5.4 CLOTHIANIDIN (238) / THIAMETHOXAM (245)

RESIDUE AND ANALYTICAL ASPECTS

Residue and analytical aspects of clothianidin were considered for the first time by the 2010 JMPR Meeting. The 2010 Meeting established an acceptable daily intake (ADI) of 0–0.1 mg/kg bw per day and estimated the acute reference dose (ARfD) as 0.6 mg/kg bw. The 2010 Meeting defined the residue (for compliance with the MRL and for estimation of dietary intake) for plant and animal commodities as sum of clothianidin and its Z-isomer. The residue is considered not fat soluble.

In 2011 the manufacturer requested JMPR to reconsider the residue definition for clothianidin since the Z-isomer cannot be isolated as such and the Z-isomer should not be included in the residue definition. JMPR agreed to re-evaluate the clothianidin residue definition during the 2011 JMPR meeting. The manufacturer submitted new spectral data to elucidate the equilibrium between clothianidin and its Z-isomer. As the results apply equally to clothianidin and the thiamethoxam metabolite CGA 322704, the Meeting decided to consider the expression of residue definitions for both compounds.

Chemical structure

The Meeting received quantum mechanical calculations, NMR data and X-ray data to elucidate the equilibrium between clothianidin and its Z-isomer.

Quantum mechanical calculations revealed that the E-isomer form is the most stable form and that at room temperature an equilibrium of 1.5% Z-isomer and 98.5% E-isomer (E/Z ratio 66:1) in water is formed. The calculated transition state barriers between the E- and Z-isomer forms (with 10.5 kJ/mol energy difference) corresponding to the variation of three torsonial angles are 58.6, 46.0 and 62.8 kJ/mol, respectively. These transition state barriers are so low that the conversion between the E- and Z-isomer forms at room temperature is rapid and an equilibrium is formed rapidly. The E/Z equilibrium with a ratio of E:Z of 66:1 is formed irrespective whether the starting material is an E/Z mixture (thiamethoxam metabolite CGA 322704) or the E-isomer (clothianidin).

In order to verify the theoretical calculations, NMR experiments at low temperatures were performed with a clothianidin solution in deuterated acetonitrile. As the measurement temperature goes down from room temperature to -4 °C, the lifetime of the unfavoured Z-isomer is increased for a time long, enough to be detected by NMR. Based on spectral data it was confirmed that the E-isomer form is the most prominent form in equilibrium. An E/Z equilibrium with an E/Z ratio of 27:1 is formed in a deuterated acetonitrile solution at –40 °C. At ambient temperature there is no chance to isolate the Z-isomer, because it will always immediately transform back to the E-isomer.

Definition of the residue

The compound clothianidin is equivalent to the E form of CGA 322704, a metabolite arising from thiamethoxam use. Thiamethoxam exists as an E/Z mixture and the 2010 JMPR had insufficient data to conclude on the E/Z equilibrium of the CGA 322704 metabolite. The JMPR 2010 included the Z-isomer in the residue definition.

Based on the additionally submitted structural studies, an E/Z equilibrium with a ratio of E:Z of 27:1 at -40 °C is formed irrespective whether the starting material is an E/Z mixture (thiamethoxam metabolite CGA 322704) or the E-isomer (clothianidin). These new study results demonstrate that experimental separation of the minor Z-isomer from the E-isomer is not possible at ambient temperature because the Z-isomer will always immediately transform back to the E-isomer. For this reason, the Z-isomer of CGA 322704 need not be mentioned in the residue definition for either clothianidin or thiamethoxam.

The Meeting recommended the following as revised residue definition for clothianidin:

Definition of the residue for compliance with the MRL or for estimation of the dietary intake for plant commodities: *clothianidin*

Definition of the residue for compliance with the MRL or for estimation of the dietary intake for animal commodities: *clothianidin.*

The Meeting recommended the following as revised residue definition for thiamethoxam:

Definition of the residue for compliance with the MRL for plant and animal commodities: *thiamethoxam*

Definition of the residue for estimation of the dietary intake for plant and animal commodities (except poultry*): thiamethoxam and clothianidin* (considered separately)

Definition of the residue for estimation of the dietary intake for poultry: *sum of thiamethoxam, CGA 265307 and MU3, expressed as thiamethoxam; and clothianidin* (clothianidin to be considered separately from thiamethoxam).

The changes above do not impact on the recommendations for clothianidin and thiamethoxam nor the dietary risk assessments made by the 2010 JMPR.