## 5.9 DITHIOCARBAMATES (105) / MANCOZEB (050)

### RESIDUE AND ANALYTICAL ASPECTS

Mancozeb was evaluated in 1993 in the CCPR periodic review programme. Since then, in 2012, the Meeting evaluated residue data on mancozeb and maneb, however, made no recommendation for MRLs. Currently, a number of MRLs for dithiocarbamates are established based on the residue data derived from use of mancozeb, maneb, metiram, thiram, ziram and propineb.

Dithiocarbamates-Mancozeb was listed by the Forty-fifth Session of the CCPR (2013) for the evaluation of additional MRL in 2014 JMPR. The Meeting received supervised residue trial data from Thailand (chili pepper) and the Republic of Korea (ginseng and the processed products). In addition, India submitted monitoring data on spices (cardamom, coriander, cumin, fennel and black pepper).

The mancozeb residue is defined as total dithiocarbamates, determined as $CS_2$, evolved during acid digestion and expressed as mg $CS_2$/kg, for compliance with MRLs. Dithiocarbamate residues are not fat soluble.

In 1993, the JMPR established a group (or in any combination) ADI of 0–0.03 mg/kg bw for ethylene-bis-dithiocarbamates (EBDCs: mancozeb, maneb, metiram and zineb) and an ADI of 0–0.004 mg/kg bw for their metabolite ethylenethiourea (ETU). The parent EBDC and ETU are defined as the residues for evaluating dietary intake. The Meeting is assessing combined residues of mancozeb and ETU using the ratio of the ADIs (7.5) to express residues in terms of mancozeb-toxicity-equivalents (MTE).

#### *Methods of analysis*

The analytical method used for the determination of dithiocarbamates in chili pepper was considered by the JMPR in 1995. According to the method, dithiocarbamate residues in chili pepper were converted to $CS_2$ by treatment with hydrochloric acid in the presence of stannous chloride. The $CS_2$ in the head-space was determined by GC-ECD and the limit of quantification was 0.05 mg $CS_2$/kg. The validity of the analytical results was supported by a set of recovery test and procedural recoveries.

Mancozeb and ETU in ginseng and its processed products were directly measured using analytical method ABY0064.

The method ABY0064 is based on the direct determination, by HPLC-MS/MS, of a derivatized EBDC (EBDC-dimethyl produced by *S*-methylation). In the method, disodium EDTA and iodomethane are used for decomposing and methylating EBDC compounds, and then the extracts are cleaned up with $C_{18}$ SPE cartridge. In the mass analysis, individual EBDCs are distinguished using compound-specific transition ions.

The method ABY0064 was fully validated with analytical matrices of orange, olive and their processed products. The recoveries of mancozeb were within an acceptable range (70–120%) at fortification levels of 0.01 mg/kg and 0.1 mg/kg. The LOQs were 0.01 mg/kg. In ginseng residue trials, procedural recoveries were acceptable and the LOQs were 0.01 mg/kg or 0.02 mg/kg.

A method developed for determination of ETU was fully validated for the same matrices used in a validation study of ABY0064. The recoveries and RSDs were within an acceptable range at fortification levels of 0.01 mg/kg and 0.1 mg/kg and the LOQs were 0.01 mg/kg. In ginseng residue trials, procedural recoveries were acceptable and the LOQs were 0.01 mg/kg.

Spectrometry was used for the analysis of dithiocarbamates in spices. Dithiocarbamate residues in spices were converted to $CS_2$ and two cupric complexes of N,N-bis (2-hydroxyethly) dithiocarbamic acid, which were measured at 453 nm. LOQs of dithiocarbamates in spices (cardamom, coriander, cumin, fennel and pepper) were 0.1 mg/kg. At fortification levels of 0.1–1.0 mg $CS_2$/kg, recoveries were 88–110% in cumin, coriander, fennel, cardamom and black pepper.

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

Storage stability tests for ginseng samples were performed simultaneously with freezer storage of field trial samples or processed samples. Mancozeb and ETU residues were stable during the study period, 103 days until analysis of mancozeb and ETU for fresh ginseng and 11–100 days (mancozeb analysis) or 55–100 days (ETU analysis) for the processed products.

In residue trials of chili pepper, analysis of mancozeb, as $CS_2$, was conducted on the day the samples were harvested.

***Results of supervised trials on crops***

The MRLs for mancozeb are expressed as $CS_2$. For trials using the headspace method, residues are reported in terms of $CS_2$. For trials using the HPLC-MS/MS method, residues are reported as mancozeb and ETU. For those trials, maximum residue estimates are made by converting mancozeb to $CS_2$-equivalents.

To estimate dietary intakes, residues are expressed in terms of mancozeb toxicity-equivalents (MTE). The conversion factor for ETU to MTE is the ratio of the ADI for mancozeb to that of ETU, which is 7.5. Thus, when residues were measured as mancozeb and ETU, the total MTE was estimated by multiplying the ETU residue by 7.5 and adding the result to the measured mancozeb residue. The resulting ETU-equivalent was then converted to MTE using the 7.5 factor. The molecular weights of these compounds are $CS_2$=76.1 g/mol, ETU=102.2 g/mol, and mancozeb=541.0 g/mol, assuming that the 2 moles of ETU are formed from one mole of mancozeb, leading to the following conversion factors:

$CS_2$ mancozeb equivalent: $541.045/(4\times76.139)= 1.777 \times CS_2$ mg/kg

Mancozeb MTE equivalent is: mancozeb mg/kg (measured as mancozeb)

MTE for ETU = 7.5×ETU mg/kg

MTE for combined residues of mancozeb measured as $CS_2$ mg/kg and ETU mg/kg:

$MTE_{(MCZ+ETU)} = 1.777\times CS_2$ mg/kg + 7.5× ETU mg/kg

*Fruiting vegetables, other than Cucurbits*

*Peppers, Chili*

Mancozeb is registered in Thailand for use on chili peppers at a GAP of 3 x 0.4 kg ai/hL, with 5 day intervals and a PHI of 7 days. A total of six trials were conducted in Thailand in 2005–2008, matching the GAP.

The residues, as $CS_2$ were (n=6): 0.31, 0.48, 0.75, 0.80, 1.2 and 1.7 mg $CS_2$/kg.

The Meeting estimated a maximum residue level of 3 mg $CS_2$/kg, an STMR of 1.4 mg MTE/kg and an HR of 3.0 mg MTE/kg for chili pepper. Using the default factor of 7 for dried chili pepper, the Meeting estimated a maximum residue level of 20 mg $CS_2$/kg, a STMR-P of 9.8 mg MET/kg and an HR-P of 21 mg MET/kg for dried chili pepper.

*Root and tuber vegetables*

*Ginseng*

Mancozeb is registered in the Republic of Korea for use on ginseng at a GAP of 5×0.12 kg ai/hL, with 10 day intervals and a PHI of 45 days. Four trials matching the GAP conducted in the Republic of Korea in 2013 were submitted. Two trials were conducted on the same dates of application in sites

closely located and with the same application method; therefore, the trials are not considered to be independent. Only three trials could be considered for estimation of a maximum residue level.

The measured concentrations of mancozeb in ginseng were (n=3): 0.05, 0.05 and 0.11 mg/kg, which is equivalent to 0.028, 0.028 and 0.062 mg/kg as $CS_2$.

The measured concentrations of ETU in ginseng were (n=3): < 0.01, 0.01 and 0.04 mg/kg.

The Meeting estimated a maximum residue level of 0.15 mg $CS_2$/kg.

For dietary intake, the STMR is 0.125 mg MTE/kg and the HR is 0.41 mg MTE/kg.

***Results of monitoring studies on spices***

Monitoring of spices was conducted for dithiocarbamates in India during 2009–2014. Residues in spices came from the use of mancozeb and other dithiocarbamates. Spice samples were analysed based on the determination of $CS_2$.

The numbers of samples analysed were: 383 for cumin seed, 1,037 for cardamom, 248 for coriander seed, 272 for black pepper and 286 for fennel seed.

In all of the cardamom (1,037 samples) and black pepper (272 samples), $CS_2$ residues were < 0.1 mg/kg.

In coriander seed, $CS_2$ residues were < 0.1 (247), 0.4 mg $CS_2$/kg.

In fennel seed, $CS_2$ residues were < 0.1 (283), 1.1, 2.0 and 2.8 mg $CS_2$/kg.

In cumin seed (383 samples), $CS_2$ residues ranged from 0.11 mg/kg to 17 mg $CS_2$/kg, with a median of 3.6 mg $CS_2$/kg.

For compliance, the Meeting estimated maximum residue levels of 0.1 mg $CS_2$/kg for black pepper, cardamom, coriander seed, and fennel seed, and 10 mg $CS_2$/kg for cumin seed. The Meeting noted that the maximum residue estimate covers at least 98% of the observed residues.

For dietary intake, the Meeting estimated STMRs of < 0.18 mg MTE/kg for black pepper, cardamom, coriander seed, and fennel seed, and 6.4 mg MTE/kg for cumin seed.

***Fate of residues during processing***

The Meeting received information on the fate of mancozeb residues during the processing of ginseng. Conversion of residues to their $CS_2$, mancozeb, and/or ETU equivalents was done, as needed, as described above for supervised residue trials.

| RAC and processed | Pf, best estimate | | STMRRAC | | Median-P | | HRRAC | | Highest residue-P | |
|---|---|---|---|---|---|---|---|---|---|---|
| | mancozeb | ETU* | mancozeb (mg/ kg) | ETU (mg/kg) | mancozeb (mg /kg) | ETU equiv. (mg/kg) | mancozeb (mg/ kg) | ETU (mg/kg) | mancozeb (mg /kg) | ETU equiv. (mg/kg |
| Ginseng | | | 0.05 | 0.01 | | | 0.11 | 0.04 | | |
| Ginseng, dried including red ginseng | 1.5 | 4.2 | | | 0.075 | 0.1197 | | | 0.17 | 0.3389 |

* Fraction yield of ETU = $[ETU]_{proc}/([ETU]_{rac} + 0.378\times[mancozeb]_{rac})$

In dried ginseng, each processing factor for mancozeb, ETU and $CS_2$ residue was calculated as follows:

For mancozeb, the concentration of mancozeb in dried ginseng was divided by the concentration of mancozeb in fresh ginseng.

For ETU, the concentration of ETU in dried ginseng was divided by the sum of ETU and mancozeb (expressed as ETU equivalents) in fresh ginseng in order to account for mancozeb as a potential source of ETU during processing. The stoichiometric conversion factor for mancozeb to ETU is 0.377 (102.2 g ETU/mol ÷ 271.2 g mancozeb/mol).

For compliance, the Meeting estimated a maximum residue level of 0.3 mg $CS_2$/kg, based on a maximum residue level of 0.15 mg $CS_2$/kg for ginseng and the processing factor of dried ginseng, 1.5 (1.5×0.15=0.225 mg/kg).

For dietary intake, the Meeting estimated an STMR-P of 0.075+7.5×0.1197=0.97 mg MTE/kg and an HR-P of 0.17+7.5×0.33894=2.71 mg MTE/kg.

## RECOMMENDATIONS

On the basis of the data from supervised trials the Meeting concluded that the residue levels listed below are suitable for establishing maximum residue limits and for IEDI and IESTI assessment.

The mancozeb residue is defined as total dithiocarbamates, determined as $CS_2$, evolved during acid digestion and expressed as mg $CS_2$/kg, for compliance with MRLs in plant and animal commodities.

For estimation of dietary intake in plant and animal commodities, the residue definition is mancozeb and ETU.

Dithiocarbamate residues are not fat soluble.

## DIETARY RISK ASSESSMENT

### *Long-term intake*

A group ADI (or in any combination) for ethylene-bis-dithiocarbamates (EBDCs: mancozeb, maneb, metiram and zineb) is 0–0.03 mg/kg bw. The International Estimated Daily Intakes (IEDIs) for mancozeb were estimated based on the 17 GEMS/Food Consumption Cluster Diets using only the STMR or STMR-P values estimated by the current JMPR. The results are shown in Annex 3 of the 2014 JMPR Report. The IEDIs ranged 0-6% of the maximum ADI. The Meeting concluded that the long-term intake of residues of mancozeb from uses added by the current JMPR is unlikely to present a public health concern.

### *Short-term intake*

The ARfD for mancozeb and its metabolite ETU is not available currently. The Meeting noted that the dithiocarbamates were last evaluated in 1993 before the ARfD established by the JMPR.