TTCアプローチの実例

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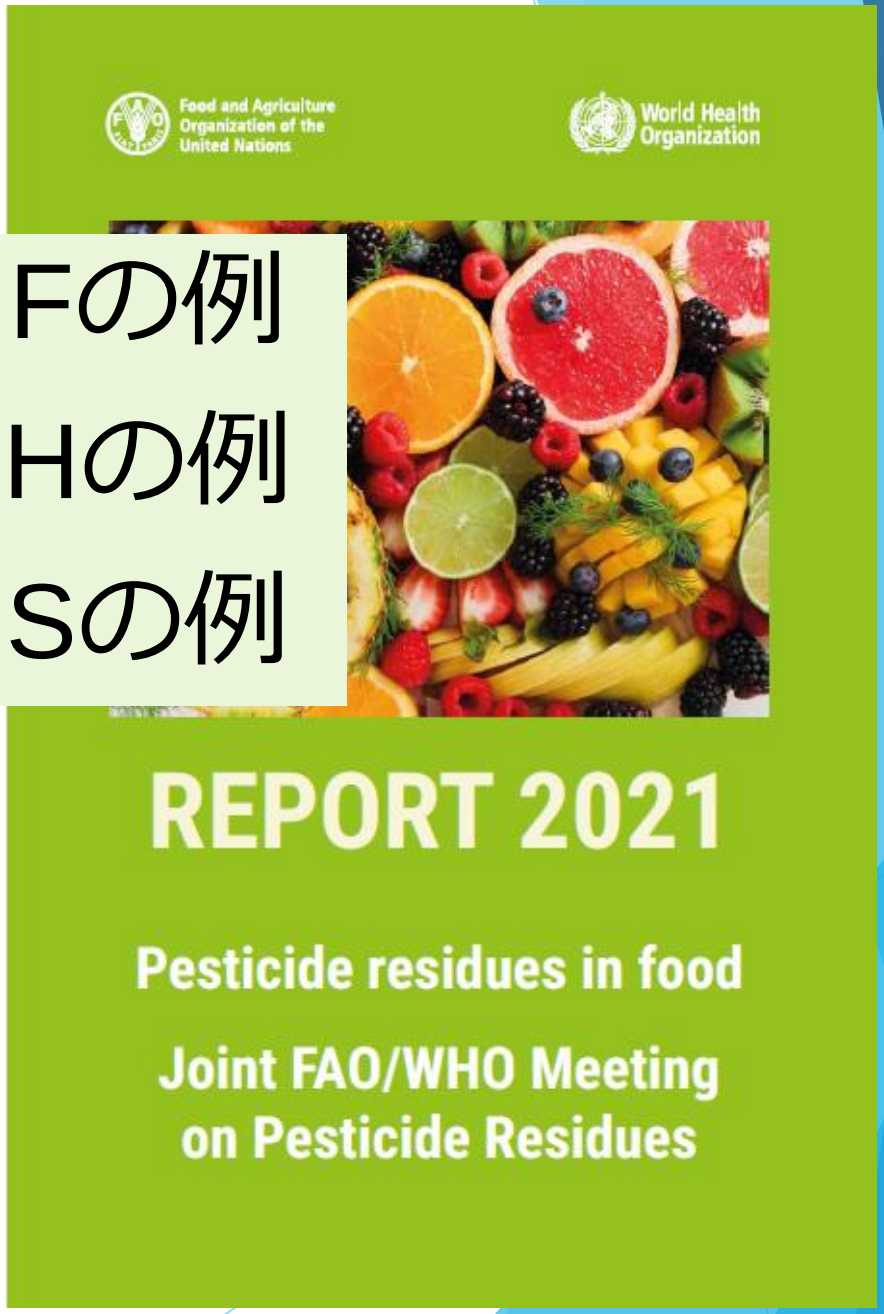
入江　真理

1．殺菌剤Fの例
2．除草剤Hの例
3．殺虫剤Sの例



殺菌剤Fの例

Definition of the residue

Plant commodities

On deciding which compounds should be included in the residue definition for risk assessment, the Meeting considered the likely occurrence of the compounds and the toxicological properties of the candidates M11, M21 and M30. All three metabolites were analysed in various food and feed commodities from supervised field trials, but residues were only found in cereal commodities. These metabolites were also identified in plant metabolism studies, but always as minor components of the residue (up to 30% of parent).

Metabolites M11, M21 and M30 were either not detected in the rat or only at small amounts (M21 at < 1–6% AD), and no indications of genotoxicity were identified. Therefore, the TTC approach for a Cramer Class III compound was applied.

Cramer Class III

同定できているが毒性情報が不十分な代謝物：M11, M21, M30

Estimated long-term exposures were based on uses in plant and animal commodities and using maximum values found in supervised field trials. Actual measured concentrations from field trials were used where metabolites M11, M21, and M30 were analysed in the field trials. In trials where only F was measured, a maximum value was estimated assuming 30% contribution of each metabolite relative to parent. The estimated long-term maximum dietary exposures for metabolites M11, M21 and M30 were 0.81 µg/kg bw per day –for each metabolite.

The Meeting noted that the estimated exposures for metabolites M11, M21 and M30 are each below the threshold of toxicological concern for Cramer Class III compounds (1.5 µg/kg bw per day), and concluded that dietary exposure to these metabolites is unlikely to present a public health concern.

作物残留試験での分析（M11, M21, M30）
①有　→　実測値
②無　→　親化合物の分析値と
植物代謝試験での親化合物に
対する比率からの算出値

M11, M21, M30それぞれ
0.81 µg/kg bw/d < 1.5 µg/kg bw/d
なので、
これらの代謝物の経口暴露推定量は、人の健康影響はないと判断

In primary metabolism studies, significant residues of unidentified hydroxylated metabolites and/or their conjugates were detected in mandarin fruit, pea seed and oilseed rape seed, ranging between 19–67% TRR. These metabolites occurred at lower or similar levels relative to parent, except for pea seed. Since no genotoxicity was indicated for hydroxylated metabolites, the TTC approach for Cramer Class III compounds was applied. Estimated long-term exposure was based on consumption of plant and animal commodities and using maximum values of parent found in supervised field trials corrected for the estimated fraction of the hydroxylated metabolites.

水酸化されているが、水酸基のポジションが不明な代謝物及びその結合物

親化合物と同等レベルの残留

Cramer Class III

The following factors were derived from results in metabolism studies (mandarin, pea, oilseed rape) comparing parent and total hydroxylated metabolites (free and conjugated) and assigning them to associated crops to reflect their nature, where possible. If a crop could not be assigned to a matching matrix from the metabolism studies, the most conservative factor of 3.6 was applied (e.g. bulb and root vegetables).

植物代謝試験での親化合物に対する比率

Stone fruit, blueberries:	0.6 (mandarin fruit, 28 DAT);
Banana:	0.06 (mandarin fruit, 0 DAT);
Green beans, sweet corn:	3.6 (green pea);
Dried peas, soya beans, cereal grain, maize:	3.0 (dry pea);
Sugar cane, soya bean forage, sugar beet tops, maize forage, rape forage:	0.8 (mandarin leaf);
Oilseeds (oilseed rape, sunflower, cotton seed), peanuts, tree nuts:	2.1 (rape seed);
Straw, hay, stover, almond hulls, cotton gin by-product:	0.5 (pea straw);
Bulb onion, garlic, potato, sugar beet:	3.6 (unassigned).

The estimated long-term maximum dietary exposure, calculated for the total of hydroxylated metabolites, was 0.75 µg/kg bw per day.

The Meeting noted that the estimated exposure is below the threshold of toxicological concern for Cramer Class III compounds (1.5 µg/kg bw per day) and concluded that dietary exposure to these metabolites is unlikely to present a public health concern.

水酸化代謝物
0.75 µg/kg bw/d < 1.5 µg/kg bw/d
なので、
これらの代謝物の経口暴露推定量は、人の健康影響はないと判断

Animal commodities

On deciding which compounds should be included in the residue definition for risk assessment, the Meeting considered the likely occurrence of the compound and its toxicological properties for the candidates M1, M12 and M31. The three metabolites were detected in animal metabolism studies in their free and conjugated (conjugated fraction: M1: 83–100%; M12: 0% (ruminant); 64% (poultry); M31: 72–100%) forms in liver and kidney. However, levels of M1 (free and conjugated) and M12 (free) in their free form found in liver and kidney during ruminant and poultry feeding studies were low. Since the method used in the feeding studies did not include a hydrolysis step, residue levels could be underestimated for total free and conjugated M12 in poultry. M1 and M12 were observed in the rat and are of no greater toxicity than parent and are covered by its toxicological reference values. Therefore, the Meeting decided to include the metabolites into the residue definition for dietary exposure purposes. Metabolite M31 was not detected in the rat and no indications on genotoxicity were identified. Therefore, the TTC approach for a Cramer Class III compound was applied. Potential long-term exposure to M31 was estimated using the maximum values found in liver and kidney in the metabolism studies.

同定できているが毒性情報が不十分な代謝物：M31

Cramer Class III

M31: 0.01 µg/kg bw/d < 1.5 µg/kg bw/dなので、
この代謝物の経口暴露推定量は、人の健康影響はないと判断

The estimated long-term maximum dietary exposure, calculated for metabolite M31 was 0.01 µg/kg bw per day.

The Meeting noted that the estimated dietary exposure to M31 is below the threshold of toxicological concern for Cramer Class III compounds (1.5 µg/kg bw per day) and concluded that dietary exposure to this metabolite is unlikely to be of public health concern.

Definition of the residue for dietary risk assessment を決定

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Dietary risk assessment

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MRL recommendation（勧告）

除草剤Hの例

Definition of the residue

Plant commodities

In deciding which compounds should be included in the residue definition for dietary risk assessment, the Meeting considered the likely occurrence of the compounds and the toxicological properties of the candidates M sulfone, M oxazole sulfoxide, M19R, M15A and 3-chloroallyl alcohol.

The Meeting concluded that the TTC approach for genotoxicity could be applied for M-sulfone, M19R and M15A and the TTC approach using Cramer Class III could be applied for M-oxazole sulfoxide.

同定できているが毒性情報が不十分な代謝物：
M sulfone, M19R, M15A, 3-chloroallyl alcohol, M oxazole sulfoxide

Genotoxicity

Cramer Class III

M sulfone is measured as DME by the common moiety analytical method but the individual residue cannot be determined. Therefore, the field trial data analysed with a specific analytical method were used for the estimation of exposure. The chronic dietary exposure was estimated based on uses on head cabbage, dry peas, carrot and artichoke because the residue data for M-sulfone itself were available.

The Meeting noted that the estimated chronic dietary exposure to M sulfone (0.028 µg/kg bw per day) exceeds the threshold of toxicological concern for genotoxicity (0.0025 µg/kg bw per day).

M sulfone
当該代謝物単独の残留分析値が存在するキャベツ、えんどうまめ、にんじん、アーティチョークのデータに基づき経口暴露推定量を算出
0.028 µg/kg bw/d > 0.0025 µg/kg bw/d

3-Chloroallyl alcohol was the major hydrolysis product (31% AR after 30 days) and is the free form of M15A (glucose conjugate). M15A was the major residue in spinach (21–23% TRR, 0.79–1.1 mg eq/kg) and M19R was the major residue in carrot mature leaves (14% TRR, 0.12 mg eq/kg) at a 2 × GAP rate of 0.50 kg ai/ha. Those three metabolites cannot be measured by the common moiety analytical method. The Meeting noted that M15A and M19R were not observed in the rat metabolism study and no information is available on their toxicity.

M19R and M15A are expected to occur in leaves with exposure to sunlight. Therefore, the chronic dietary exposure was estimated based on uses on leafy greens and head cabbage. The maximum residues of M19R and M15A in the plant metabolism studies, with adjustment to the GAP rate (50% the rate used in the metabolism studies), were used to estimate the chronic dietary exposure. It was noted that 3-chloroallyl alcohol (free form of M15A) was only detected in the hydrolysis study. Estimated exposures were:

M19R: 0.091 µg/kg bw per day

M15A: 0.84 µg/kg bw per day

M19R, M15A
日光照射により生成することが考えられることから、植物代謝試験での最大残留濃度とleafy greens及びキャベツへの使用に基づき経口暴露推定量を算出

The Meeting noted that the estimated exposures to M19R and M15A exceeded the threshold of toxicological concern for genotoxicity (0.0025 µg/kg bw per day).

M oxazole sulfoxide is generated from M sulfoxide during high temperature processing of plant commodities. This compound can be measured by a common moiety analytical method but individual residues of the compound cannot be determined. The Meeting could not estimate the chronic dietary exposure for M oxazole sulfoxide.

Because the Meeting was unable to conclude on the toxicological relevance of the metabolites M sulfone, M19R, M15A and M oxazole sulfoxide the Meeting could not reach a conclusion on the residue definition for dietary risk assessment.

M oxazole sulfoxide
当該代謝物は単独の残留濃度を測定する分析法がないため、経口暴露推定量を算出できない。

結論
M sulfone, M19R, M15A, M oxazole sulfoxideについて、それらの毒性評価に懸念があるため、Residue definition for dietary risk assessmentを決定できず。

Animal commodities

In deciding which compounds should be included in the residue definition for dietary risk assessment, the Meeting considered the likely occurrence of the compound and the toxicological properties of the candidate M sulfone.

M sulfone resides cannot be identified in animal commodities since no specific analytical method is available. However, the estimated chronic dietary exposure to M sulfone from plant commodities exceeds the threshold of toxicological concern for genotoxicity.

M sulfone
当該代謝物の残留濃度を測定する分析法がないが、農作物からの経口暴露推定量がTTC for genotoxicityを超過している。

Definition of the residue for dietary risk assessment を決定できず

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MRL recommendationできず

殺虫剤Sの例

Rotational cropsに関して抜粋

In rotational crops, residues of S and metabolites in food commodities (mature lettuce, turnip, wheat grain) were all < 0.01 mg eq/kg except in mature lettuce (120-day PBI) where total 549098 residues (free and conjugated) made up 55% TRR (0.012 mg/kg).

同定できているが毒性情報が不十分な代謝物　かつ後作物に特有の代謝物：549098

The Meeting concluded that metabolites 550820, 550839, 549098 and the dehydrogenated S -enol can be assessed against the TTC for a Cramer Class III compound and should not be included in the residue definition for risk assessment.

Cramer Class III

The Meeting concluded that low concentrations of free and conjugated 549098 might be expected in leafy vegetables grown in rotation with S -treated crops.

The Meeting estimated a dietary exposure for metabolite 549098 (free and conjugated) of 0.025 µg/kg bw per day.

The Meeting concluded that the estimated dietary exposure to residues of 549098 (free and conjugated) from uses considered by the JMPR is below the TTC for Cramer Class III compounds and is unlikely to present a public health concern. Should further uses be considered in the future, these conclusions may need to be re-evaluated.

549098

0.025 µg/kg bw/d < 1.5 µg/kg bw/d

この代謝物の経口暴露推定量は、人の健康影響はないと判断

今後、使用を拡大する場合は、TTC評価のアップデートが必要

Rotational cropsに関連して

2. General consideration items

2.10 Information on residues in rotational crops following use on paddy rice

The Meeting noted that according to the current edition of the FAO Manual on "Submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed" (FAO, 2016, 3rd Edition),[1] information on rotational crops following treatment in paddy rice are not required.

The present Meeting reconsidered this position, taking into account information on the agricultural practice for paddy rice cultivation and International Harmonised Guidelines (OECD TG504; *OECD Guidelines for the Testing of Chemicals, Residues in Rotational Crops (Limited Field Studies)*), indicating potential crop rotation for this crop. Therefore, uptake of soil residues by follow-on crops needs to be considered in estimating maximum residue levels, STMR and HR values. It was decided that the information given in the FAO Manual from 2016 does not reflect current agricultural practice and considers data on rotational crops (confined rotational crop information, conditional information on field rotational crop studies) as necessary to support uses on paddy rice. The FAO Manual will be amended for the next revision accordingly.

2.10 *Information on residues in rotational crops following use on paddy rice*

The Meeting noted that according to the current edition of the FAO Manual on "Submission and evaluation of pesticide residues data for the estimation of maximum residue levels in food and feed" (FAO, 2016, 3rd Edition),[1] information on rotational crops following treatment in paddy rice are not required.

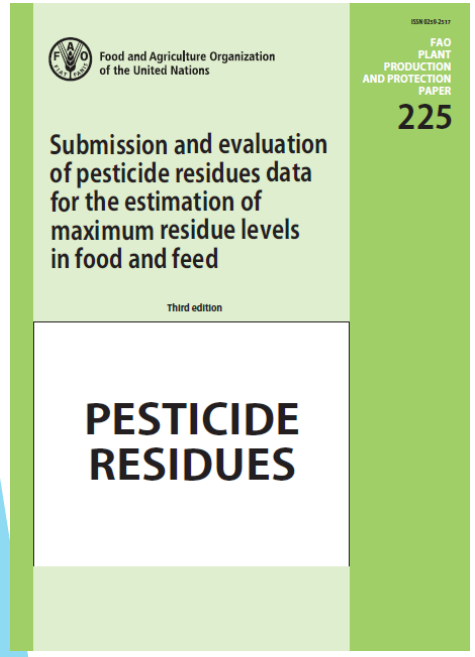

Table 3.3 Requirements for submission of data on environmental fate for the JMPR

Type of study	Type of use and requirement (yes/no/conditional)						Comments
	Foliar	Soil	Plants of root, tuber, bulb, or peanut (at/after pegging)	Seed dressing (including seed potato)	Herbicide (for weeds in crop)	Paddy rice	
Rotational crops-confined	Yes	Yes	Yes	Yes	Yes	No	Not required where no crop rotation (e.g., orchard crops). Soil and crop should be analysed for radiolabelled residues.
Rotational crops-field	Conditional	Condi-tional	Conditional	Conditional	Conditional	No	Requirement conditional on results of confined rotational crop study.
Field dissipation studies	Conditional	Condi-tional	Conditional	Conditional	Conditional	No	Requirement conditional on results of confined rotational crop study.

The present Meeting reconsidered this position, taking into account information on the agricultural practice for paddy rice cultivation and International Harmonised Guidelines (OECD TG504; *OECD Guidelines for the Testing of Chemicals, Residues in Rotational Crops (Limited Field Studies)*), indicating potential crop rotation for this crop. Therefore, uptake of soil residues by follow-on crops needs to be considered in estimating maximum residue levels, STMR and HR values. It was decided that the information given in the FAO Manual from 2016 does not reflect current agricultural practice and considers data on rotational crops (confined rotational crop information, conditional information on field rotational crop studies) as necessary to support uses on paddy rice. The FAO Manual will be amended for the next revision accordingly.

水稲栽培の実態から考えると、maximum residue levelsやSTMR、HRの算出に当たって、土壌中に残留する農薬（代謝・分解物を含む）の後作物（次作物）への取り込みについて考慮が必要。