The PBT Assessment of Veterinary Pharmaceuticals

A reason for equivalent concern

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GDCh

What is PBT or vPvB?

PBT Pharmaceuticals are compounds that possess the following three inherent properties as indicators of hazard:

- **Persistent or very persistent,**
- **Bioaccumulative or very bioaccumulative,**
- **Toxic**

Why a separate PBT assessment?

For PBT substances a „safe“ concentration in the environment cannot be established with sufficient reliability.
Therefore , for PBT/vPvB substances the main focus shifts from exposure to the inherent safety of a substance.
This way of thinking is called hazard assessment.

Current procedure

CRITERIA

For screening PBT

Potentially **P**

Not readily biodegradable

Standard tests for veterinary pharmaceuticals

OECD 301 A-F

OECD 307 (housing, pasture management)
OECD 308 (aquaculture)

Potentially **B**

Log Kow ≥ 4,5

OECD 107/ 117/ 123,
OECD 122 Draft for ionisable substances

OECD 305 (In revision, including fish feeding study)

Potentially **T**

No screening criteria for pharmaceuticals, chronic ecotoxicity data needed

No acute tests required - use of OECD 201/ 210/211 results

OECD 201 / 210 / 211
CMR label

For the definitive PBT Assessment PBT/vPvB

Persistent

DT50 > **60 d in marine water**
or
DT50 > **40/60 d in fresh- or estuarine water**
or
DT50 > **180 d in marine sediment**
or
DT50 > **120/180 d in fresh- or estuarine sediment**
or
DT50 > **120/180 d in soil**

Bioaccumulative

BCF > **2000/5000**

Toxic

NOEC < 0,01 mg/l for marine or freshwater organism, or

Substance is classified as:

carcinogenic (category 1 or 2) or
mutagenic (category 1 or 2) or,
toxic for reproduction (category 1, 2, or 3), e.g. for endocrine disruptors

or
there is **other evidence of chronic toxicity**

STEPWISE APPROACH

Log Kow ≥ 4,5?
or exists other relevant information about bioaccumulation, e.g.
BCF, BAF
BMF > 1?
yes

Follow the questions, if any answer is no, no further testing is required

Conclude potentially B, B or vB
Further testing is required

Stepwise procedure is recommended

According UBA :
First P (clarification of persistence), then B, then T

1. Test on ready biodegradability (OECD 301)
2. Simulation laboratory study on testing of persistence (e.g. OECD 307),
3. Bioaccumulation study with fish (OECD 305)
4. Long-term toxicity test, firstly non-vertebrate species, unless there are indications that fish is the most sensitive group.

Not readily biodegradable?
yes

Further P testing is recommended
DT50 > 120 d in soil?
Other criteria fulfilled?
Yes, P fulfilled

DT50 > 180 d in soil?
Yes, vP fulfilled

Further B testing is recommended
BCF > 2000?
Yes, B fulfilled

BCF > 5000?
Yes, vB fulfilled

Further T testing
NOEC < 0,01 mg/l
or other criteria fulfilled
Yes, T fulfilled

PBT confirmed

vPvB confirmed

Open issues

Generally

- **No guidance is given where in the risk assessment of VMP and how to perform the PBT assessment**
- **No consequences for authorisation**
- **Relevant data are submitted only in phase II, Tier B**

Practically

- **For determination of logD for ionisable substances no finalised guidance exists (only draft version, OECD 122)**
- **Indicators like BCF calculated from monitoring data can provide supplementary information on bioaccumulation**

Pay attention to

- **Normalisation of the DT50 values to the average European outdoor temperature of 12 °C (see TGD, point 2.3.6)**
- **Normalisation of BCF data to lipid content of 5 %**
- **Additional criteria for toxicity, e.g. endocrine disruptors, CMR substances, etc.**

Outlook

- **EU wide harmonisation of PBT assessment and its consequences for authorisation (ongoing discussions in CVMP and ECHA)**
- **Revision of VICH guidelines in view of data requirements (PBT assessment in phase I)**