BEMS Reports. 2018; 4(2): 37-38.
A Multifaceted Peer Reviewed Journal in the field of Biology, Medicine, Engineering and Science
www.bemsreports.org | www.phcog.net

Special Commentary on Maximum Acceptable Toxicant Concentration (MATC)

K.S. Rao*

INTRODUCTION

MATC is a value that is calculated through aquatic toxicity tests to help set water quality regulations for the protection of aquatic life. Using the results of a partial life-cycle chronic toxicity test, the MATC is reported as the geometric mean between the No Observed Effect Concentration (NOEC) and the Lowest Observed Effect Concentration (LOEC).

The MATC is used to set regulatory standards for priority pollutants under the US federal Clean Water Act. Regulatory guidelines give two acceptable concentrations of pollutants to protect against effects: chronic or acute.

MATC is a range of concentrations of a toxic substance in an environment that is between 'No Observable Adverse Effect Level (NOAEL)' and the 'Lowest Observable Adverse Effect level (LOAEL)'. In other words, MATC is the highest concentration at which a pollutant can be present and not exert an adverse effect on the Biota, used to experimentally determine the toxicity of the chemical.

Chronic Toxicity Tests

In a toxicity test, the NOEC and LOEC are derived as a comparison from the negative control, or the experimental group that does not contain the chemical in question. The NOEC is the highest concentration that does not cause a statistically different effect than the negative control. Likewise, the LOEC is the lowest concentration tested that does cause a statistically different effect than the negative control. The MATC is the geometric mean between these two values, such that: MATC=$\sqrt{(NOEC)(LOEC)}$

The MATC is calculated to protect against chronic effects on overall function or health of an organism, not death. A partial life cycle test must be used. This type of toxicity test uses organisms in their most sensitive life stages, usually during times of early reproduction and growth, but not juveniles. https://en.wikipedia.org/wiki/Maximum_acceptable_toxicant_concentration - cite_note-Rand2-3. The MATC is the highest concentration that should not cause chronic effects, however, for regulatory purposes; a maximum concentration to protect against acute effects must exist as well.

Applying MATC to Acutely Toxic Concentrations

The MATC can be applied to the results of an acute toxicity test to obtain a concentration that would protect against adverse effects during an acute exposure. An LC_{50}, or the concentration at which 50% of the organisms die during an acute toxicity test is used to derive a value called the Acute to chronic ratio (ACR).

The MATC can be used to calculate the ACR as follows: ACR={LC_{50} \over MATC}.

The ACR is useful for estimating an MATC for species in which only acute toxicity data exists, or for setting regulatory guidelines for the protection of aquatic life through water quality criteria by the US EPA.

Regulatory Uses

The US EPA is the governmental organization responsible for writing and enforcing environmental regulations passed by Congress. The Clean Water Act which was passed in 1972.

Section 304(a)(1) of the Clean Water Act is the Water Quality Criteria (WQC) developed for the protection of aquatic life and human health. The MATC and ACR are used in a sequence of calculations to obtain the Criterion Maximum Concentration and Criterion Continuous Concentration (CMC and CCC, respectively) for the chemicals being regulated.

The CMC and CCC are two of the six parts of the aquatic life criterion under the WQC and are the actual regulatory values for all priority pollutants tested. The CMC is the highest concentration of a chemical in water that aquatic organisms can be exposed to acutely without causing an adverse effect. Likewise, the CCC is the highest concentration of a chemical in water that aquatic organisms can be exposed to indefinitely without resulting in an adverse effect. Typically, the CMC is higher than the CCC.

Many of these methods use the same test organism or are designed for the same exposure time. Common test organisms include, but are not limited to,

Cite this article : Rao KS. Special Commentary on Maximum Acceptable Toxicant Concentration (MATC). BEMS reports. 2018;4(2):37-8.

K.S. Rao

Advinus Therapeutics Ltd, 21 and 22, Phase II, Peenya Industrial Area, Bengaluru – 560058, Karnataka, INDIA.

Correspondence

Dr. K.S. Rao, (M.V.Sc., Ph.D., DABT)

Senior Director – Strategic Business Development, Advinus Therapeutics Ltd, 21 and 22, Phase II, Peenya Industrial Area, Bengaluru – 560 058, Karnataka, INDIA.

Ph.no: +91-733-783-0074

Email: ks.rao@advinus.com

History

- Submission Date: 04-08-2018;
- Review completed: 17-08-2018;
- Accepted Date: 03-09-2018.

DOI : 10.5530/bems.4.2.9

Article Available online
http://www.bemsreports.org

Daphnia, fathead minnow, rainbow trout. Acute toxicity tests are normally 24–96 hrs, whereas chronic tests will typically run for a week or longer. Water Quality Criteria (WQC) are reported as one number that the actual concentration must remain below.

Maximum Allowable Carryover (MAC or MACO)

The MAC approach is often used to set cleaning validation acceptance criteria for the carryover of the previously manufactured API (Product A) into the subsequently manufactured API (Product B). These levels are determined according to the potential pharmacological, safety, toxicity, stability and contamination effects on the next product produced with the same surface or equipment. A limitation of this approach is that it does not account for the carryover of the inactivated molecule between lots of different products (i.e., A → B, or B → A).

Another issue with the MAC approach is that every time a new product is introduced into a facility there is a risk that one or more of the new MAC limits for the previously validated products could be below the existing acceptance limits for cleaning validation.

The determination of MACO for a pharmaceutical agent to the subsequently manufactured product is an inexact science. Each approach has its own set of assumptions and limitations. Any firm that relies on MACO values for their cleaning validation studies must understand the assumptions used in deriving the MACO values. It is the responsibility of pharmaceutical manufacturers and cleaning validation scientists tasked with setting MACO values to estimate a value that is safe for consumers without being so demanding that resources are spent unnecessarily.

I am going to describe one simple and most often used process for calculating MACO. (http://apic.cefic.org/pub/pub-cleaning-validation.pdf)

The basis for establishing MACO limits is a mathematical calculation that allows a certain fraction of the therapeutic dose to carry over into the Maximum daily dose (MDD) of the following product. The dose fraction allowed to carry over is referred to as Maximum allowable carryover (MACO) and is based on the acceptable daily intake (ADI) of the API being cleaned. Industry uses various approaches to determine the ADI values for active ingredients and involve using Minimum recommended therapeutic daily dose (MRTDD), Lowest marketed dose (LMD), or No Observable Effect Level (NOEL)/LD50 (Lethal dose 50%) values divided by a safety factor.

A safety factor of 1000 is widely used because it can be thought of as comprising a factor of 10 for adjusting a therapeutically effective dose to a therapeutically non-effective dose, a factor of 10 to accommodate for individual variability in response and a factor of 10 for making cleaning validation studies robust. The dose-reduction fraction is a measure of the risk involved and is assessed by the manufacturer depending on the actual manufacturing situation.

In most cases, not much data exists for carry over drugs, other than an acute toxicity (LD_{50}). In such cases, NOEL is calculated by using the Lethal Dose 50 (LD_{50}) of the drug, as follows:

NOEL = (LD_{50} X 70 Kg)/2000

Where,

LD50 – Lethal Dose;

70 Kg – Average Adult Doses;

2000 – A empirical constant.

For example: If the LD_{50} of a drug is 331 mg/kg, then its NOEL will be calculated as below:

NOEL = 331 X 70/2000 = 11.6 mg

Now this NOEL value is used to calculate the Maximum Allowable Carry Over (MACO) as follows:

MACO = NOEL*MBS/SF*TDD

Where,

MBS = Maximum Batch Size;

SF = Safety Factor (1000 for oral drugs);

TDD = Total Daily Dose of next product.

For example: If Total Daily Dose of the next product is 500 mg and the batch size is 400 Kg then MACO can be calculated as follows:

MACO = (11.58 mg*400000000 mg)/(1000*500 mg)

= 4632000000/500000

= 9264 mg or 9.264 g

Calculation of MACO values from toxicity data are frequently done when therapeutic dosage data is not available or not relevant. It is generally employed if the previous product is an intermediate and the following product an API.

CONCLUSION

For a drug with 331 mg/kg of LD50 should not be carried over more than 9.264 g in next batch having 500 mg daily dose and 400 kg batch size. This criterion is used to calculate the cleaning validation limits.

Disclaimer

This newsletter is solely intended for educational purpose. Some of the contents of this newsletter may have been adopted without or with modification from other published resources.

Cite this article : Rao KS. Special Commentary on Maximum Acceptable Toxicant Concentration (MATC). BEMS reports. 2018;4(2):37-8.