CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX ALIMENTARIUS COMMISSION

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DRAFT STANDARDS AND RELATED TEXTS AT STEP 8 OF THE PROCEDURE (INCLUDING THOSE SUBMITTED AT STEP 5 WITH A RECOMMENDATION TO OMIT STEPS 6 AND 7 AND AT STEP 5 OF THE ACCELERATED PROCEDURE)

HISTORY OF THE DEVELOPMENT AND DISCUSSION IN CODEX ON THE MAXIMUM RESIDUES LIMITS (MRLS) FOR BOVINE SOMATOTROPINS (BSTS)

Background

1. The 34th Session of the Commission in response to the concerns raised by some delegations as to the delay to take a decision regarding the MRLs for bovine somatotropin (bSTs), which have been held at Step 8 since the 23rd Session of the Commission (1999), requested the Codex Secretariat to prepare a paper, which would describe the history of the development and discussion of the MRLs in Codex, including a summary of the JECFA evaluation[1].

Discussion in the Codex Alimentarius Commission

2. The draft Maximum Residue Limits (MRLs) for bovine somatotropins (bSTs) (see Annex 1) were considered for adoption by the Codex Alimentarius Commission at its 21st session (Rome, 3-8 July 1995)[2], 22nd session (Geneva, 23-28 June 1997)[3], and 23rd session (Rome, 28 June-3 July 1999)[4].

Arguments in favour of the adoption

3. Thorough scientific evaluation of the compound by JECFA; bSTs were used in several countries; adoption of the MRLs would confirm the work of the (Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the Codex Committee on Residues of Veterinary Drugs in Foods (CCRVDF) while preventing the application of non tariff barriers to international trade.

Arguments in favour of postponing the adoption

4. New information had become available indicating that the administration of bSTs could reduce livestock immune defences, which could make those animals more susceptible to viral and bacterial infection and an increased incidence of mastitis and consequent increased use of antibiotics; use of bSTs had no benefit for consumers and would not improve milk quality or safety. The importance of taking other legitimate factors than sound scientific analysis and evidence as stated in the *Statements of Principle on the Role of Science*[5] into consideration was also emphasized.

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[1] REP11/CAC paras 88-89
[2] ALINORM 95/37 paras 47-48
[3] ALINORM 97/37 paras 64-70
[4] ALINORM 99/37 paras 75-80
[5] "*When elaborating and deciding upon food standards Codex Alimentarius will have regard, where appropriate, to other legitimate factors relevant for the health protection of consumers and for the promotion of fair practices in food trade"* (Ref. para 2 of *Statements of Principle on the Role of Science,* Procedural Manual of the Codex Alimentarius Commission)

5. At the 21st and 22nd sessions of the Commission a roll-call vote was requested by European delegations (Spain and the Netherlands) on behalf of the Member States, on the adjournment of the debate on the adoption of maximum residue limits for bSTs at Step 8. The motion passed in both sessions[6]. At the 22nd session of the Commission, the delegation of the Netherlands proposed the suspension pending the re-evaluation of scientific data by JECFA and the CCRVDF and the examination of the application of the "other legitimate factors" in relation to bSTs by the Codex Committee on General Principles (CCGP). The Chairperson of the CCRVDF requested those delegations and observers who indicated that new information existed relevant to the protection of public health resulting from the use of bSTs in dairy cows to submit such information to the JECFA Secretariat by 30 September 1997 so that such information could be evaluated by the 50th JECFA session in February 1998.

6. At its 23rd session the Commission, after having considered reports by the Chairpersons of CCRVDF and the CCGP[7], decided "*to hold*" the draft MRLS for bSTs at Step 8 "*in accordance with the provisions contained in the introductory paragraphs of the Uniform Procedure for the Elaboration of Codex Standards and Related Texts*"[8].

7. The matter was neither referred to CCRVDF nor considered by the 24th session of the Commission and subsequent sessions. At the 26rd Session (Rome, 30 June – 7 July 2003)[9] , 27th Session (Geneva, 28 June – 3 July 2004[10]), 31st Session (Geneva, 30 June – 4 July 2008)[11], 32nd Session (Rome, 29 June – 4 July 2009)[12] and 33rd Session (Geneva, 5-9 July 2010)[13], the Commission only noted that no request had been received to change the status of the standard and, therefore, agreed to continue to hold the draft standard at Step 8.

8. At its 31st session the Commission further noted that the next session of the Executive Committee (62nd session), as part of the Critical Review process, would monitor the progress of standards development for all texts that had not yet been adopted by the Commission, including these draft MRLs, against the pre-determined time frame and would report its findings to the Commission.

9. At the 34th Session (Geneva, 4-9 July 2011)[14], in view of the concern of some delegations raised concern as to the delay to take a decision regarding the MRLs for bSTs, the Commission agreed to consider the draft MRLs at its next session. In order to facilitate its discussion, the Commission requested the Codex Secretariat to prepare a paper, which would describe the history of the development and discussion of the MRLs in Codex, including a summary of the JECFA evaluation.

Development of the MRLs in the Committee on Residues of Veterinary Drugs in Foods (CCRVDF)

10. The 5th CCRVDF (Washington D.C., 16-19 October 1990) included bSTs[15] in the priority list of substances to be evaluated by JECFA, at the request of the USA. [16]

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[6] The tallies were: 21st CAC: 33 votes in favour; 31 votes against; 6 abstentions; 22nd CAC: 38 votes in favour; 21 votes against; 13 abstentions.

[7] The CCRVDF Chairperson reported that the 50th Meeting of JECFA had re-evaluated BST and that the previous MRLs "not specified" for BST were confirmed when the substance was used in accordance with good veterinary practice. The CCRVDF, however, had been unable to reach a consensus on the adoption of the MRLs and the Chairperson had advanced them to Step 8 in order to submit them to the Commission for consideration. The CCGP Chairperson noted that the application of "other legitimate factors" in the case of BST had been considered twice by the Committee, and also that this Committee had been unable to reach a consensus on the issues at hand.

[8] The *Uniform Procedure for the Elaboration of Codex Standards and Related Texts*, provides, that, under Step 8, "*the draft standard is submitted through the Secretariat to the Commission together with any written proposals received from Members and interested international organizations for amendments at Step 8 with a view to its adoption as a Codex standard*". The Uniform Procedure also indicates, in its introduction, that the Commission may "*also decide that the draft be held at Step 8*". (Ref. para. 5 of "*Procedures for the Elaboration of Codex Standards and Related Texts*. Procedural Manual of the Codex Alimentarius Commission)

[9] ALINORM 03/41, para 34

[10] ALINORM 04/27/41, para 22

[11] ALINORM 08/31 /REP para. 64

[12] ALINORM 09/32/REP para. 65

[13] ALINORM 10/31/REP para. 61

[14] REP 11/CAC paras 88-89

[15] It was recommended that *bovine somatotropin* be listed as bovine *somatotropins* because this substance exists in several different forms.

[16] ALINORM 91/31 paras 113-115 and Appendix VII

11. The 7th CCRVDF (Washington D.C., 20-23 October 1992) recommended the adoption of the proposed draft MRLs for bSTs at Step 5[17], on the basis of the assessment of the 40thmeeting of JECFA.

12. The 8th CCRVDF (Washington D.C., 7-10 June 1994) advanced the MRLs for the bSTs to Step 8 of the Procedure for consideration by the Commission. The Committee was informed that there was a moratorium on the licensing of bSTs in the European Community (EC) until the end of 1994. While not objecting to advancing the MRLs for bSTs to Step 8, the EC could not take a formal position at that time in regard to the adoption of the MRLs.[18]

13. At the 11th CCRVDF (Washington D.C., 15-18 September 1998) after a lengthy discussion with divergent opinions, the Chairperson noted that there was no consensus. However, as no specific scientific objections had been raised on the basis of the summary report of the 50th JECFA, the decision of the Chairperson was to advance the MRLs for bSTs for adoption at Step 8 to the 23rd session of the Commission. It was emphasized that this decision was subject to subsequent scrutiny of the final JECFA report and toxicological monographs. Furthermore, the outcome of the discussion on other legitimate factors relevant to bSTs by the CCGP would have a bearing on the final consideration of MRLs for bSTs by the Commission[19].

Discussion in the Committee on General Principles (CCGP) in relation to application of "other legitimate factors"

14. In reviewing the application of the statements of principle on the role of science and the extent to which other factors should be taken into account in the case of bSTs and pST (porcine somatotropin), the 13th CCGP (Paris, 7-11 September 1998) recognized that no consensus existed on the application of other factors in the case of BSTs and that further discussion was needed[20]. It agreed that although the general and specific issues under consideration were related, they should be clearly identified in order to avoid confusion and to facilitate discussion. To this effect, the CCGP agreed that two papers should be prepared by the Secretariat on these issues: i) consideration of other legitimate factors in the framework of risk analysis as recommended by the Commission, and ii) application of other legitimate factors to the case of bSTs. The CCGP agreed to return to these matters at its next Session

15. The CCGP reasserted the primary role of science in health related issues, as reflected in the work on risk analysis in relation to food safety. The CCGP had an extensive discussion on the application of the second statement of principle concerning "*other legitimate factors relevant for the health protection of consumers and for the promotion of fair practices in the food trade*".[21]

16. The 14th CCGP (Paris, 19-23 April 1999) continued the discussion on the application of "other legitimate factors" in the case of bSTs and noted that Delegations remained divided on the consideration of other factors [22]as requested by the Commission in the mandate given to the Committee and that as a result it had not been possible to arrive at a consensus decision. The 14th CCGP agreed to inform the Commission

[17] ALINORM 93/31A para. 32 and Appendix V
[18] ALINORM 95/31 paras 48-49 and Appendix II
[19] ALINORM 99/31 paras 65-70 and Appendix II
[20] Delegations "in favour" stated that the consideration of other legitimate factors in the decision process was essential and several elements should be considered in the case of BST; that toxicological evaluation was not the only element to be considered and that technological justification and need had to be considered. These delegations also emphasized the importance of consumer concerns as a legitimate factor, in order to ensure that Codex standards were based on consensus and were largely accepted. Delegations "against" stressed that science-based risk assessment should be the determining factor when addressing a food safety issue such as the setting of MRLs for veterinary drugs. They recognized that while other factors were integrated in the definition of policy at the national level, the purpose of international standards was to provide a reference for the protection of health, as defined under the SPS Agreement, when sanitary measures were concerned.
[21] ALINORM 99/33, paras 59-70
[22] Delegations "in favour" referred explicitly to animal health and welfare as legitimate factors that had to be taken into account in relation to the use of BST; it was also suggested that different consideration should be given to the evaluation of substances used for therapeutic purposes than those use for production efficiency and growth promotion and to the need to address consumer concerns expressed in several countries especially in relation to the acceptability of products by consumers. Delegations "against" stated that apart from the protection of consumers' health, no other legitimate factors needed to be addressed since the scientifically-based risk analysis should be the determining factor. They expressed concern that consideration of other factors that were more legitimately addressed at the national level, would lead to paralysis of the Codex system.

accordingly[23]. The 23rd session of the Commission decided to hold the MRLs at Step 8 in accordance with the provisions contained in the introductory paragraphs of the *Uniform Procedure for the Elaboration of Codex Standards and Related Texts*[24] (*see* para.5).

17. The *Statements of Principle concerning the Role of Science in the Codex Decision-Making Process and the Extent to which other Factors are taken into Account* were adopted by the 21st Session of the Commission in 1995[25] and included in the Procedural Manual of the Codex Alimentarius Commission. In 2001, the 24th session of the Commission adopted the *Criteria for the Consideration of the Other Factors Referred to in the Second Statement of Principle*, to be included in the Appendix to the Procedural Manual after the *Statements of Principle*[26].

JECFA evaluations of bovine somatotropins (bSTs)

18. JECFA has evaluated bSTs at its 40th (Geneva, 9-12 June 1992) and 50th (Rome, 17-26 February 1998) meetings; the assessment and recommendations of JECFA were considered by the 7th CCRVDF and the 11thCCRVDF, respectively.

19. BSTs was evaluated by JECFA for the first time at its 40th meeting, which assessed four analogues of natural bovine somatotropin (bST) that are produced by recombinant DNA techniques (rbSTs): somagrebove, sometribove, somavubove and somidobove.

20. The 40th JECFA concluded that the lack of oral activity of rbSTs and insulin-like growth factor-I (IGF-I) and the low levels and non-toxic nature of the residues of these compounds, even at exaggerated doses, results in an extremely large margin of safety for humans consuming dairy products from rbST-treated cows. In view of the lack of impact on human food safety, the 40th JECFA established an ADI "not specified" for rbSTs with applied to somagrebove, sometribove, somavubove and somidobove. MRLs "not specified" were established for these rbSTs in bovine milk and edible tissues.[27] The term "not specified" was used because of the lack of oral activity of rbSTs and insulin-like growth factor I (IGF-I) and the low levels and non-toxic nature of the residues of these compounds, which results in an extremely large margin of safety for humans consuming meat and dairy products for rbSTs-treated cows. [28]

21. The 50th JECFA considered information relating to the following concerns:

- The increased use of antibiotics to treat mastitis in cows, which lead to a higher rate of "violative" drugs residues (i.e. residues exceeding regulatory limits) in milk, possibly because of an increase in the incidence of mastitis in cows treated with rbSTs;
- The possibility that increased levels of IGF-I in the milk of cows treated with rbSTs might lead to increased cell division and growth of tumours in humans;
- The potential effect of rbSTs on the expression of certain viruses in cattle, especially retroviruses;
- The possibility that the incubation period of bovine spongiform somatotropin (BSE) is shortened due to an increased in the production of pathogenic prion proteins induced by IGF-I;
- The possibility that early exposure of human neonates to milk from rbST-treated cows increases their risk of developing insulin-dependent diabetes mellitus.

22. After reviewing the available information, the 50th JECFA concluded that rbSTs can be used without appreciable health risk to consumers. This conclusion was based on the following factors:

- The insignificant changes in the quantities of milk discarded due to the detection of residues during testing after the introduction of rbSTs into commercial use;
- The low levels of residues of rbSTs and IGF-I in milk;
- The degradation of IGF-I in the gut and its naturally high levels in the gastrointestinal secretions;

[23] ALINORM 99/33A, paras 77-85
[24] ALINORM 99/37, para. 78
[25] ALINORM 95-37 paras 23-25
[26] ALINORM 01/41, para 98 and Appendix III
[27] WHO Technical Report Series (TRS) 832
[28] The JECFA applied the terms ADI "not specified" and MRLs "not specified" to veterinary drugs for the first time during the evaluation of rbSTs.

- The extremely low levels of IGF-I ingested from milk when compared to endogenous production;
- The lack of evidence that rbSTs stimulate the expression of retroviruses;
- The lack of information directly linking treatment with rbSTs and BSE; and
- The absence of significant changes in the composition of milk from cows treated with rbSTs that may contribute to the additional risk of development of insulin-dependent diabetes mellitus.

23. The Committee reaffirmed its previous ADI and MRLs "not specified" for somagrebove, sometribove, somavubove and somidobove. [29]

Discussion at the 34th Session of the Codex Alimentarius Commission

24. Following the concerns raised by some as to the delay to take a decision regarding the MRLs for bovine somatotropin, the 34th Session of the Commission agreed to consider the draft MRLs for bovine somatotropin at its next session (*see* Annex 1). In order to facilitate its discussion, the Commission requested the Codex Secretariat to prepare a paper, which would describe the history of the development and discussion of the MRLs in Codex, including a summary of the JECFA evaluation (as presented in the above paragraphs) (Ref. REP11/CAC, paras 88-89).

[29] WHO Technical Report Series (TRS) 888.

Annex 1

Draft MRLS for Bovine Somatotropins (at Step 8)

ADI: Not specified (1992). The ADI applies to somagrebove, sometribove, somavubove, somidobove.

Residue Definition: Not applicable

Species	**Tissue**	**MRL (µg/kg)**		**Step**	**JECFA**	**CCRVDF**
Cattle	Muscle	Not specified	1/	8	40, 50	7IV, 8II
Cattle	Liver	Not specified	1/	8	40	7IV, 8II
Cattle	Kidney	Not specified	1/	8	40	7IV. 8II
Cattle	Fat	Not specified	1/	8	40	7IV. 8II
Cattle	milk	Not specified	1/	8	40	7IV, 8II

ADI "not specified" means that available data on the toxicity and intake of the veterinary drug indicate a large margin of safety for consumption of residues in food when the drug is used according to good practice in the use of veterinary drugs. For that reason, and for the reasons stated in the individual evaluation, the JECFA concluded that use of the veterinary drugs does not represent a hazard to human and that there is no need to specify a numerical ADI.

1/ MRL "not specified" means that available data on the identity and concentration of residues of the veterinary drug in animal tissues indicate a wide margin of safety for consumption of residues in food when the drug is used according to good practice in the use of veterinary drugs. For that reason, and for the reasons stated in the individual evaluation, the JECFA concluded that the presence of drug residues in the named animal product does not present a health concern and that there is no need to specify a numerical MRL.