Ethoprophos: Timelines, actions and decision taken by Bayer

On June 1, 2023, an article by Mie and Rudén was published in the journal Environmental Health, in which crop protection product manufacturers are accused of having allegedly withheld studies on developmental neurotoxicity from the EU approval process and thus having hindered the evaluation of various active substances. Bayer is mentioned in connection with three active ingredients.

Bayer's position in this regard can be also found in this public statement: Transparency in Crop Protection | Bayer Global

Bayer made a submission for ethoprophos to the EU authorities in April 2002, in accordance with EU law governing the approval of pesticidal substances (Directive 91/414/EEC) at the time. In addition to a large number of studies on toxicity, studies on developmental neurotoxicity were also submitted initially and at a later stage in the approval process. A further study required by the US authorities was planned, but not yet completed at the time of the EU evaluation of the data package. The results of this study were consistent with the effects observed in an already submitted study, thus it did not provide additional information which could have an impact on the assessment. Consequently, based on the studies already available, EU regulators were able to carry out a complete risk assessment, including developmental neurotoxicity. All studies were passed on to AMVAC when the active ingredient was divested in 2010.

In this context and in line with Bayer's commitment to transparency, the following overview provides further information with regards to timelines as well actions and decision taken by Bayer for the active ingredient ethoprophos:

***2002**: Bayer submits a complete dossier for EU approval process*

In April 2002, Bayer submitted the ethoprophos approval dossier to EU authorities under Directive 91/414/EEC.

***2004**: Bayer submits a new DNT study, requested by US authorities, also to EU authorities*

In August 1999, the US Environmental Protection Agency (EPA) had issued a broad data call-in[1] for Developmental Neurotoxicity (DNT) studies[2] for 140 substances (link), including ethoprophos.

The **DNT study**[3] (n° M-240197-01-1), as requested by US authorities under the data call-in, was **finalized in September 2004**, two years after the required data for the EU approval process for ethoprophos had been submitted (April 2002).

Bayer experts found that this **DNT study showed new safety information** and – *in line with EU requirements* – **Bayer submitted it to the EU authorities during the ongoing EU approval assessment period (in October 2004)**.

The **final assessment of ethoprophos** by the European Food Safety Authority (EFSA) was published in **2006** and ***"did not show any evidence of developmental neurotoxicity"***.

***2005**: A repeat-dose CCA which US-EPA also had requested was finalized, and showed no new information which could have an impact on the EU assessment*

[1] The US system uses a **data call-in** approach. Here, the US-EPA would define the scientific area that needs further investigation, foster a discussion with stakeholder from academia, industry and civil society on how to support such objective and the US-EPA would then decide on the exact requirements. Industry would then get a specified time to generate and submit the requested data, followed by an evaluation and decision by US-EPA. This process is different from the EU approval process.

[2] The US-EPA had recently (in August 1998) established new test guidelines for DNT (link), hence the data call-in process for DNT followed shortly after that.

[3] Developmental neurotoxicity (DNT) investigates potential toxic effects of a specific substance on the developing nervous system. DNT studies investigate if the offspring (young animals) is more sensitive than their parents (adult animals).

Bayer have already submitted to both the EU and US authorities **an 'acute comparative cholinesterase assay (acute CCA)'** (n° M-241516-01-1)[4].

As a follow-up of the acute CCA, the US authorities **requested a 'repeat-dose CCA'** (n° M-252722-01-1), which was **submitted to the US authorities in June 2005**. The results from the repeat-dose CCA were **consistent with the effects[5] observed in the earlier acute CCA** (already submitted to the EU as the DNT study) and was thus **already known to EU authorities and considered in their risk assessment**.

In 2005, Bayer experts therefore concluded that the repeat-dose CCA **did *not* contain any new safety information that suggested an impact on the EU risk assessment**. For this reason, in accordance with EU requirements[6], it was **not submitted to EU authorities**.

***2006**: EU & US authorities reach similar scientific conclusions, confirming the Bayer experts' assessment of the (new) repeat-dose CCA study*

At the end of their respective assessment processes, both the US-EPA (with access to the repeat dose CCA) and the EFSA (without access to the repeat dose CCA), independently **derived very similar reference values to be used in risk assessments**. This confirmed our experts´ assessment, that the results from the repeat-dose CCA would not have impacted the risk assessment.

Consequently, ethoprophos was re-registered for 10 years in the EU, and it remains registered in the US until today.

***2010**: Further developments*

In December 2010, **Bayer divested ethoprophos to AMVAC**. Bayer can therefore not comment on the subsequent renewal process.

[4] CCA studies contribute to the assessment of developmental neurotoxicity by measuring the effects on a certain enzyme activity.
[5] This repeat-dose CCA study results were consistent with the effects observed in the previous studies, and a different sensitivity of maternal and offspring animals was already described before.
[6] **Directive 91/414/EEC did not contain any provision for data submission during the pending approval process**. In practice, the EU process prerequisites that the dossier contains all required data. The period between submission of the dossier (and its completeness check) and approval lacks any regulation for submission of regular data to complement the dossier, which is only possible in exceptional cases. The current and also earlier EU pesticide regulations require, however, that after the approval decision any information which "suggests" that the approval criteria are not met any longer, i.e. potential harmful effects on human ("adverse data"), has to be notified immediately and do not impose requirements to provide unnecessary information not meeting these criteria. Comparable provisions for the period between dossier submission and approval decision do not exist. It is and was always without doubt for Bayer, however, that the same standard must apply also during this period to safeguard an appropriately efficient but under all circumstances robust safety evaluation process. Bayer has fully complied with these standards.