CODEX ALIMENTARIUS COMMISSION

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World Health Organization

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**Agenda 9** **FFP/34 CRD/22**

**JOINT FAO/WHO FOOD STANDARDS PROGRAMME**
**CODEX COMMITTEE ON FISH AND FISHERY PRODUCTS**

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# US Comments on Uncertainty Factor for Histamine Level

Use of the no observed adverse effect level (NOAEL) of 50mg as a hazard level alone without employing an uncertainty factor (UF) for interindividual differences:

- Use of this value without an UF is the exception to the typical approach and not what is commonly done.
- Typical approach is to use UF=10 with NOAEL from human data to account for normal or common interindividual variability.
- Usually need to have clear, very strong reasons or data characteristics to **not** include 10-fold UF; this is **not** the case with these data. If anything, the opposite is true. There are a number of reasons for this 10-fold UF should be included. Some examples are outlined clearly in the Histamine Discussion Paper (e.g., metabolic differences, alcohol or Rx drug use)
- Typical safety assessment approach is to protect all consumers, not just healthy individuals.

We support asking Codex Committee on Contaminants in Foods (CCCF) for advice about use of UF. This group should have an understanding about and experience with the safety/hazard assessment approach. Their input should help with the consideration of an added margin of safety in determining a level of concern or "maximum concentration or level of histamine (or L)."

The margin between the no adverse effect level (NOAEL) of 50 mg in fish and the dose of adverse histamine reactions or effects (LOAEL) is not great.

- Two studies that administered histamine in fish resulted in histamine reactivity in healthy subjects at 90 mg and 100 mg (or LOAELs).
- Two other studies that administered histamine in beverages saw adverse symptoms occurring at doses lower than these "fish" doses, so it is possible.
- Therefore the margin between no reaction (50 mg) and reaction (90-100 mg) appears to be only 40-50 mg with respect to fish intake (and possibly lower).
- This means that there may be only 40-50 mg histamine in the diet from other sources during a meal (e.g., wine.)
- Not having an UF to build in a margin of safety/exposure with respect to the "fish" histamine content between no reaction and reaction is potentially problematic.

Often the total dietary exposure to a compound from all sources is considered in the comparison to a toxicological reference value. It appears in the Codex/FAO analyses the cumulative exposure to histamine from all dietary sources was not considered on top of no added margin of safety or uncertainty considerations.

It is very important to keep in mind that these NOAEL and LOAEL values are **not** "absolute" cut-off points. They are **estimates** from available dose-response data and in this case it is from a very limited number of studies with small number of subjects. The "real" NOAEL may actually be 40 mg and/or the "real" LOAEL may actually be 80 mg. We don't know because these other doses have not been tested to have the data on them. Because the NOAEL and LOAELs from studies are only **representative estimates** of the best data we have and are NOT absolute "true" values, is one of the main reasons we also typically employ UF in deriving a toxicological reference value (e.g., ADI, TDI, RfD).

The 200 ppm histamine content for fish alone (i.e., L) with no added margin of safety doesn't account for histamine content of any other food item to be combined with fish (like in a fish recipe) that may also contain histamine

- It is common for fish sauce and/or fish paste to be part of fish recipes.
- FDA reviewed available data on histamine content of fish sauce and paste and found a large range in histamine content with some containing very high amounts.
- For example, fish sauce and fish paste can contain significant levels of histamine while adding negligibly to the weight of the 250 g fish content used in the "L" calculation but increase the histamine level over 50 mg or 200 ppm.
- This is the margin between the NOAEL or L for fish histamine content alone and the LOAEL for fish histamine content alone.
- This suggests if other dietary sources of histamine are considered such as that in fish sauce and paste along with fish histamine (i.e., some form of cumulative dietary exposure) it is not difficult to approach the histamine adverse effect level.
- If the typical UF is included, this would also serve to address the possibility of variable sources of histamine and variable possible exposures levels.