

## 5 Evaluation of data for Acceptable Daily Intake and Acute Reference Dose for humans, maximum residue levels and Supervised Trials Median Residue values

### 5.1 2,4-D (020)

#### RESIDUE AND ANALYTICAL ASPECTS

The herbicide 2,4-D (2,4-dichlorophenoxyacetic acid) is currently registered for use in a variety of salt, amine, and ester formulations. It was first evaluated by the JMPR in 1970 and has undergone numerous subsequent evaluations.

The 1998 JMPR evaluated 2,4-D under the Periodic Re-evaluation Programme and established an ADI of 0–0.01 mg/kg bw for the sum of 2,4-D and its salts and esters expressed as 2,4-D and decided an ARfD was unnecessary. The residue definition established by the 1998 JMPR is 2,4-D for enforcement of MRLs and for dietary risk assessment for plant and animal commodities. The residue is not fat soluble.

The 2017 JMPR evaluated data to support the use of 2,4-D on genetically modified (GM) cotton. Due to questionable storage stability data for both 2,4-D and 2,4-DCP in GM cotton seed, it was not possible for the Meeting to recommend an MRL.

At the Fifty-first Session of the CCPR, 2,4-D was scheduled for evaluation of additional storage stability data by the 2019 JMPR.

The new data and the 2017 JMPR evaluation consider GM cotton in which expression of the aryloxyalkanoate dioxygenase-12 (AAD-12) protein confers tolerance to 2,4-D and associated increased metabolism of 2,4-D (hereafter referred to as AAD-12 cotton).

#### ***Stability of residues in stored analytical samples***

The new storage stability study supports the stability of 2,4-D and 2,4-DCP in AAD-12 cotton seed for 8 months of freezer storage at  $\leq -18$  °C.

The Meeting noted that the study designs, the analytical procedures and conduct of the study considered by the 2017 JMPR and the study considered by this Meeting, were identical. Based on all the data at each time point 2,4-D and 2,4-DCP were found to be stable on storage in AAD-12 cotton seeds stored at  $\leq -18$  °C. The Meeting also noted that the data evaluated by the 2017 JMPR demonstrated that 2,4-D and 2,4-DCP were stable on storage in other AAD-12 cotton fractions (at least 6 months for gin by-products and at least 3 months for hulls, untoasted meal, toasted meal and crude oil). No decline was observed over the storage intervals investigated. In addition, the 1998 JMPR concluded that 2,4-D was stable in conventional soya bean.

The Meeting concluded that based on the weight of evidence, 2,4-D and 2,4-DCP can be regarded as stable in AAD-12 cotton seeds for the 5 months of storage of the residue trial samples.

#### ***Definition of the residue***

The 2017 Meeting concluded that the residue definition for compliance with the MRL for cotton should be 2,4-D. The 2017 JMPR did not conclude on the residue definition for dietary risk assessment as no maximum residue level could be estimated.

In deciding which additional compounds should be included in the residue definition for dietary risk assessment for AAD-12 cotton the Meeting considered the likely occurrence of the compounds and the toxicological properties of the candidates.

In AAD-12 cotton seed 2,4-DCP was found at 3.2% TRR and conjugates of 2,4-DCP were found at 23% TRR (approximately 5 fold higher than 2,4-D). In AAD-12 cotton gin trash, 2,4-DCP

accounted for 2.6% TRR and its conjugates accounted for 38% TRR (approximately equal to the levels of 2,4-D).

The residue trials and processing studies confirm that residues of 2,4-DCP may occur in human foods. Therefore, the Meeting decided based on its occurrence, 2,4-DCP and its conjugates should be included in the residue definition for dietary risk assessment. A toxicological data package was not submitted for 2,4-DCP and the WHO Core Assessment Group recommended a full toxicological evaluation for 2,4-DCP.

As the WHO Core Assessment Group could not conclude on the toxicity of 2,4-DCP, the Meeting was unable to conclude on the residue definition for dietary risk assessment for AAD-12 cotton seed.

### ***Results of supervised residue trials on crops***

#### ***AAD-12 cotton***

The critical GAP provided to the 2017 JMPR for AAD-12 cotton was for the USA.

The GAP is 1 application made pre-emergence/pre-planting at a rate of 1060 g ae/ha followed by 1–2 applications post-emergence at a rate of 1060 g ae/ha. The interval between the post-emergence applications is 12 days with the latest application at growth stage BBCH 65.

A total of 16 trials from the USA approximating the GAP were evaluated by the 2017 Meeting.

Residues of 2, 4-D in rank order in undelinted AAD-12 cotton seeds were (n = 16): < 0.01(13), 0.014, 0.016 and 0.070 mg/kg.

The Meeting estimated a maximum residue level of 0.08 mg/kg for cotton seeds. As the Meeting could not conclude on the residue definition for dietary risk assessment, an STMR and HR could not be estimated.

#### ***Animal feeds***

##### ***Cotton gin trash/ cotton gin by-products***

The critical GAP provided to the 2017 JMPR for AAD-12 cotton was for the USA.

The 2017 Meeting considered residues data for 2,4-D in cotton gin by-products. A total of five trials included the analysis of cotton gin by-products.

Residues of 2, 4-D in AAD-12 cotton gin by-products in rank order were (n = 5): < 0.01, 0.039, 0.11, 0.28, 0.56 mg/kg

The Meeting was unable to estimate a median and highest residue for cotton gin by-products as a conclusion on the residue definition for dietary risk assessment could not be reached.

#### ***Fate of residues on processing***

The 2017 JMPR evaluated information on the fate of 2, 4-D residues during processing of AAD-12 cotton. Four processing trials were undertaken. No residues of 2, 4-D were detected in the RAC or the processed fractions. 2,4-DCP residues were found in the RAC and processed fractions. The best estimate processing factors derived by the 2017 JMPR for 2, 4-DCP were 1.16 (hulls), 2.96 (untoasted meal), 1.96 (toasted meal), 0.55 (crude oil) and 0.07 (refined oil).

The Meeting decided that as no residues of 2,4-D were detected in the RAC, in contrast to the positive residues found in field trials, it was not possible to estimate maximum residue levels for processed cotton fractions.

As the Meeting could not conclude on the residue definition for dietary risk assessment for AAD-12 cotton, STMR-P and HR-P were not estimated for processed cotton fractions.

***Residues in animal commodities***

As the Meeting could not conclude on the residue definition for dietary risk assessment for AAD-12 cotton, it was not possible to calculate dietary burdens for livestock.

**RECOMMENDATIONS**

The Meeting was unable to conclude on the residue definition for dietary risk assessment for AAD-12 cotton seed

**DIETARY RISK ASSESSMENT**

No maximum residue levels are recommended, nor are levels estimated for use in long-term and acute dietary exposure assessments as the Meeting could not reach a conclusion on the residue definition for dietary risk assessment for AAD-12 cotton.

