codex alimentarius commission

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

WORLD HEALTH ORGANIZATION

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**Agenda Item 6(b)** **CX/PR 99/8**
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**JOINT FAO/WHO FOOD STANDARDS PROGRAMME**

**CODEX COMMITTEE ON PESTICIDE RESIDUES**
**Thirty-first Session**
**The Hague, The Netherlands, 12 - 17 April 1999**

# DRAFT AND PROPOSED DRAFT EXTRANEOUS MAXIMUM RESIDUE LIMITS

## NEED FOR EMRL FOR TOXAPHENE IN FISH

(Prepared by Germany)

### BACKGROUND

1. The Twenty-first Session of the Codex Alimentarius Commission referred to this Committee a proposal to elaborate MRLs in fish. The Committee at its 28th and 29th Sessions discussed this proposal and agreed that there was no need to establish MRLs/EMRLs for fish for the time being as there were neither significant problems in trade of fish nor apparent health concerns arising from uses of pesticides in aquaculture, or from environmental contamination. The Committee also agreed that it might consider this issue in the future.

2. The Codex Alimentarius Commission at its 22nd Session (June 1997) concurred with the Committee's opinion that the elaboration of MRLs for fish was of low priority. The Delegation of Germany stated that residues of pesticides in fish was a growing problem, especially in relation to increasing amount of organochlorine compounds in water. The Commission requested the Committee to monitor the gravity of the problem for necessary action.

3. At the 30th Session of the Committee, the Delegation of Germany expressed the view that as its monitoring demonstrated that the levels of residues of toxaphene in the North Sea, Irish Sea and Baltic Sea had been increasing and toxaphene is a potential carcinogen for humans, it was desirable that an EMRL(s) should be elaborated for fish. Germany offered to provide its monitoring data and a new method of analysis. It was noted that the Committee would consider the need for criteria for setting EMRLs under agenda item 8(b) of that Session which might have certain implications on this issue. The Committee requested Germany to prepare a paper on the need for elaborating an EMRL(s) for toxaphene in fish for consideration at its 31st Session taking into consideration the *FAO Manual on the Submission and Evaluation of Pesticide Residues Data for the Estimation of Maximum Residue Levels in Food and Feed* and CX/PR 98/8.

### INTRODUCTION

4. According to the document prepared for the 30th Session for consideration of the need for criteria for estimation of Extraneous Maximum Residue Limits (CX/PR 98/8) and the *FAO Manual on the Submission and Evaluation of Pesticide Residues Data for the Estimation of Maximum Residue Levels in Food and Feed*, EMRLs can be elaborated if:

(a) any intentional application of the compound can be safely excluded,
(b) the compound persists for more than three years following application (persistence),
(c) the compound can be regularly detected in food and animal feed at a level of "regulatory significance",

(d) potential health risks cannot be excluded in the absence of EMRLs and
(e) trade problems might arise.

5. In the light of these criteria, the elaboration of an EMRL for toxaphene in fish is warranted. In a large number of countries, toxaphene has no longer been approved since the mid-80s. However, even now we cannot completely rule out the possibility of its applications in some countries.

6. Toxaphene used to be one of the most important pesticides in quantitative terms. World-wide, approximately a total of 1,330,000 tons of toxaphene is estimated to have been introduced over time into the environment.

7. A large part of the quantities applied was dispersed into the atmosphere and carried to distant regions and ultimately into the oceans. More than 15 years after the ban of its application in many countries, toxaphene is found today in all oceans, with far higher levels detected in the oceans in the northern hemisphere than in those in the southern hemisphere. As a consequence, toxaphene residues are found in almost all salt-water fish in the northern hemisphere.

8. The toxaphene residues detected in fish are, in general, proportional to the mean fat content of the fish species and increase with age. As a result, the highest residue rates are observed in long-lived high-fat fish. Typical examples are halibut (10 - 20 % fat, life expectancy up to 20 years) and redfish (3 - 5 % fat, life expectancy up to 30 years).

9. Along with the Federal Republic of Germany, several other states have established maximum residue levels for toxaphene in fish, which is why trade problems cannot, as a rule, be excluded.

**TOXICOLOGICAL EVALUATION OF TOXAPHENE RESIDUES**

10. Used as an insecticide, toxaphene is a complex mixture of several hundred bicyclic compounds that mostly consist of 10 carbon atoms, 6 to 11 chlorine atoms and 7 to 12 hydrogen atoms per molecule.

11. While toxaphene has been extensively studied, only a part of the studies complies with state-of-the-art requirements. The individual toxaphene components differ widely in terms of acute toxicity.

12. For technical-grade toxaphene, the oral $LD_{50}$ in rats was found to be about 80 - 90 mg/kg bw, indicative of a high acute toxicity. In the subchronic trials, the NOAEL (no observed adverse effect level) in rats was 0.35 mg/kg bw/day, and in dogs 0.2 mg/kg bw/day.

13. No studies on the chronic toxicity of toxaphene are available.

14. The carcinogenicity studies, conducted on only two dosed groups and two untreated groups, revealed an increased incidence of thyroid tumours in rats and that of hepatocellular tumours in mice. As toxaphene induces xenobiotic-metabolizing enzymes in the liver, the development of thyroid neoplasms in rats can be explained through the increased degradation of thyroxin (T4) and the resulting increase in thyreotropine (TSH) production. The lowest carcinogenic dose tested was 540 - 556 mg/kg-feed in rats and 99 mg/kg-feed in mice. A NOAEL was not established.

15. Owing to its carcinogenicity in animal trials, toxaphene was classified by the:

(a) IARC (1979) as belonging to group 2B (possibly carcinogenic to humans),
(b) EC (1991) as belonging to category 3 (potential human carcinogens) and
(c) Senate Committee of the German Research Association for the Examination of Agents in the Workplace with Adverse Health Effects (1998) as belonging to category 2 (human carcinogen).

16. Most *in vitro* mutagenicity tests suggested that toxaphene was genotoxic, yet these effects were weaker in the presence of xenobiotic-metabolizing enzymes. The available *in vivo* study in mice was not suggestive of any genotoxicity, but chromosome aberration tests in professionally exposed individuals yielded controversial results and required further elucidation. Whereas the EC (1991) did not classify toxaphene as a genotoxic substance, the Senate Commission of the German Research Association for the examination of agents in the workplace with adverse health effects (1998), based on the mutagenic effect *in vitro*, did not exclude that the oncogenesis observed in animal experiments was due to a genotoxic mechanism.

17. A reproduction toxicity study did not reveal any adverse effects on fertility and offspring development. For systemic toxicity, a NOAEL of 0.29 - 0.38 mg/kg bw/day was established (corresponding to a concentration in feed of 4 mg/kg). Developmental toxicity studies (embryotoxicity, teratogenicity) in rats and mice suggested that developmental toxicity only occurred at dose levels toxic for the mothers. In rats, the lowest tested dose producing maternal toxicity and developmental toxicity was 15 mg/kg bw/day, no NOAEL was established; in mice, the NOAEL for developmental toxicity was 25 mg/kg bw/day.

18. In a toxicokinetic study in rats, oral doses of toxaphene were rapidly absorbed and almost completely metabolized (dechlorinated). Within 7 - 9 days, 15 - 23 % were excreted in urine and 36 - 37% in faeces, and, within 14 days, approximately 50 - 60% in urine and approximately 30 - 40% in faeces. The highest toxaphene residue levels in rats, dogs and monkeys were detected in adipose tissue, while the other tissues and organs contained significantly lower residue levels. The three toxaphene components that accounted for the bulk of residues were identical in monkeys and fish.

19. No ADI level has as yet been established for toxaphene.

**ANALYTICAL METHODS FOR THE QUANTIFICATION OF TOXAPHENE RESIDUES IN FISH**

20. Quantification of all 200 - 300 toxaphene components is extremely difficult and results are hardly comparable in the absence of exact conventions. As a matter of fact, however, only a few components selectively accumulate in fish. Selective accumulation of toxaphene components has been proven to occur also in monkeys, chickens, mother's milk, blubber, seal fat and polar bear tissue.

21. In fish, these three toxaphene components account for roughly 25% of the total toxaphene level. These three accumulated polychlorobornanes can be relatively easily analyzed as indicators of toxaphene contamination in fish tissues.

22. The suitability of a widely used analytical method[1] to quantify these three toxaphene indicator components was proven in a collaborative trial[2] whereupon the method was published.

**RESIDUE DEFINITION**

23. In the light of the particular analytical problems encountered, the residue definition cannot comprise the total of all toxaphene components. Instead, it is more convenient to use the above-mentioned analytical method for residue definition and to restrict analysis to the three most heavily accumulating toxaphene components. These compounds are:

- 2-endo,3-exo,5-endo,6-exo,8,8,10,10-Octachlorobornane (Parlar No. 26)
- 2-endo,3-exo,5-endo,6-exo,8,8,9,10,10-Nonachlorobornane (Parlar No. 50)
- 2,2,5,5,8,9,9,10,10,-Nonachlorobornane (Parlar No. 62).

24. Against this background, both the residue definition and the MRL for toxaphene in fish were laid down in the German Maximum Residue Limit Ordinance on the basis of these three indicators.

**ESTIMATION OF A PROPOSED EMRL FOR TOXAPHENE IN FISH**

25. The following issues have been suggested in the document CX/PR 98/8 for risk assessment by the JMPR:

(a) EMRLs are to be determined on the basis of random monitoring.
(b) If the estimation of EMRLs on the basis of random monitoring was to lead to economic disruptions, or strategies for residue minimization are not feasible, EMRLs may also be estimated on another basis.

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1 A congener-specific method for the quantification of campheclor/toxaphene residues in fish and other foodstuffs; L. Alder, B. Vieth; Fresenius J Anal Chem (1996) 354:81-92.

2 Collaborative Study on Toxaphene Indicator Compounds (Chlorobornanes) in Fish Oil; L. Alder, K. Bache, H. Beck and H. Parlar; Chemoshere (1997) 35:1391-1398.

(c) The statistical evaluation of data is to be in line with the stipulations in the *FAO Manual on the Submission of Pesticide Residues Data for the Estimation of Maximum Residue Levels in Food and Feed*.
(d) If possible, EMRLs should be established for commodity groups.

26. The data base comprises the toxaphene levels found in 1,128 fish samples. The majority of these samples have been analyzed within the framework of German food monitoring activities. Additional data have been obtained through studies. In each case, sampling was done on a random basis (random monitoring).

27. As the results of these studies show, the individual fish species differ with respect to mean toxaphene residue levels (see the figure below).

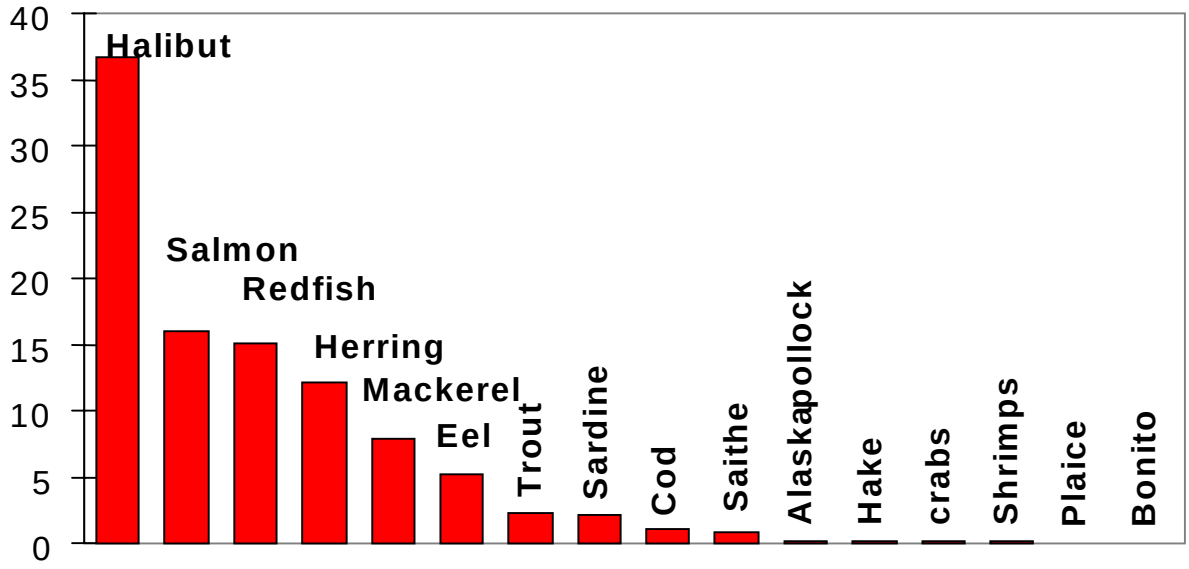


Figure: Mean toxaphene levels (µg/kg fresh weight; total of the three indicator compounds) in fish species that are particularly important for human consumption.

28. For this reason, either different EMRLs (Extraneous Maximum Residue Limits) must be established for the individual fish species or one single EMRL estimated for all fish. The latter, however, must take into particular consideration those fish species which are highly contaminated.

29. In line with the rule (d) in paragraph 25, only one EMRL should be established for fish. The estimation of this EMRL should then be based on the residue levels found in halibut, redfish and herring.

30. Residue levels in (farmed) salmon should not be included, since toxaphene residues can be largely avoided in this fish species. The presence of such residues is mainly attributable to feed contamination.

31. If such an EMRL were estimated on the basis of the fish species with the highest accumulation rates, common (unavoidable) residue levels would not create any barriers to trade. By contrast, fish from exceptionally contaminated waters could be excluded from trade to ensure consumer protection. (In this context, note the statements in paras 12 – 15).

**CONSIDERATION OF A SUITABLE VIOLATION RATE**

32. According to the *FAO Manual*, EMRLs are acceptable if 99.5% of the samples are below the proposed value (maximum violation rate 0.5%). However, this estimation parameter is still under intense discussion[3]. The European Community, for example, proposed a violation rate of 2 - 5%. These suggestions correspond to residue levels calculated for the 95% to 99.5% percentiles.

[3] Secretariat'a note: See CX/PR 99/7 and ALINORM 99/24, paras 85-89.

33. The following table presents the distribution of toxaphene residues as found in the samples of the individual fish species. Owing to the inadequate number of specimens for various fishes, however, it did not make sense to calculate all values.

Table: Levels (mg/kg fresh weight) of toxaphene indicator compounds in various fish species

| | Halibut | Herring | Redfish | Halibut, herring & redfish | Mackerel | Eel | Rainbow trout | Saithe (coalfish) | all samples |
|---|---|---|---|---|---|---|---|---|---|
| mean value | 0.036 | 0.008 | 0.015 | 0.010 | 0.011 | 0.003 | 0.001 | 0.000 | 0.004 |
| median value | 0.029 | 0.006 | 0.014 | 0.007 | 0.011 | 0.000 | 0.001 | 0.000 | 0.001 |
| 95% percentile | 0.070 | 0.028 | 0.024 | 0.034 | 0.018 | 0.013 | 0.003 | 0.002 | 0.019 |
| 97.5% percentile | | 0.038 | | 0.044 | 0.019 | 0.018 | 0.004 | 0.002 | 0.027 |
| 98 % percentile | | 0.040 | | 0.045 | | 0.019 | 0.004 | 0.002 | 0.031 |
| 99.5% percentile | | 0.053 | | 0.062 | | 0.023 | | 0.004 | 0.042 |
| Maximum value | 0.076 | 0.058 | 0.032 | 0.076 | 0.025 | 0.075 | 0.004 | 0.005 | 0.076 |
| sample number | 17 | 292 | 19 | 328 | 37 | 213 | 115 | 318 | 1128 |

34. A comparison shows that the level of the 95% percentile is usually 100% to 300 % higher than the corresponding mean value. The highest mean value, the highest 95% percentile and the highest maximum level were observed in halibut. However, the sample number for halibut is very small.

35. Provided that only one EMRL for toxaphene is established for all fish species, we propose a value of ***0.1 mg/kg*** based on the sum of toxaphene indicator compounds (reference basis: fresh weight).

36. Regarding the sum of toxaphene indicator compounds, the following toxaphene components must be taken into consideration:

- 2-endo,3-exo,5-endo,6-exo,8,8,10,10-Octachlorobornane (Parlar No. 26)
- 2-endo,3-exo,5-endo,6-exo,8,8,9,10,10-Nonachlorobornane (Parlar No. 50)
- 2,2,5,5,8,9,9,10,10,-Nonachlorobornane (Parlar No. 62).

37. According to this maximum level as proposed, at least 95% of all salt-water fish would be marketable. It is currently being examined within the framework of German food monitoring activities, whether also a higher proportion (98% percentile or 99.5% percentile) of residues in halibut is below this proposed maximum level. These data will also be submitted to the JMPR for evaluation.