Process and Considerations in Establishing ADI for Food Additives

– *International Perspective*

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Outline

1. A brief introduction of JECFA
2. What is ADI?
3. ADI establishment by JECFA

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WHAT IS JECFA?

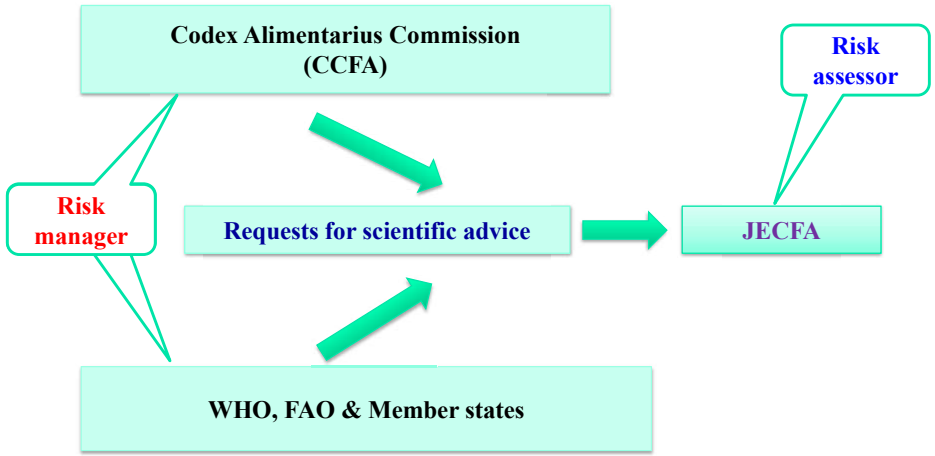
Joint FAO/WHO Expert Committee on Food Additives (JECFA)

60 YEARS OF EXCELLENCE (1956-2016)

JECFA is an international scientific expert committee administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and WHO. It has been meeting since 1956, initially to evaluate the safety of food additives. Its work now also includes the evaluation of contaminants, naturally occurring toxicants and residues of veterinary drugs in food.

- **>2600 food additives including flavors have been evaluated**
- **JECFA generally meets once a year to evaluate food additives (Geneva / Rome)**

WHAT IS JECFA?



WHO IS JECFA?

- Members: Invited by FAO and WHO for a meeting, who will draw conclusions and agree on the report - (Chairman, Vice-Chairman, two rapporteurs)
- FAO and WHO Experts: who assess available data and documentation, prepare drafts and contribute to the discussion during the meeting
- Secretariat of JECFA: from FAO and WHO
- Relevant Codex Committees (CCFA): Chairs, Codex Secretariat

Private meetings: by invitation only - no observers, no sponsors!

WHO IS JECFA- Experts *Rosters*

FAO and WHO establish separate listings of experts [ROSTERS]

- FAO: specifications of food additives

FAO Roster of experts for the
Joint **FAO/WHO** Expert Committee on Food Additives (JECFA)
- Food additives, contaminants and natural toxins –

NAME	POSITION	AFFILIATION	COUNTRY
Gabriel Olaniran Adegoke	Professor	University of Ibadan	Nigeria
Kofi Edirisah Aidoo	Professor	Glasgow Caledonian University	United Kingdom

- WHO: toxicological evaluations of food additives

Joint FAO/WHO Expert Committee on Food Additives (JECFA)

WHO Roster of Toxicological and Epidemiological Experts
2016 - 2020

Last Name	First Name	Affiliation	Country	Area of Expertise
Adeyemo	Olanike	University of Ibadan	Nigeria	Veterinary Drugs

WHO IS JECFA- Experts *Rosters*

- **FAO/WHO: Exposure assessment**

FAO/WHO Roster of experts for the Joint FAO/WHO Expert Committee on Food Additives (JECFA)
– Exposure assessment of chemicals in food –

Dr	Abbot	Linda	United States Department of Agriculture, Washington D.C.	USA

- **Appointments to roster based on scientific credentials and a balance of scientific expertise**
- **Selection process respects regional representation and gender balance**
- **Being in the ROSTER does not mean being in the JECFA meeting**

Declaration of Interest (DOI)

- Any potential or perceived interests will be evaluated before any tasks are assigned
- The WHO Joint Secretary will take into account whether monographers have been involved with a particular compound, which may be perceived as a conflict or bias
- Interests to be considered include the following examples:
  - Experts have worked for or have an interest in the sponsoring company
  - Experts have performed some of the studies to be evaluated
  - Experts have recently been closely involved with preparing an evaluation of a compound for a national or supranational body

DECLARATION OF INTERESTS FOR WHO EXPERTS

EMPLOYMENT AND CONSULTING

Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of the meeting or work?

1a	Employment	Yes ☐	No ☒
1b	Consulting, including service as a technical or other advisor	Yes ☐	No ☒

Confidentiality

- According to WHO rules and procedures, expert meetings are private in nature, and participation is by invitation only
- The data used and discussions held at the meeting are to be held in strict confidence
- Experts have to accept these rules and confirm with signature that they will adhere to them
- On request, original documents have to be returned

WORLD HEALTH ORGANIZATION ORGANISATION MONDIALE DE LA SANTE

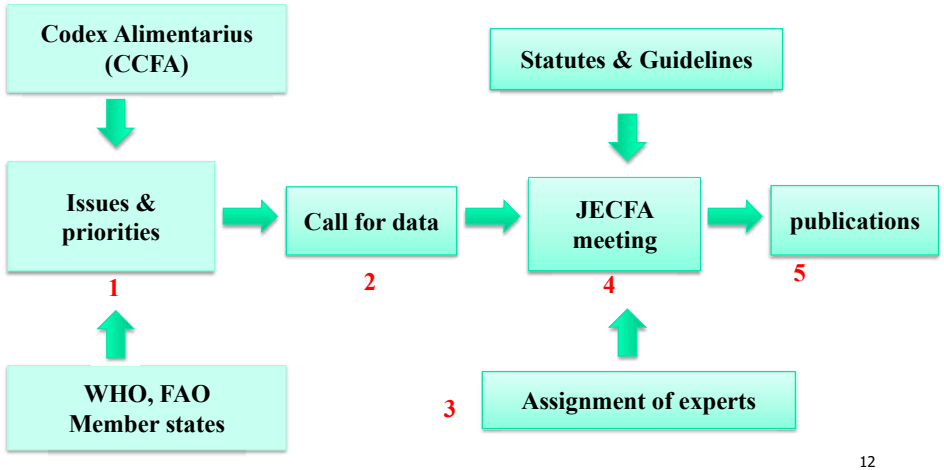
84th JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES (JECFA)
Rome, 6 – 15 June 2017

CONFIDENTIALITY UNDERTAKING

Core principles of scientific advice

Soundness	Need for scientific excellence (experts, process)
Responsibility	accountability, safeguard the integrity of the process, consider experts answerable for their views
Objectivity	Neutrality of experts and advice
Fairness	Conduct of process; respect of all participants for each other and for their scientific views.
Transparency	Mechanisms that ensure that process and advice are clearly understandable to others
Inclusiveness	Group balance: minority scientific opinion, balance of required skills and expertise

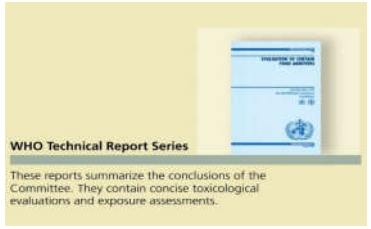
General Process Flow of JECFA meeting

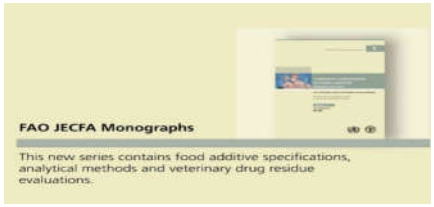


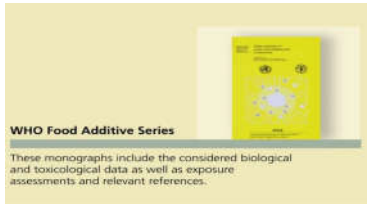
JECFA output

JECFA reports and publications freely available (print / e-publication)

Summary report: 2-3 weeks after meeting, key conclusions only







Outline

What is ADI?

- Acceptable Daily Intake
- For substances intentionally added to food, such as food additives
- The ADI is defined as an estimate of the amount of a food additive, expressed on a body weight basis, that can be ingested daily over a lifetime without appreciable health risk.
- JECFA generally establishes the ADI on the basis of the lowest relevant NOAEL in the most sensitive species.
- The ADI is expressed in amount (e.g. mg) per kilogram of body weight, usually as a range from 0 to an upper limit. e.g. 0-6 mg/kg bw

What is ADI?

- Calculation of the ADI can be described as follows:

ADI =POD/UF

- where **POD** is point of departure. NOAELs or BMDs (BMDLs) are the common POD or reference point.
- **UF** is the uncertainty factor, a term often used synonymously with safety factor.
- Historically, a default uncertainty factor of 100 has been used to account for the inherent uncertainties in extrapolating toxicity data from experimental animal studies to potential effects in humans as well as variation within the human species.
- Additional uncertainty factors may be used to allow for important database deficiencies, such as the absence of a chronic study

ADI "not specified"

- When the estimated dietary exposure to the food additive is expected to be well below any numerical value that would ordinarily be assigned to it, JECFA uses the term ADI "not specified".
- JECFA defines this term to mean that, on the basis of available data, the total daily exposure to a food additive arising from its use at the levels necessary to achieve the desired effect and from its acceptable background in food does not, in the opinion of JECFA, represent a hazard to health.
- A food additive meeting this criterion must be used within the bounds of good manufacturing practice – that is, it should be technologically efficacious and should be used at the lowest level necessary to achieve this effect, it should not conceal inferior food quality or adulteration, and it should not create a nutritional imbalance.
- e.g. Carob bean gum: ADI "not specified" at the 25th JECFA meeting

Temporary ADI

- When the available data on a new food additive had some limitations or the safety of a food additive for which JECFA had previously assigned an ADI was brought into question by new data, JECFA often establishes a "temporary" ADI.
- When establishing a temporary ADI, JECFA always uses a higher than usual uncertainty (safety) factor, usually increasing it by a factor of 2.
- The additional biochemical or toxicological data required for the establishment of an ADI are clearly stated, and a review of these new data is conducted before expiry of the provisional period.
- In many cases, long-term studies are requested, but timetables are not met, which means that JECFA has had to extend temporary ADIs for further periods of time, usually one year.
- In instances where data have not been forthcoming, JECFA has withdrawn temporary ADIs as a safety precaution.
- e.g. Allura Red AC: a temporary ADI of 0-7 mg/kg bw (the 24th JECFA meeting)

Group ADIs

- If several substances that produce similar toxic effects are to be considered for use as food additives, it may be appropriate in establishing an ADI to consider the group of substances in order to limit their overall dietary exposure.
- When JECFA is considering a substance for which toxicological information is limited but that substance is a member of a series of substances that are very closely related chemically (e.g. fatty acids), it may be possible for JECFA to base its evaluation on the group ADI established for the series of substances.
- In some instances, group ADIs can be established primarily on the basis of metabolic information. For example, the safety of esters used as food flavoring agents could be assessed on the basis of toxicological information on their constituent acids and alcohols, provided that it is shown that they are quantitatively hydrolysed in the gut.

Outline

The NOAEL approach to deriving the ADI

- *No-observed-adverse-effect level (NOAEL)*: Greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or lifespan of the target organism under defined conditions of exposure.

- The NOAEL approach has been used for over 50 years, and testing guidelines have been developed to ensure that toxicological data are suitable to identify the adverse effect of concern and also to define a NOAEL.

The NOAEL approach to deriving the ADI

Step 1: Data selection

- The critical steps in this approach are selection of the appropriate data and determination of the NOAEL.

Step 2: Selection of NOAEL

- The selection of the NOAEL identifies the highest dose level that does not produce a statistically significant effect.

Step 3: Implementation

- Calculation of the ADI is given by the equation:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{UFs}}$$

The BMD approach to deriving the ADI

- BMD (benchmark dose): A dose of a substance associated with a specified low incidence of risk, generally in the range of 1–10%, of a health effect; the dose associated with a specified measure or change of a biological effect.
- BMDL (Benchmark dose lower confidence limit): The lower boundary of the confidence interval on the benchmark dose.
- The BMD method has a number of advantages, including the use of the full dose–response data in the statistical analysis.
- Software packages are available: e.g. BMDS (US EPA); PROAST (the Dutch National Institue for Public Health and the Environment)
- By now, JECFA has not yet used the BMD approach to establish an ADI for food additives.

ADI establishment for Allura Red AC

EXPLANATION:

- Allura Red AC is a monoazo dye that is widely used as a synthetic food colour in many countries around the world.
- JECFA previously evaluated Allura Red AC at its 18th, 23rd, 24th and 25th meetings.
- At its 24th meeting, JECFA established a temporary ADI of 0–7 mg/kg bw based on long-term rat studies.
- At its 25th meeting, JECFA established a full ADI of 0–7 mg/kg bw.
- At 82nd JECFA meeting, Allura Red AC was re-evaluated at the request of CCFA.

ADI establishment for Allura Red AC

Step 1: DATA selection- *from sponsor & literature search*

- In response to JECFA's request for further data on Allura Red AC, new studies on biochemical effects, genotoxicity, reproductive and developmental toxicity, neurobehavioural effects and observations in humans were submitted by the sponsor.
- JECFA also considered other related information retrieved from a literature search.

ADI establishment for Allura Red AC

Step 1: DATA selection- *Literature search*

- The search of the scientific literature was conducted in March 2016 using the PubMed database of the United States National Library of Medicine.
- Use of the linked search terms "Allura Red" and "food additive" yielded 91 references, of which only two were considered relevant for the toxicological assessment.
- Use of the linked search terms "Allura Red" and "toxicity" yielded 18 references, one of which was potentially relevant but already identified in the search using the terms "Allura Red" and "food additive".

ADI establishment for Allura Red AC

Step 1: DATA selection- *Chemical and technical considerations*

- Allura Red AC consists mainly of disodium 6-hydroxy-5-(2-methoxy-5-methyl-4- sulfonato-phenylazo)-2-naphthalene-sulfonate and subsidiary colouring matter together with sodium chloride and/or sodium sulfate as the principal uncoloured components.
- It is manufactured by coupling diazotized 4-amino-5-methoxy-2-methylbenzenesulfonic acid with 6-hydroxy-2-naphthalene sulfonic acid.
- The resulting dye is purified and isolated as the sodium salt. Specified impurities include uncombined starting materials, subsidiary colouring matter related to the primary dye component, lead and unsulfonated primary aromatic amines.

ADI establishment for Allura Red AC

Step 1: DATA selection- *Biochemical aspects*

- Allura Red AC is poorly absorbed in rats and dogs, with up to 95% of the total intake being excreted in the faeces.
- Cresidine sulfonic acid was found to be the major metabolite of Allura Red AC in both the urine and faeces of rats and dogs .

ADI establishment for Allura Red AC

Step 1: DATA selection- *Toxicological studies*

- *Acute toxicity*: low oral acute toxicity in mice (Sasaki et al., 2002), rats (Weir, 1965a), rabbits (Weir, 1967) and dogs (Weir, 1965b).
- *Short-term studies of toxicity:* in several species, including rats (Weir & Crews, 1966a), dogs (Weir & Crews, 1966b; Olson et al., 1970) and pigs (Sondergaard et al., 1977), revealed no compound-related.

ADI establishment for Allura Red AC

Step 1: DATA selection- *Toxicological studies*

long-term studies of toxicity and carcinogenicity:

- Rats were given Allura Red AC in the diet at a level of 0%, 0.37%, 1.39% or 5.19% [Olson, et al, 1970].
- the only effect seen was decreased body weight at the highest dose tested.
- No evidence of carcinogenicity was observed in the study.

ADI establishment for Allura Red AC

Step 1: DATA selection- *Toxicological studies*

Genotoxicity studies:

- No evidence for genotoxic potential of Allura Red AC was found in numerous *in vitro* mutagenicity studies (Brusick, 1976; Anonymous, 1977a; Brown et al., 1978; Viola & Nosotti, 1978; Muzzall & Cook, 1979; Prival et al., 1988; Fujita et al, 1995; NTP, 2000; Zeiger & Margolin, 2000)
- or *in vivo* assays (Anonymous, 1977b, 1978; Jorgenson et al., 1978; Abramsson-Zetterberg & Ilbäck, 2013; Honma, 2015; Pant, 2015).

ADI establishment for Allura Red AC

Step 1: DATA selection- *Toxicological studies*

Reproductive and developmental toxicity:

- In mice, no reproductive toxicity at dose levels up to 2520 mg/kg bw per day over two generations was reported (Tanaka, 1994).
- In a study in rats (Vorhees et al., 1983), reduced reproductive success and reduced cerebellar weight in the offspring of all treated animals were observed. The reported effects in this study showed no dose–response relationship.
- Developmental toxicity studies in rats (Collins, 1974; Collins & Black, 1980; Collins et al., 1989b) and rabbits (Reno, 1974) did not show any compound-related embryotoxic or teratogenic effects.

ADI establishment for Allura Red AC

Step 1: DATA selection- *Observations in humans*

- JECFA noted that it had previously considered a study that investigated the possibility of a relationship between hyperactivity in children and the consumption of beverages containing a mixture of food colours, including Allura Red AC, and a preservative, sodium benzoate (McCann et al., 2007).
- As concluded previously by JECFA (WHO, 2012), this study was of limited value because of inconsistencies in the findings and the use of mixtures of food colours.

ADI establishment for Allura Red AC

Step 2: NOAEL selection

- a long-term study of toxicity and carcinogenicity[Olson, et al, 1970]
- Rats were given Allura Red AC in the diet at a level of 0%, 0.37%, 1.39% or 5.19%.
- the only effect seen was decreased body weight at the highest dose tested.
- No evidence of carcinogenicity was observed in this study.
- The **NOAEL** was 1.39% (equivalent to 695 mg/kg bw per day, calculated using default dose conversion factors) based on the reduced body weight observed at 5.19% Allura Red AC in the diet, the highest dose tested.

ADI establishment for Allura Red AC

Step 3: Evaluation

- $\text{ADI} = \frac{\text{NOAEL}}{\text{UFs}}$
- Where the NOAEL is 695 mg/kg bw per day, the UF is 100.
- The calculated ADI is 0–7 mg/kg bw
- JECFA concluded that the new data do not give reason to revise the ADI and confirmed the ADI of 0–7 mg/kg bw.

Thank you for your attention