently

- Simple example
  - If homogeneous contamination
  - Each cells have the same

probability to cause infection (r)
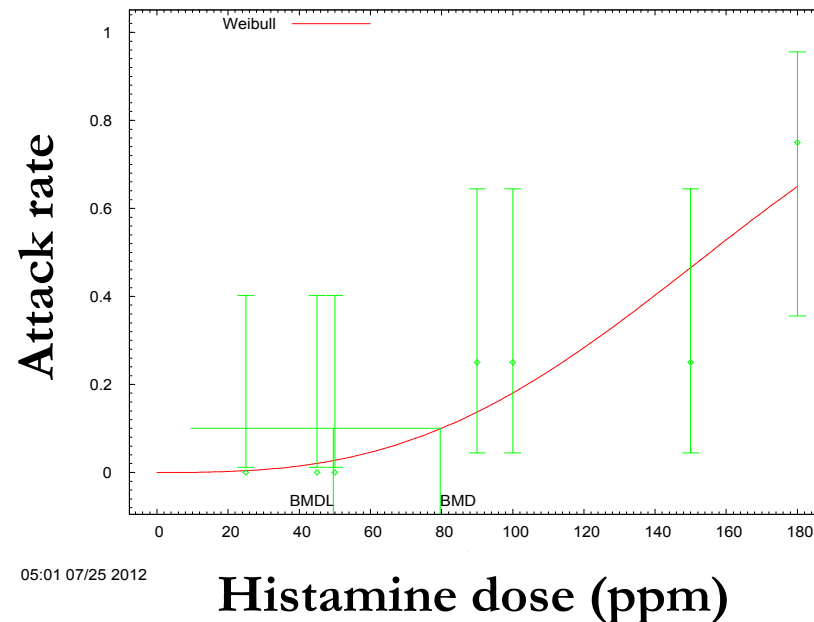
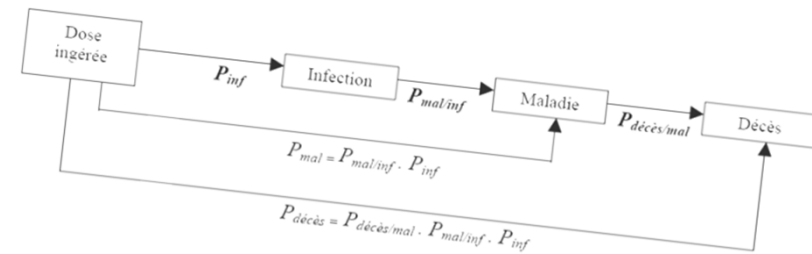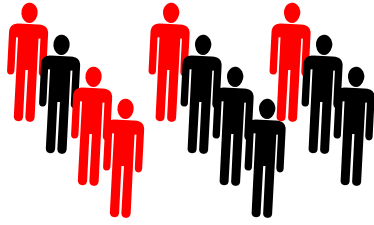$Pill(d)=1 - exp(-r \times dose)$

If $r=10^{-6}$

Models used for toxin

- « Benchmark dose (BMD) methodology »

- BMDx = dose that induces effects in x% of the exposed population

- *"Reference"* value classically used in toxicology (also for allergen) = BMD_{10} or its lower 95%-confidence interval ($BMDL_{10}$)

- Tools:
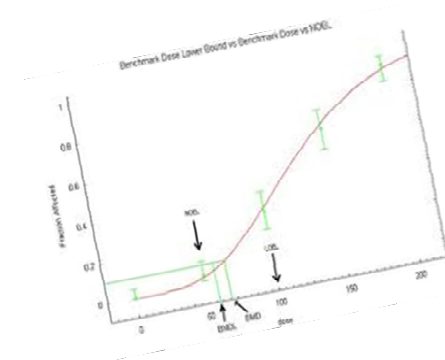 - RIVM PROAST
  - EPA BMDS

FAO/WHO (2012)

05:01 07/25 2012

1. Dose-response modeling
2. Data available and modeling for *Staphylococcus aureus* enterotoxins
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2. Data available and modeling for *Staphylococcus aureus* enterotoxins

- General information on outbreaks
- Data collected during investigation
- BMDL for SEA
- What use of DR

Staphylococcal enterotoxins

- Staphylococcal food poisoning (SFP) is one of the most common food-borne diseases
- SFP is caused by ingestion of staphylococcal enterotoxins (SEs: SEA, SEB, …)
- In France, quantification of SEs is (often) performed during outbreak investigation

- Doses of approximately 20 to 100 ng have been reported effective in causing SFP

Objective: to establish a dose response model for SEs

General information on outbreaks

- 63 outbreaks (mainly French)
  - Period: 2010 to 2014
  - The causative food is identified
  - At least one SE quantified
- For description of effects: 63 outbreaks can be used
- For dose response:
  - Only possible for SEA
  - Not systematically known: number of people exposed
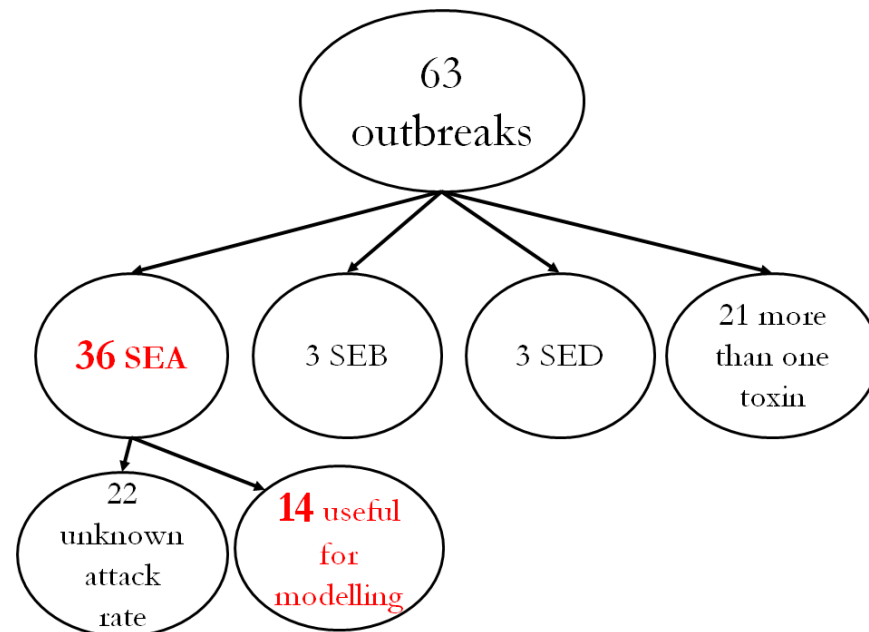
Data collected during investigation

- Effects: in the epidemiological investigation form
  - Time of onset of symptoms in hours
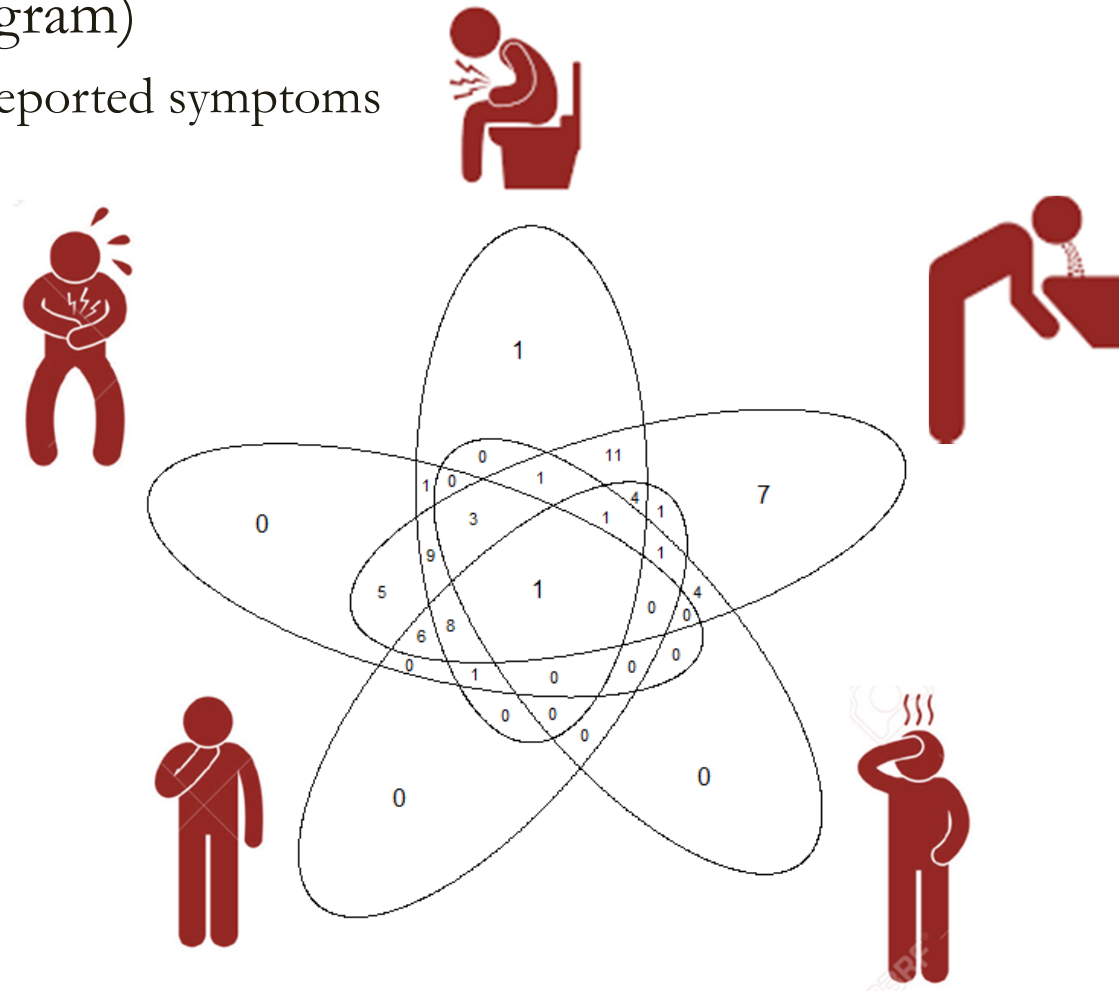 - Observed symptoms (to choose within a list)

- Microbiological information (EURL CPS methods)
  - Presence: extraction-dialysis-qualitative detection test
  - Quantification for each enterotoxin : double sandwich ELISA

Description of symptoms

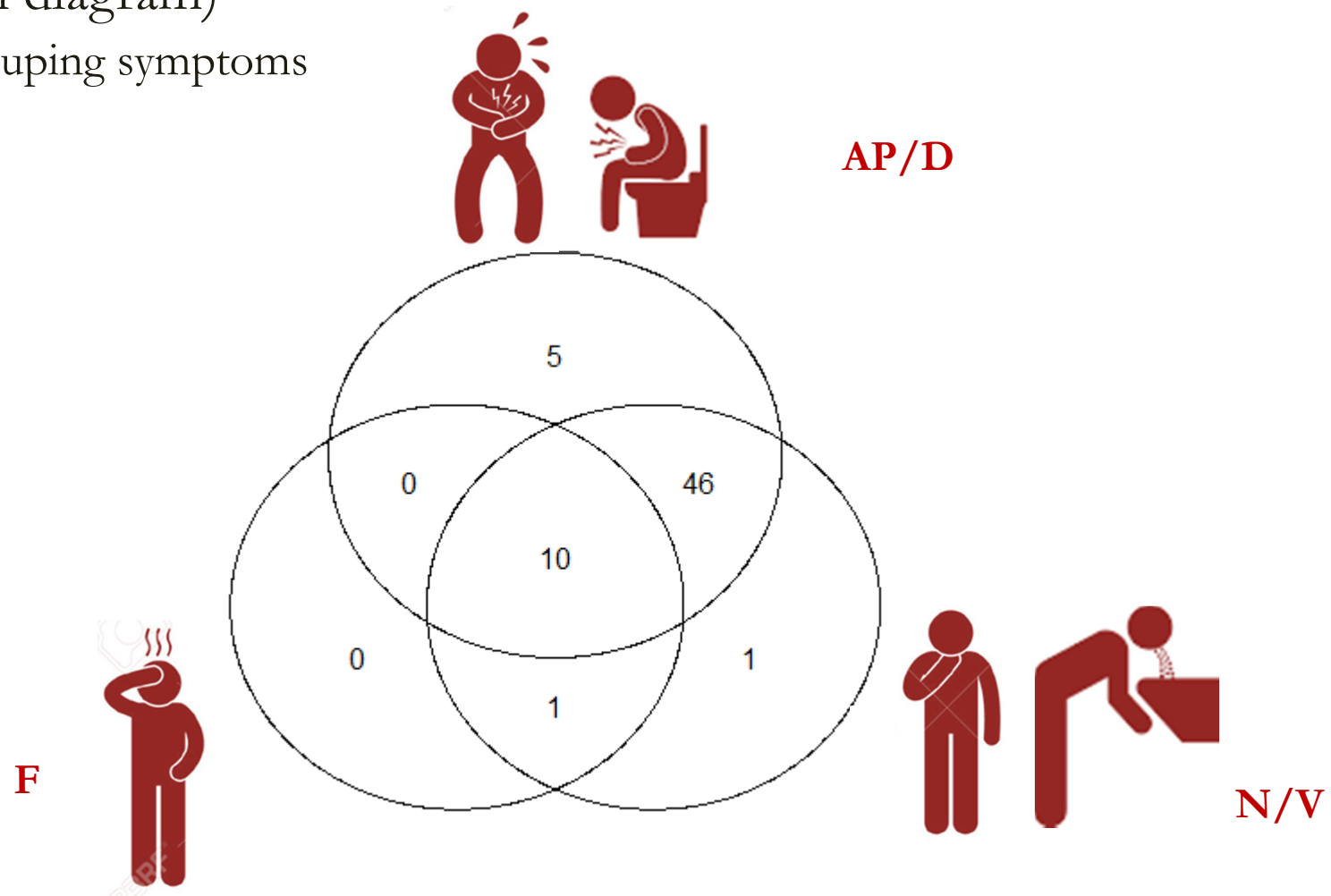Repartition of the identified symptoms in the 63 SFP outbreaks (Venn diagram)

Individual reported symptoms
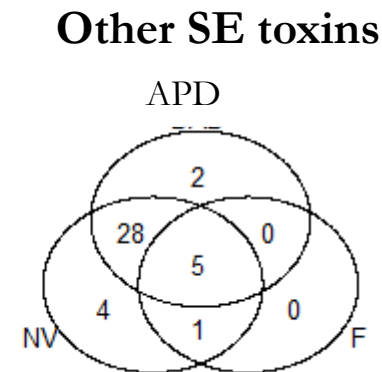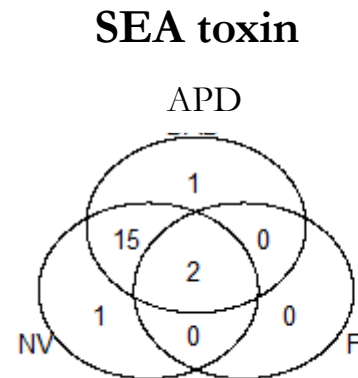
Description of symptoms

Repartition of the identified symptoms in the 63 SFP outbreaks (Venn diagram)
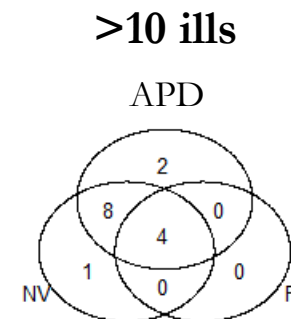
By grouping symptoms

AP/D

F

N/V

5

0

46

10

0

1

1

Description of symptoms

- Symptoms:
    - importance toxin types? No

SEA toxin

APD

1

15   0

2

1   0

NV   0   F

Other SE toxins

APD

2

28   0

5

4   0

NV   1   F

    - Same symptoms for large outbreaks? No

<10 ills

APD

1

30   0

4

2   0

NV   1   F

>10 ills

APD

2

8   0

4

1   0

NV   0   F
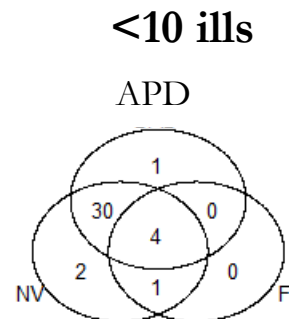
Time of onset of symptoms

- Distribution of times of onset of symptoms of the 63 SFP outbreaks

Relative frequency

Time of onset (h)
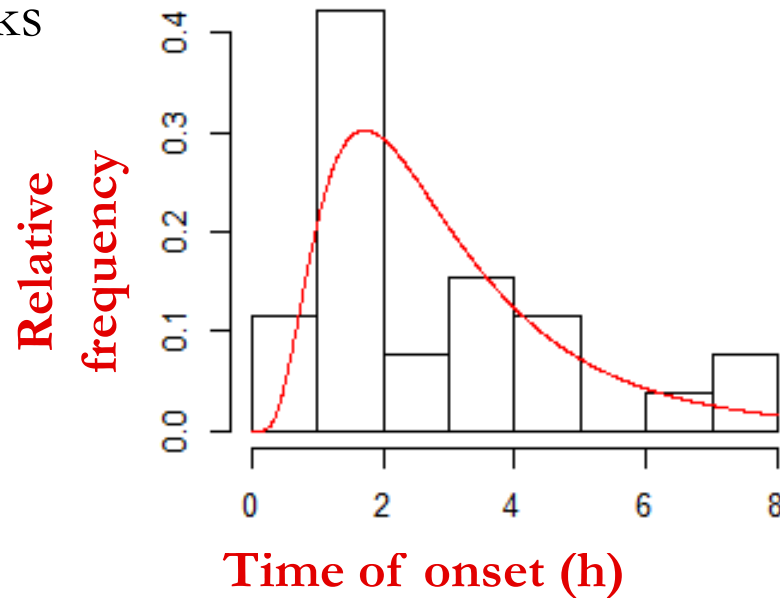
- Variability **not** explained by :
  - The nature of SE involved
  - The amount of toxin
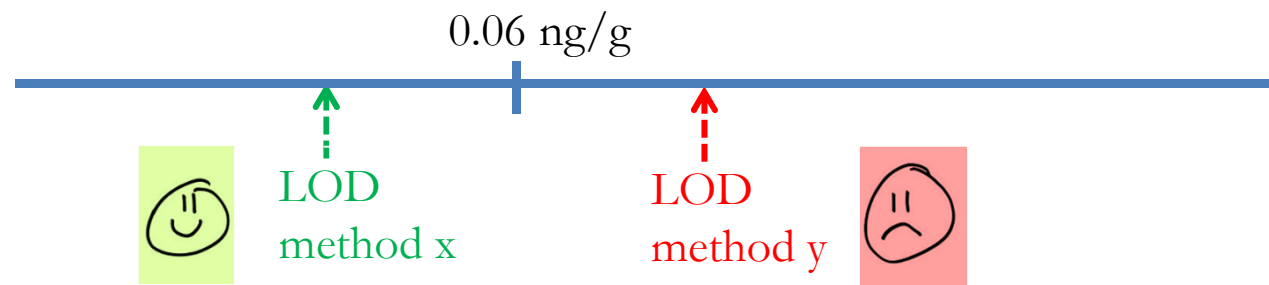
A BMD for SEA

- Weibull model
- BMDL10 for SEA ~ 6 ng
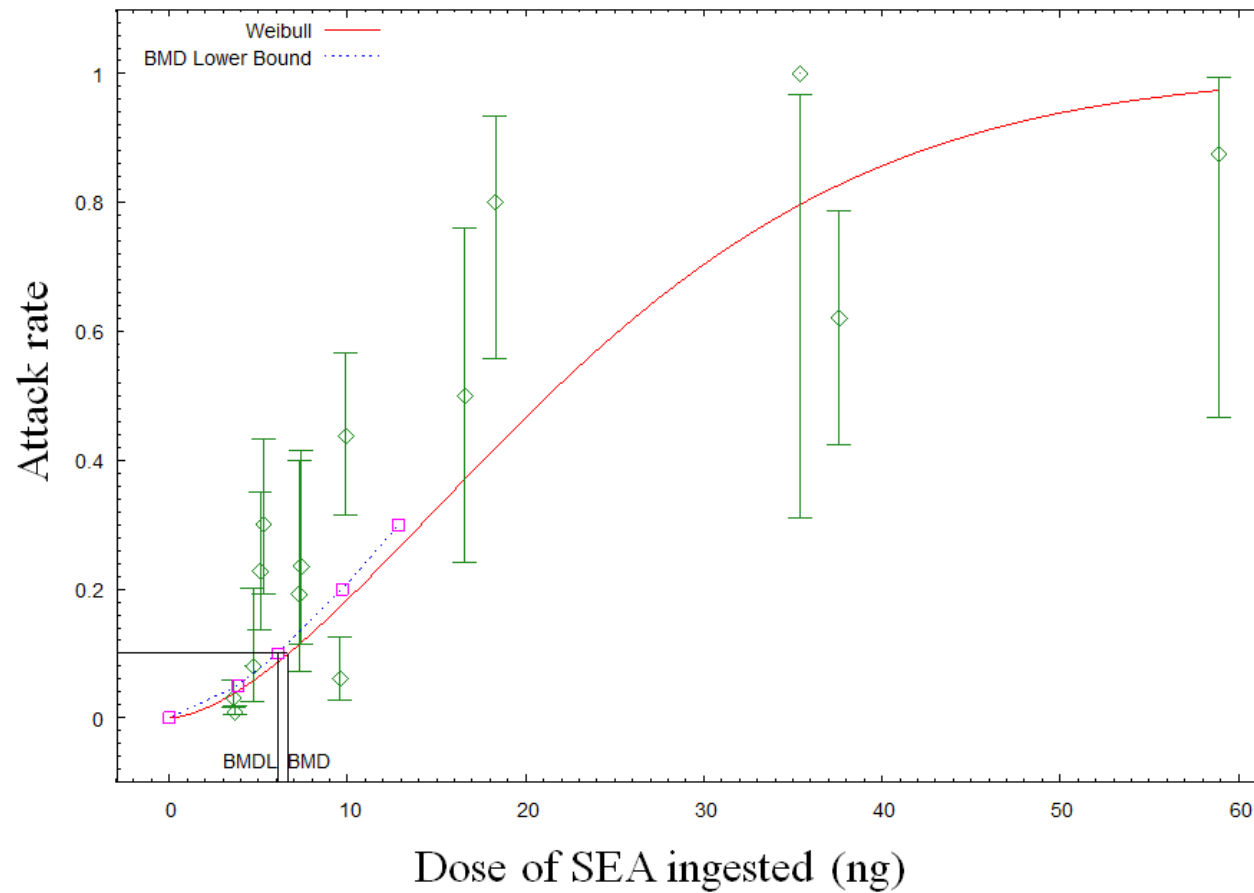
What use of dose response for SEs

Are SE detection methods able to detect concentration that causes illness?

- BMDL10 for SEA ~ 6 ng

- For a 100 g serving size, the LOD for qualitative methods should be lower than 0.06 ng/g for SEA

0.06 ng/g

LOD method x

LOD method y

Perspectives

- Bayesian approach for taking into account uncertainty on doses
- Continuous gathering data (interest for other toxins and understanding the effect of cocktail of SEs)

What use of dose response for SEs

Quantative microbial risk assessment

- Contamination in cfu of raw food, or during process : N0

+

- Predictive microbiology models exist for S. aureus (growth and/or inactivation)

+

- Relation (missing) between cfus and SE production

+

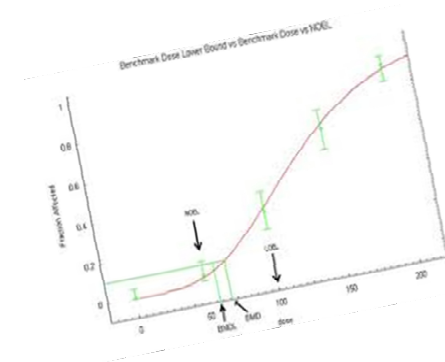- Relation that gives illness for known SE concentration

Perspectives

- To confirm/adapt used thresholds (10^4, $10^{6.5}$ cfu/g)
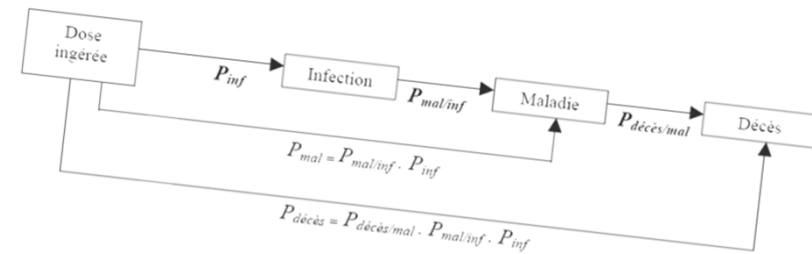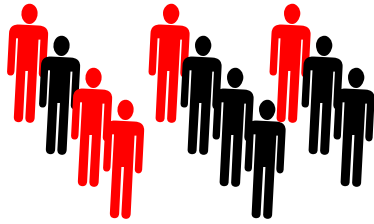
$$P_{mal} = P_{mal/inf} \cdot P_{inf}$$

$$P_{décès} = P_{décès/mal} \cdot P_{mal/inf} \cdot P_{inf}$$

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3. Conclusion and Perspectives

- Conclusion
- Perspectives

Conclusion

- Successful construction of dose response for SEA

- Outbreaks are unique data to learn on dose-response

- BMDL10 for SEA used in the context of acceptance of detection method (LOD of the method should permit to detect BMD

Yet ….

- Bayesian approach for taking into account uncertainty on doses

- Continuous gathering data (interest for other toxins and understanding the effect of cocktail of SEs)
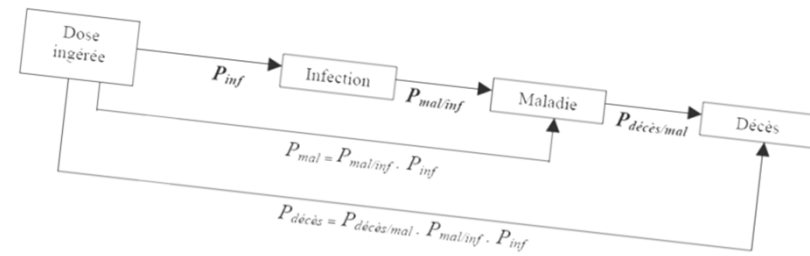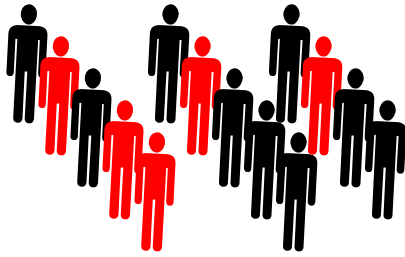
Perspectives

- Uncertainty: Did we fully take it into account?
  - Yes for attack rate
  - For ingested dose ? (concentration x ingested food mass)
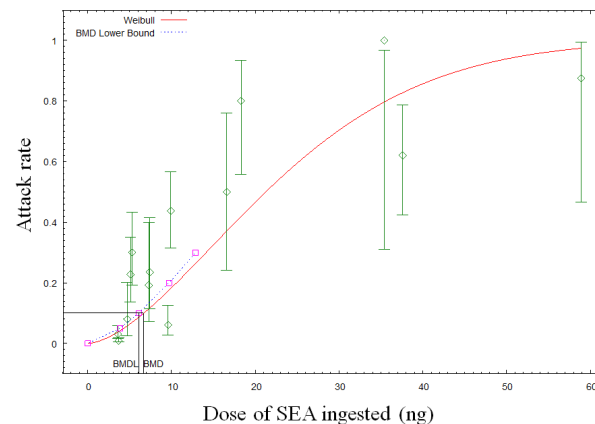
Ongoing: Bayesian approach for taking into account uncertainty on doses

- Continuous gathering data :
  - interest for other toxins
  - understanding the effect of cocktail of SEs (simply additive effect?)

Thank you for your attention!