

Critical Steps Involved in Fixation of Maximum Residue Limit (MRL) of Pesticides in India

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Introduction :

A Maximum Residue Limit (MRL) is the maximum concentration of pesticide residue legally permitted in a food or feed commodity (FAO, 2002). An MRL is assessed as representing the maximum residue level expected to be found in a foodstuff or feed if a pesticide is applied according to good agricultural practice (GAP) (MacLachlan and Hamilton, 2010). Under the joint FAO/WHO Food Standards Programme, the MRLs were established at the international level by the Codex Alimentarius Commission. Besides, each country sets its MRL values; for example, in India, MRLs are determined by the Food Safety and Standards Authority of India, Ministry of Health and Family Welfare, Government of India, under the Food Safety and Standards Act (FSSA), 2006 (Khandelwal *et al.*, 2022).

The need for fixation of MRL lies underneath the population and food scenario. It cannot be denied that the world's population is more than three times larger than it was in the mid-twentieth century. The global human population reached 8.0 billion in mid-November 2022 from an estimated 2.5 billion people in

1950, adding 1 billion people since 2010 and 2 billion since 1998 (www.un.org), whereas, the current population of India is *more than 1.4 billion*. India is projected to surpass China to become the world's most populous country by this year, 2023 (World Population Prospects, 2022).

Despite all this, global food production is incredibly efficient. The world's farmers produce enough food to feed 1.5 x the global population (Erdman, 2018). Considering these and keeping good health in mind people are moving towards safe and quality food that should be free from any pesticide among all xenobiotics. Xenobiotics are defined as chemicals to which an organism is exposed that are extrinsic to the normal metabolism of that organism (Croom, 2012). Pesticides are the vital input in agriculture and have become a social need since they help to maintain food production and fight vector-borne diseases. India, where the pesticide usage is 0.27 kg ha⁻¹ (Khandelwal *et al.*, 2022), stands 12th in pesticide use globally and 3rd in Asia after China and Turkey (Nayak and Solanki, 2021).

The alarming fact is that, resistance in pests has been developed as a result of

excessive and injudicious use, which has led to the use of much higher doses of pesticides in food commodities to protect the crop, and this excessive application has resulted in higher residue levels in food commodities, which has hindered international trade. That is why it was important to set certain limits of pesticide residues present in food commodity. Due to that, the concept of maximum residue limit (MRL) of pesticides was introduced (Khandelwal *et al.*, 2022).

Role of FSSAI in MRL fixation :

At International level, Codex Alimentarius Commission (CAC) has been

periodically prescribing guideline documents for the fixation of MRL since 1970s, based on the recommendation of Joint FAO/WHO Meeting on Pesticide Residues (JMPR). In India, a document/guideline in the form of a Standard Operating Procedure (SOP) was not available. Therefore, in 2021 Food Safety and Standards Authority of India documented a guideline called “Draft Guidance Document & Standard Operating Procedures for fixation of Maximum Residue Limits (MRLs) of pesticides in food commodities” which consists of 10 sections.

Table 1. Chronological events with dates for preparation of the draft guidance document for fixation of MRL in India [FSSAI, 2021] :

TIMELINE	EVENTS
21.05.2015	Panel on Residues of Pesticides and Antibiotics of FSSAI in its 36th meeting recommended constitution of a working group
07.10.2016	The Working Group met 8 times and submitted its report to FSSAI
25.01.2016	This report was placed before the Scientific Panel on Pesticides and Antibiotic Residues in its 47th meeting. The Panel constituted a group comprising 4 of members to review the report submitted by the Working Group
06.04.2017 08.05.2017 10.08.2017 02.11.2017 27.02.2018	The Review Group held five meetings and the group requested for a special expert view for finalization of the SOP
10.04.2018	The Review Group submitted its report to Scientific Panel in its 51st Meeting
09.04.2021	The comments of the Review Group were examined in detail by the Scientific Panel on Pesticide Residues in its various meetings. Based on the comments of the Review Group and suggestions and comments offered by the members of the panel, the Standard Operating Procedures on fixation of Maximum Residue limits have been prepared and enclosed.

Table 2. Sections of the draft guidance document [FSSAI, 2021] :

SECTION	CONTENT
1	Introduction to the document
2	SOP related to the generation of residue data as per the GAP
3	Sampling and residue analysis
4	Importance of metabolism studies in MRL fixation
5	The guidelines for risk assessment keeping in view the latest international procedures for utilization of GAP and critical GAP (cGAP) data in OECD MRL calculator
6	Dietary exposure of pesticide residues to human beings
7	Health Based Guidance Value
8	Risk characterization
9	Fixation of MRL of pesticides in processed foods.
10	Fixation of MRL on animal feed, meat, milk, offals and eggs

Methods for fixation of maximum residue limit :

Conventional method :

For determining the level of average residue that is likely to be present in food after the use of the pesticide in accordance with Good Agricultural Practice (GAP), including all of the label instructions proposed for the product, it is needed to conduct extensive supervised residue trials in various geographical areas during typical growing periods of the year and according to the farming practices of the region.

To get a clear view of the worst-case scenario, these experiments are done under maximum use settings, i.e., at the recommended application rate, maximum

frequency of application, and often up to twice the recommended application rate to analyze the residue level under suspected pesticide misuse.

The expected level of pesticide residue in individual foods or diets is compared to a health standard called Acceptable Daily Intake (ADI) to ensure that the maximum residue limit is acceptable from a public health standpoint (ADI). The ADI is a realistic approach in determining the food additives and is means of achieving some uniformity in the approach to regulatory control (MRL & PHI).

On the basis of all known information at the time of evaluation of the chemical, the ADI is the daily intake of a pesticide

which appears to be without appreciable risk to the consumer's health over a lifetime based on all the fact known at that time. 'Without appreciable risk' refers to the practical certainty that the injury will not result even after a lifetime of experience. It is expressed in mg of the pesticide per kg of body weight per day (MacLachlan and Hamilton, 2010). It is determined by toxicological studies conducted using specified test animals for at least two years in order to investigate the pesticide's overall spectrum of toxicity and set a No Observed Adverse Effect Level (NOAEL) (Khandelwal et al., 2022).

The NOAEL is defined as the highest dose level in mg residue/ kg body weight/ day that doesn't produce any detectable toxic effect on the most sensitive two or more test species, such as rats, rabbits and pigs. The NOAEL, which is determined from long-term toxicological research, is used to calculate the ADI for humans through dividing by a safety factor of 10 to 1000, depending on the data available and any toxicological concerns. A safety factor of 10, 100, 1000 is considered for interspecies, intraspecies and newborns in human beings (Khandelwal et al., 2022).

ADI [mg/kg of body wt.] (for humans) = NOAEL/Safety factor

When the ADI is multiplied by the average body weight of a man, which is usually 50 kg based on Indian Studies (Food Safety and SAI, 2021), the Maximum Permissible Intake (MPI) is obtained.

Besides, the Theoretical Maximum Daily Intake (TMDI) of the pesticide through a daily average diet of man can be obtained using extensive supervised trials conducted in a region as follows: Food consumed per day x food factor x maximum

residue concentration found in raw food commodity from supervised trials. (Food factor = the percentage of the item in question in the consumer's overall daily diet. The National Institute of Nutrition, Hyderabad has developed food factors for people of all ages and sex groups in India (Khandelwal et al., 2022).

The MRL in question is now finalised by comparing MPI to TMDI. When TMDI is less than MPI, the maximum residue contribution found in the food commodity during the supervised field trial is used to determine the MRL for that pesticide in the test crop. If TMDI is more than MPI, the pesticide is considered too dangerous to use on that test crop.

When four insecticides are sprayed on the same crop or one insecticide is sprayed on the different crop, the cumulative TMDI of the four insecticides in the same crop or the same insecticide on different crops is considered, and if the cumulative TMDI is less than MPI, the maximum residue data is considered an MRL for that crop (Khandelwal et al., 2022).

Although each insecticide or the same insecticide used in different crops, has its own MRL. Similarly, when it is found from the controlled trials that the residual level of a pesticide in a food commodity is below detectable levels, the MRL is set at the analytical method's minimum limit of detection (Khandelwal et al., 2022).

Furthermore, before validating the MRL, it must be determined that the sum of all pesticide residues from all food uses will not exceed the MPI by calculating projected dietary intake. This ascertains that food safety is not put at risk [Food Safety and SAI, 2021; WHO,2020].

Using OECD MRL Calculator :

To harmonize the calculation of MRLs across the OECD (Organization for Economic Cooperation and Development), the Residue Chemistry Expert Group of the OECD Working Group on Pesticides constituted an expert group in 2008 to propose a new MRL calculation procedure. The guiding principles of this procedure were :

- (1) the procedure must be a practical implementation of sound statistical methods
- (2) it must be simple to use without requiring extensive statistical knowledge from a user
- (3) it should produce a clear and unambiguous MRL proposal for most residue datasets produced by field trials
- (4) it should harmonize the EU and NAFTA procedures as much as possible

The Working Group on Pesticides approved the draft OECD MRL Calculator and its User Guide in December 2010 and recommended that the same to be forwarded to the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology, for consideration as an OECD publication (OECD MRL calculator, 2011).

The calculation process is rooted on mean+4SD methodology. The OECD MRL Calculator is statistically based, scientifically defensible and internationally harmonized. For each given dataset, the calculator calculates MRLs through multiple approaches (EU I, EU II, 95/99, Mean+3SD) and all the values will be listed in the output table. The OECD MRL calculator affords the best approach for the calculation, depending on the sample size

and the distribution of the residue data. The OECD MRL calculator is an MS Excel spreadsheet for calculation of MRL using single dataset and multiple datasets. In single dataset spreadsheet, if the datasets are smaller (4-6), estimate of MRL is of high uncertainty and if the datasets are larger (10-15), it becomes more reliable. (Food Safety and SAI, 2021)

Conclusion :

The MRL is usually determined by field trials conducted in different agroclimatic zones of India, where the crop has been cultivated following Good Agricultural Practice (GAP). As far as the conventional method is concerned, TMDI and MPI values are compared for establishing the MRL. Along with that, the OECD has developed an MRL Calculator which is made up of an Excel spreadsheet, simple to use without requiring the user to have extensive statistical knowledge. In India, FSSAI played huge role in drafting a guideline mentioning all the critical steps need to be taken into consideration for fixing MRL. The levels established in India are based on thorough scientific experiments. Considering that, this database can form a core for consideration in setting up MRLs for different pesticides at global level.

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Abbreviations used in the manuscript :

- ADI : Acceptable Daily Intake
- EU : European Union
- FAO : Food and Agriculture Organization
- FSSAI : Food Safety and Standards Authority of India
- GAP : Good Agricultural Practice
- cGAP : Critical GAP (25% more than the recommended pesticide dose)
- JMPR : Joint FAO/WHO Meeting on Pesticide Residues
- MPI : Maximum Permissible Intake
- MRL : Maximum Residue Limit
- NAFTA : North American Free Trade Agreement
- NIN : National Institute of Nutrition
- NOAEL : No Observed Adverse Effect Level
- OECD : Organization for Economic Co-operation and Development
- PFA : Prevention of Food Adulteration Act
- SOP : Standard Operating Procedure
- TMDI : Theoretical Maximum Daily Intake
- WHO : World Health Organization