in collaboration with

Survey on pre-natal developmental toxicity (PNDT) testing

Aims to assess relevance of rabbit gastro-intestinal toxicity for chemcial risk assessment.

Click here to participate in the survey

About the project

Testing for prenatal developmental toxicity (PNDT) is a requirement under the EU REACH and Biocidal Products Regulations. The preferred species are the rat and the rabbit, and testing in two species is often required.

However, rabbits are known to be susceptible to gastrointestinal (GI) imbalances and therefore may be an inappropriate species for the testing of some substances like antibiotics and poorly absorbed materials.

Hence, there is a concern that, for certain substances, testing in rabbits may not provide relevant information for risk assessment, due to species sensitivity to gastrointestinal effects.

This questionnaire survey is aimed at CROs, MS CA experts and consultants involved in the performance and/or evaluation of PNDT studies.

Completing the questionnaire should take between 10-15 minutes. Your participation is highly valued and appreciated.

Aim of the project

The project aims to conclude on the human relevance of rabbit PNDT studies for hazard identification where GI toxicity was observed.

Project team

This project is being conducted by a consortium of EcoMole, VUOS and ReachSpektrum following a tender launched by the European Chemicals Agency (ECHA).

Project funding

The project is funded by the European Chemicals Agency (ECHA) based on the procurement procedure No. ECHA/2017/256

Our team is happy to answer any questions you might have.

Rabbit gastrointestinal toxicity in prenatal developmental (PNDT) studies

* 1. Is your institution involved in the performance and/or evaluation of prenatal developmental toxicity/teratogenicity/embryo-fetal development (PNDT/EFD) studies?

- ◯ YES, BOTH performance and interpretation of PNDT
- ◯ YES, BUT ONLY interpretation of PNDT studies
- ◯ No

2. Which type of PNDT studies have you been performing?

- [ ] Studies according to OECD TG 414
- [ ] Segment II studies according to ICH S5(R3)
- [ ] US EPA Health Effects Test Guideline OPPTS 870.3700
- [ ] Other (please specify)

3. In which regulatory scheme you have been performing the PNDT studies?

- [ ] REACH
- [ ] Biocides
- [ ] Plant Protection Products
- [ ] Pharmaceuticals
- [ ] Veterinary medicine
- [ ] Food additives
- [ ] Cosmetics

Other (please specify)

4. Which species are you using for PNDT studies?

- [ ] Rat
- [ ] Rabbit
- [ ] Mouse
- [ ] Mini pig
- [ ] Other (please specify)

5. Have you observed differences in sensitivities between those species which you have assessed?

- ◯ Yes (maternal and developmental toxicity)
- ◯ Yes (maternal toxicity)
- ◯ Yes (developmental toxicity)
- ◯ No

6. Which type of PNDT studies have you been evaluating?

- [ ] Studies according to OECD TG 414
- [ ] Segment II studies according to ICH S5(R3)
- [ ] US EPA Health Effects Test Guideline OPPTS 870.3700
- [ ] Other (please specify)

7. In which regulatory scheme you have been evaluating the PNDT studies?

- [ ] REACH
- [ ] Biocides
- [ ] Plant Protection Products
- [ ] Pharmaceuticals
- [ ] Veterinary medicine
- [ ] Food additives
- [ ] Cosmetics

Other (please specify)

8. Which species have you seen used for PNDT studies?

- [ ] Rat
- [ ] Rabbit
- [ ] Mouse
- [ ] Mini pig
- [ ] Other (please specify)

9. Have you observed differences in sensitivities between those species which you have assessed?

- ◯ Yes (maternal and developmental toxicity)
- ◯ Yes (maternal toxicity)
- ◯ Yes (developmental toxicity)
- ◯ No

10. Please rank the species based on their sensitivity for **maternal toxicity**, most sensitive first.

- [ ] Rat
- [ ] Rabbit
- [ ] Mouse
- [ ] Mini pig
- [ ] Other

11. Please rank the species based on their sensitivity for **developmental toxicity**, most sensitive first.

- [ ] Rat
- [ ] Rabbit
- [ ] Mouse
- [ ] Mini pig
- [ ] Other

12. Please rank the species based on their sensitivity for maternal toxicity, most sensitive first.

- [ ] Rat
- [ ] Rabbit
- [ ] Mouse
- [ ] Mini pig
- [ ] Other

13. Please rank the species based on their sensitivity for developmental toxicity, most sensitive first.

- [ ] Rat
- [ ] Rabbit
- [ ] Mouse
- [ ] Mini pig
- [ ] Other

14. Please rank the species based on their sensitivity for maternal toxicity, most sensitive first.

- [ ] Rat
- [ ] Rabbit
- [ ] Mouse
- [ ] Mini pig
- [ ] Other

15. Please rank the species based on their sensitivity for maternal toxicity, most sensitive first.

- [ ] Rat
- [ ] Rabbit
- [ ] Mouse
- [ ] Mini pig
- [ ] Other

16. Please rank the species based on their sensitivity for developmental toxicity, most sensitive first.

- [ ] Rat
- [ ] Rabbit
- [ ] Mouse
- [ ] Mini pig
- [ ] Other

17. Please rank the species based on their sensitivity for developmental toxicity, most sensitive first.

- [ ] Rat
- [ ] Rabbit
- [ ] Mouse
- [ ] Mini pig
- [ ] Other

Performance of PNDT studies in rabbits

18. In the past 10 years, how many main PNDT studies have you performed using rabbits?

- ◯ None
- ◯ < 10
- ◯ 10-50
- ◯ >50

Performance of PNDT studies in rabbits

19. How many months do you need for performing a PNDT study in rabbits, including dose-range-finding study/studies and the study report?

20. Did you ever consider rabbits as a species NOT suitable for PNDT testing due to substance-specific biological or physio-chemical properties?

- ◯ No
- ◯ Yes (please specify the criteria you have been using)

Additional comments

21. In case rabbits showed gastrointestinal effects and/or had a LOAEL for maternal toxicity in rabbits that was significantly lower relative to rats, did you investigate further the reason and/or relevance for humans?

- ◯ No
- ◯ Yes (please specify below)

Additional comments

Dose-range-finding and pilot studies in rabbits for PNDT

22. How many dose-range finding and pilot studies are you usually performing (on average) before conducting the main PNDT study in rabbits?

- ◯ None
- ◯ 1
- ◯ 2
- ◯ >2

Additional comments

23. Is it necessary to use pregnant rabbits for a dose-range-finding or pilot study

- ◯ No
- ◯ Yes (please specify below)

Additional comments

24. How many doses do you usually use for a dose-range-finding study?

- ◯ 2
- ◯ 3
- ◯ >3

Additional comments

25. Do you include a control group (vehicle only) in dose-range finding studies?

- ◯ Yes
- ◯ No
- ◯ Depends (please specify below)

26. How many rabbits per dose are you usually using for a dose-range-finding study?

- ◯ <3
- ◯ =3
- ◯ >3

Additional comments

27. Did you have cases where you did not perform the main PNDT study in rabbit due to observed gastrointestinal effects in the dose-range finding or pilot study?

- ◯ No
- ◯ Yes (please specify which type of effect)

28. In case rabbits showed in a dose-range-finding study gastrointestinal effects and/or had a LOAEL for maternal toxicity that was significantly lower than rats, what was the consequence for the performance of a definitive PNDT study?

- ☐ PNDT study in rabbits performed at low, maternally non-toxic doses as identified in the dose-range finding study
- ☐ No PNDT study in rabbits performed
- ☐ Only PNDT study in rats performed
- ☐ PNDT study in another non-rodent species performed (specify in the freetext)
- ☐ PNDT study in a second rodent species - in addition to rat - performed (please specify below)

Additional comments

Performance of PNDT studies in species other than rat and rabbit

29. In the past 10 years, how many main PNDT studies in**mice** have you performed?

- ◯ None
- ◯ <10
- ◯ 10-50
- ◯ >50

Performance of PNDT studies in species other than rat and rabbit

30. Why did you use mouse as species for PNDT testing, for which regulatory purpose, in which combination with another species?

31. How reliable do you judge the results of PNDT studies in mice for hazard identification?

- ◯ Reliable
- ◯ Reliable with restrictions (please specify)
- ◯ Not reliable (please specify)

Additional comments

Performance of PNDT studies in species other than rat and rabbit

32. In the past 10 years, how many PNDT studies in**non-rodent species other than rabbits** have you performed?

- ◯ None
- ◯ <10
- ◯ 10-50
- ◯ >50

Performance of PNDT studies in species other than rat and rabbit

33. Which non-rodent species did you use for PNDT testing, for which regulatory purpose and in which combination with another species?

Interpretation of PNDT studies in rabbits

34. Have you ever observed gastrointestinal effects in rabbits such as clinical effects on faeces (e.g. diarrhoea), or pathology (e.g. gastrointestinal tract inflammation) or mortality/abortions, but not in rats?

- ◯ Yes
- ◯ No

Interpretation of PNDT studies in rabbits

35. How frequently did you observe gastrointestinal effects in rabbits such as clinical effects on faeces (e.g. diarrhoea), or pathology (e.g. gastrointestinal tract inflammation) or mortality/abortions, but not in rats?

- ◯ Rarely (<10%)
- ◯ Once in a while (10-30%)
- ◯ More frequently (>30%)
- ◯ I do not know

36. Did you ever observe GI toxicity in control animals

- ◯ No
- ◯ Yes (please specify below which vehicles were used and in which doses)

Additional comments

37. How frequently did you observe that the rabbit had a LOAEL for maternal toxicity that was significantly lower than rats (i.e. for the same substance, route of administration and similar doses)?

- ◯ Never (0%)
- ◯ Rarely (<10%)
- ◯ Once in a while (10-30%)
- ◯ More frequently (>30%)
- ◯ I do not know

38. How frequently did you observe that the rabbit had a LOAEL for maternal toxicity that was significantly lower than rats (i.e. for the same substance, route of administration and similar doses)?

- ◯ Never (0%)
- ◯ Rarely (<10%)
- ◯ Once in a while (10-30%)
- ◯ More frequently (>30%)
- ◯ I do not know

Interpretation of PNDT studies in rabbits

39. Could you provide information about the reasons observed/reported that led to higher maternal sensitivity of rabbits compared to rats?

- [ ] No
- [ ] Gastrointestinal imbalances/disturbance of gut flora (e.g., diarrhoea or reduced faeces production)
- [ ] Irritation/corrosion of the gastrointestinal tract
- [ ] Others (if possible provide explanation under freetext field below and provide additional background information)

Additional comments

40. Could you provide information on type of substances that led to higher maternal toxicity in rabbits compared to rats?

- [ ] No
- [ ] Irritating/corrosive substances
- [ ] Substances of low bioavailability
- [ ] Antibiotics/antimicrobials
- [ ] Others (please specify below)

Additional comments

Interpretation of PNDT studies in rabbits

41. Do you usually consider if severe gastrointestinal effects observed in rabbits but not in rats would be relevant for humans?

- ◯ No such considerations
- ◯ Effects usually considered as relevant for humans
- ◯ Effects may be considered as not relevant for humans

Interpretation of PNDT studies in rabbits

42. What is the consequence when you judged the effects observed in rabbits as not relevant for humans?

- [ ] Study disregarded
- [ ] Maternal effects not considered to derive a Point of Departure for risk assessment
- [ ] Maternal effects not considered for STOT RE classification
- [ ] Developmental effects considered for evaluation
- [ ] Developmental effects not considered for evaluation

Additional comments

43. Would you be available for further contact to elaborate on the answers above? (please supply contact details below, email, telephone)