EUROPEAN MEDICINES AGENCY

efsa

Comments on the rationale for a non-divergent position between EFSA conclusions on 4-chloroaniline (PCA) and EMA's CHMP/ICH conclusions

Legal background and scope of this document

EFSA is responsible to deliver risk assessment or scientific and technical advice to the EU risk managers as outlined in Regulation (EC) No 178/2002[1] or in other relevant sectoral legal acts, such as Regulation (EC) No 1107/2009.[2]

EMA is responsible for delivering scientific advice to the EU risk managers as outlined in Regulation (EC) No 726/2004,[3] or in other relevant sectoral legal acts.

As per Article 30 of Regulation (EC) No 178/2002, whenever a potential divergence between EFSA and another Union body responsible to provide risk assessment is identified, EFSA should cooperate with the other body with the aim of resolving the divergence, or, when this is not possible, of documenting in an appropriate manner the underlying reasoning for such divergence. The document outlining the scientific rationale for the divergence is to be shared with the European Commission and made publicly available.

The present document complies with the process and requirement briefly outlined above.

Factual background

On 13 March 2015, EFSA received a mandate[4] from the European Commission to provide its opinion on the potential exposure to PCA (4-chloroaniline, impurity and metabolite of diflubenzuron) as a residue and its potential toxicological relevance. EFSA therefore undertook a peer review of the rapporteur Member State's (RMS) review of the approval of the active substance diflubenzuron regarding PCA, reaching its conclusions in August 2015. As diflubenzuron is used in veterinary medicines as well as in pesticides EFSA involved the CVMP (Committee for Veterinary Medicinal Products) in its review.

At EMA, the CVMP originally assessed diflubenzuron in 1998,[5] following which MRLs were established in salmon. Subsequently, in 2015, the Committee reviewed its MRL opinion following a request from the Commission and in light of concerns over the metabolite PCA. EFSA was consulted during the CVMP review, which was finalised in May 2015. The resulting full report will be published following adoption of the CVMP recommendation by the Commission, in line with standard procedures. More recently, in relation to medicinal products for human use, CHMP (Committee for

[1] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, p. 1–24.
[2] Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC. OJ L 309, 24.11.2009, p. 1–50.
[3] Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. OJ L 136, 30.4.2004, P. 1–33.
[4] EFSA-Q-2015-00187 on http://registerofquestions.efsa.europa.eu/roqFrontend/ListOfQuestionsNoLogin?0&panel=ALL
[5] http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500013852.pdf

Medicinal Products for Human Use) adopted ICH guideline M7 on assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk.[6] The guideline will come into force in January 2016.

The two agencies' scientific positions

EMA - CVMP

Historically, the CVMP has taken the view that genotoxic substances are not acceptable for use in veterinary medicinal products for use in food producing animals. However, it is now accepted, that in some cases, the presence of low levels of genotoxic impurities may be unavoidable. The CVMP and its SWP (Safety Working Party) are therefore developing guidance relevant to how to derive limits for genotoxic impurities.

EMA - CHMP

The ICH guideline M7 indicates that for genotoxic substances for which carcinogenicity data is available it is possible to establish substance specific acceptable intake values. The CHMP considers that, for a patient, exposure to a genotoxin at a level associated with an excess lifetime cancer risk of 10^{-5} can be acceptable. The ICH guideline uses the dose of the substance that yields a 50% tumour incidence (TD_{50}) in animals as a starting point and extrapolates this (linearly) down to a dose that would theoretically yield a 1 in 100,000 tumour incidence.

In September 2015, a draft addendum[7] to the ICH M7 guideline has been published for consultation in which the ICH M7 approach is applied to a number of genotoxic substances considered to be common in pharmaceutical manufacturing. One of these substances is PCA. This draft addendum indicates that the available data suggest that the mode of action is likely to be indirect but that the possibility of a direct action cannot be completely ruled out. It goes on to derive an acceptable intake value. As a starting point, the use of a TD_{50} of 33.8 mg/kg/day (for hepatocellular adenomas or carcinomas), resulting in an acceptable intake value of 34 µg/day is proposed. Finalisation of the conclusions of the addendum is planned for 2016.

EFSA

As background, it should be noted that the EFSA Scientific Committee (EFSA Scientific Committee, 2005)[8] recommended that substances which are both genotoxic and carcinogenic should not be deliberately added to foods or for use earlier in the food chain, if they leave residues which are both genotoxic and carcinogenic in food. However, where genotoxic residues are found, a margin of exposure (MoE) approach can be used to guide risk management decisions. A minimum recommended MoE is 10,000 for impurities which are both genotoxic and carcinogenic (EFSA Scientific Committee, 2012)[9]

In the case of PCA as a residue arising from the representative use of diflubenzuron, EFSA was requested to examine if the Margin of Exposure approach was correctly implemented by the RMS. It will be up to risk managers to discuss whether the use of this approach is appropriate for residues of active substances in plant protection products.

EFSA concluded already in its 2012 Conclusion (EFSA, 2012)[10] that potential exposure to PCA as a residue (i.e. either for consumers or for workers and bystanders/residents) should be considered *a priori* as a concern since a threshold for a genotoxic carcinogen cannot be assumed.

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[6] EMA/CHMP/ICH/83812/2013
[7] http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500173445.pdf
[8] EFSA Scientific Committee, 2005. Opinion of the Scientific Committee on a request from EFSA related to A Harmonised Approach for Risk Assessment of Substances Which are both Genotoxic and Carcinogenic. The EFSA Journal (2005) 282, doi:10.2903/j.efsa.2005.282.
[9] EFSA Scientific Committee, 2012. Scientific Opinion on the applicability of the Margin of Exposure approach for the safety assessment of impurities which are both genotoxic and carcinogenic in substances added to food/feed. EFSA Journal 2012;10(3):2578. [5 pp.] doi:10.2903/j.efsa.2012.2578.
[10] EFSA (European Food Safety Authority), 2012. Conclusion on the peer review of the pesticide risk assessment of confirmatory data submitted for the active substance diflubenzuron. EFSA Journal 2012;10(9):2870, 26 pp. doi:10.2903/j.efsa.2012.2870.

In its 2015 Conclusion (EFSA, 2015)[11], EFSA calculated the Margin of Exposure (MoE) between estimated short term consumer intake of PCA following pesticide use and the benchmark dose (BMDL5 and BMDL10) established from carcinogenicity studies, using rat adrenal gland pheochromocytomas as the endpoint. Based on the eight exposure scenarios considered, the intake of PCA was estimated to range from 0.018 µg/kg bw per day (pear juice) to 2.818 µg/kg bw per day (processed apple).

EFSA concluded that, for all but three exposure scenarios, this minimum MoE of 10,000 was not achieved considering the BMDL10 as point of departure and for all exposure scenarios the MoE was not achieved considering the BMDL5 as point of departure.

Process

Pursuant to Article 30 of Regulation 178/2002, EFSA and EMA identified at an early stage the potential for a divergent opinion. They shared the information available and confirmed the non-existence of a substantial divergence. EMA and EFSA consider there is fundamentally no divergent scientific view between them as both Agencies considered that 4-chloroaniline (PCA) should be assessed as genotoxic and carcinogenic based on currently available data.

Rationale for EMA and EFSA -apparent divergent positions

The different outcome is caused by a different methodology used for human medicines and pesticides (i.e. the use of TD_{50} (median toxic dose) for the former vs. the MoE approach using BMDL10 and BMDL5 for the latter). It is noted that PCA was assessed in different contexts explaining the different approaches. EMA assessed PCA as an impurity or metabolite in medicinal products for human use whereas EFSA assessed PCA as a residue in food.

EFSA reiterated that it will be up to risk managers to discuss whether the use of the MoE approach is appropriate for residues of active substances in plant protection products which are both genotoxic and carcinogenic.

[11] EFSA (European Food Safety Authority), 2015. Conclusion on the peer review on the review of the approval of the active substance diflubenzuron regarding the metabolite PCA. EFSA Journal 2015;13(8):4222, 30 pp. doi:10.2903/j.efsa.2015.4222