CLASSIFICATION OF DEVELOPMENTAL TOXIC PESTICIDES AND NEGLIGIBLE EXPOSURE

Perspective of the regulator

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NEGLIGIBLE EXPOSURE

An active substance, safener or synergist shall only be approved, if not classified *toxic for reproduction category 1A or 1B*, or not considered to have *endocrine disrupting effects that may cause adverse effects*

unless

Exposure in humans is negligible:

(non-dietary)

- product is used in closed systems or

- in other conditions excluding contact with humans

and where *(dietary)*

- residues on food and feed do not exceed the *default value* (0.01 mg/kg) set in accordance Regulation (EC) No 396/2005

"NEGLIGIBLE" ?

'Negligible' is not equal to zero (the "myth" of ZERO exposure)

***Oxford English Dictionary* =**

"so small or unimportant as to be not worth considering; insignificant".

Negligible implies risk management decisions which get their basis from risk assessment

'negligible' can be considered a level so small that it does not appreciably add to the risk and can safely be ignored

(Draft Technical Guidance on Negligible Exposure under Realistic Conditions of Use - European Commission, 2015)

EFSA assesses Negligible Exposure (2017)

Active substance Pymetrozine pyridine azomethine, insecticide
Repro Cat 2 (malformations of the pubis in rats and rabbits with low maternal toxicity, NOAELs 30 and 10 mg/kg bw in rats, and rabbits also impaired sperm production in adult rodents,
possible enzyme effect – steroidogenesis ??)

Dietary **- requested uses in potato and oilseed rape:**
individual **residues of pymetrozine and metabolites unlikely to exceed 0.01 mg/kg**
But **incomplete toxicological characterization of the pertinent plant metabolites**

Non-dietary **– recommended a margin of exposure > 1000**
(NOAEL for relevant effect to actual/estimated exposure of
operators/workers/bystanders/residents (EFSA 2014)
acute exposure of operators without risk mitigation measure
= MoE < 1000

Therefore "NEGLIGIBLE" exposure can be challenged

by regulatory developments that can highlight new aspects of *Hazard identification/Characterization*, like

- endocrine-related developmental toxicity, as flagged by the inclusion of ano-genital distance (AGD) in the revised OECD TG 414 (2018)

- developmental neurotoxicity

By new approaches to define *toxicologically relevant exposures* such as

- identification of toxicologically relevant residues

- cumulative assessment groupings

Some comments on AGD

- *Newly introduced regulatory* endpoint in prenatal developmental toxicity (new OECD 414, 2018)
- the most relevant is AGD relative to body weight

- Androgen (and androgen/estrogen) dependent: highest sensitivity in fetal masculinization programming window (8-14 wk gestation in humans)
- *corroborated by human studies*: rather than an adverse effect per se is a lifelong predictor of prenatal androgen disruption

A *cross-cutting predictor*: beyond AR antagonism-ER agonism, androgen-related pathways: e.g., DBP (steroidogenesis through PPAR-a and CoAR), possibly also prolactin (Camargo et al., 2017)

- if applied and interpreted in a robust way, it can implement classification and/or NOAELs (usually more conservative)

Developmental neurotoxicity (OECD TG 426 and beyond)

- Main issue for pesticides, *not consistently tackled in the EU*
- TG 426 or DNT cohort in OECD TG 443 (EOGRT) can be *triggered* by standard adult and/or reproductive toxicity tests
- However, an accuratev appraisal of neurotoxicity and DNT may significantly impact on safety parameters (see lowering of ADI/AOEL/ARfD for neonicotinoids, EFSA 2013)

OECD-EFSA Worksop report (2017): *tiered strategy*
In vitro assays needed in new harmonized testing framework
in vitro screening and prioritization (for further testing)
inclusion of DNT in vitro data as part of weight of evidence

- In principle, a more robust and consistent tiered approach to DNT might lead to
increase active substances classified as developmental toxicants

And now let's go to

New approaches to define
***Toxicologically Relevant* Exposures**

Which may modify the definition of
Negligible

The identification of Toxicologically Relevant Residues (EFSA guidance 2016)

- Residues often *do not coincide* with the parent substance
- a number of different compounds resulting from abiotic or biotic (plant) transformation, which
- can *sum up* with the active substance (comparable toxicity, possibly using relative potency factor)
- or have qualitatively different profile

- first tier of residue assessment is the *genotoxicity* potential

- 2nd tier, othert properties of concern: while DevTox is not easily amenable to QSAR, *ReadAcross* methods can be used

There are several cases....

Toxicologically Relevant Residues (II)

- parent compound has *no DART precedents* and the tested metabolite is *qualitatively similar*,
***no further testing* to explore DART endpoints**

- if the tested metabolite is considered qualitatively different from parent compound either with or without DART precedents, then *options*:
apply an additional safety factor of 10 to the metabolite RD;
testing of the metabolite in OECD TG 422
direct testing of the DART endpoints (TG 414, 416, 443))

- the parent compound *has DART precedent and the tested metabolite is qualitatively similar*, options:
the same hazard for the metabolite would be assumed, or
testing for the DART endpoint of interest

Two examples from EFSA 2016 (III)

- Spiroxamine: Cat 2 DART – cleft palate rats (NOAEL of 30 mg/kg, vs. 10 mg/kg NOAEL used for ArfD)

- Many metabolites

- one group similar to parent compound

- The representative of another group (M03) less potent than parent in repeated dose toxicity: *DART testing is waived* for this group

- A few metabolites of qualitative and quantiatative relevance are identified and *require further assessment.*

Two examples from EFSA 2016 (IIIb)

- Epoxiconazole (EP): *Cat 1b DART* – high embryofetotoxicity in rodents and rabbits, steroid synthesis inhibition (DART NOAEL of 20 mg/kg is basis for ArfD)

- Many metabolites: for conjugated metabolites (i.e. glucosides and glucuronides) testing in vitro for enzyme effects will assess the Relative Potency in comparison to EP

- Other metabolites (group B) highly structurally similar to EP: no further testing required

- Another group of metabolites (group C) can have significant differences from EP

M06 (expected to be the *most reactive*) should be tested
in *OECD 414*
and in vitro for enzyme disruption (possibly in comparison with EP)

Cumulative exposure (EFSA, 2013)

- Consumer exposure to residues may be *viewed differently* when considering that

More than 20% of fruit/vegetable samples show residues of multiple active substances according to EU residue monitoring programmes

Compounds with similar effects in the same target organ may have additive effects, *irrespective* of chemical structure and molecular mechanism ("phenotypic effect")

the new OECD 414 requires the assessment of *thyroid activity in the dam*

(the foetal thyroid depends from maternal thyroid, thus impaired maternal thyroid = prenatal thyroid disruption), thus..

- Cumulative assessment grouping for thyroid in (EFSA 2013)

Cumulative assesssment grouping for thyroid (EFSA, 2013)

- cumulative assessment grouping defined by effects occurring at level of *organ* (thyroid follicular cells) or of *system* (hypothalamic-pituitary-thyroid axis) through changes in thyroid hormone levels

Substances affecting thyroid follicular cells,
displaying changes in T3/T4 or TSH levels,
eliciting follicular cell hypertrophy/hyperplasia or neoplasia,
are allocated in the same group (in total 96 substances).
The specific effects used to define this group are apparently interrelated to one another by a chain of events.
While the precise mechanism of action *is currently unknown* for many substances, and further refinements are expected by increased knowledge
several different mechanisms of action are expected to contribute to a final deleterious common effect, i.e. decrease in T3/T4 action.

In conclusion

New insights in testing may put new substances among those where "negligible exposure" has to be assessed because of the their classification as Developmental Toxicants

New insights in risk assessment may impact on the definition of negligible exposure

Negligible exposure *handle with care*

Thank You for patient listening!

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