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SCIENTIFIC SUB-COMMITTEE

NS0022E1 (+ Annexes I and II)

16th Session

O. Eng.

Brussels, 1 December 2000.

CLASSIFICATION OF CERTAIN CHEMICAL PRODUCTS WITH REGARD TO THE HS COMMODITY DATA BASE

(Item II.7 on Agenda)

I. BACKGROUND

- 1. The Secretariat has received some inquiries from the users of the HS Commodity Data Base (HSCDB) indicating certain classifications which have to be reviewed.
- 2. Furthermore, while examining the classification of hormones on the basis of the 2002 version of the HS, the Secretariat has also identified a number of classifications in the HSCDB that should be reviewed.
- 3. Since the Secretariat is now in the process of preparing the 2002 version of the HSCDB, it would be useful if the Scientific Sub-Committee could review any classification errors in the present version of the HSCDB in order to make necessary amendments for the 2002 version.

II. SECRETARIAT COMMENTS

Fonofos

- 4. In November 1999, the Organisation for the Prohibition of Chemical Weapons (OPCW) inquired about the classification of Fonofos. It was pointed out that according to the HSCDB, Fonofos (ISO) is classified in subheading 2931.00, whereas according to the Explanatory Note to heading 29.31, Fonofos (ISO) is excluded from that heading and is classified in heading 29.30.
- 5. In view of the above-mentioned exclusion in the Explanatory Note to heading 29.31, the Secretariat feels that HSCDB should be corrected to reflect the classification of Fonofos in subheading 2930.90. Technical information on Fonofos, taken from the Merck Index, is set out in Annex I to this document.

File No. 2837

Neodecanoic Acid

- 6. During the Regional Seminar in Shanghai (June 1999), the participant from Indonesia questioned the classification of Neodecanoic Acid in subheading 2916.19, as reflected in the HSCDB.
- 7. According to Ullmann's Encyclopedia of Industrial Chemistry (Volume A5), Neodecanoic Acid is a trade name of Exxon, which refers to an octanoic, nonanoic and decanoic acid mixture with isomers. Hawley's Condensed Chemical Dictionary indicates Neodecanoic Acid as C₉H₁₉COOH with CAS: 26896-20-8. According to the Kirk-Othmer Encyclopedia of Chemical Technology (Vol.5), the C₁₀ trialkylacetic acids, referred to as Neodecanoic Acid (CAS: 26896-20-8) or as Versatic 10 (CAS: 52627-73-3) are typically mixtures of isomers and hence structures are not given.
- 8. Based on this information it is not clear to the Secretariat whether Neodecanoic Acid could be considered to be a separate chemically defined compound of Chapter 29 and hence the Secretariat would consider headings 29.15 and 38.24 as potential headings. However, it appears that Neodecanoic Acid should fall within saturated acyclic monocarboxylic acid(s) and therefore it is the view of the Secretariat that it could not be classified in heading 29.16, as reflected in the HSCDB.

Ciprofloxacin and Enrofloxacin

- 9. In September 2000, the Secretariat received an inquiry from a private party indicating that the above mentioned two chemicals are similar in chemical structure and usage but have been classified in the HSCDB in two different headings. According to the HSCDB, Ciprofloxacin is classified in subheading 2933.59 and Enrofloxacin is classified in subheading 2941.90.
- 10. Ciprofloxacin and Enrofloxacin are two INNs corresponding to INN Lists 50 and 56, respectively. Details concerning these two substances, taken from the Merck Index, are set out in Annex I to this document. Both these substances contain a quinoline ring-system and a piperazine ring in their structures.
- 11. Based on the use of common stems in the selection of INNs for pharmaceuticals, the stem "-oxacin-" is used for antibacterials, naridixic acid derivatives. The Sub-Committee, in the past, has examined similar INN products, namely Cadrofloxacin (INN List 81) and Fandofloxacin (INN List 78) and has classified both these substances in subheading 2933.59.
- 12. The Secretariat is therefore of the view that both Ciprofloxacin and Enrofloxacin should be classified in subheading 2933.59.

Hormones

- 13. While examining the classification of hormones based on the 2002 version of the HS, the Secretariat identified a number of classification questions which are listed in Annex II to this document along with the Secretariat's classification proposals. In respect of certain products, the Secretariat has proposed more than one classification (placed in square brackets) in the absence of sufficient information.
- 14. The technical information on the above-mentioned products, taken from the Merck Index, is set out in the Annex I to this document. The Sub-Committee is invited to examine the classification of these products.
- 15. The Secretariat feels that there could be number of similar classification questions that the administrations have come across in respect of the HSCDB and therefore that it would be appropriate to gather such information in order to make necessary corrections to the 2002 version of the HSCDB. The Sub-Committee may therefore look into this aspect as well, particularly in the area of chemicals, and give its views.

III. CONCLUSION

- 16. Taking into account the Secretariat's comments, the Sub-Committee is invited to :
 - (i) examine the classification of the above-mentioned products; and
 - (ii) give its views on how to proceed in correcting any other classification errors in the HSCDB, particularly in the area of chemicals.

* * *

4261. Fonofos.

Ethylphosphonodithioic acid O-ethyl S-phenyl ester; O-ethyl S-phenyl ethylphosphonothiolothionate; N-2790; Dyfonate (Stauffer). C₁₀H₁₅OPS₂; mol wt 246.33. C 48.76%, H 6.14%, O 6.49%, P 12.57%, S 26.03%. Prepn: Szabo et al., U.S. pat. 2, 988.474 (1961 to Stauffer): Pitt, Simone, Ger. pat. 2,002,629, C.A. 73, 77392u (1970), corresp to U.S. pat. 3,642,960 (1970, 1972, both to Stauffer).

Light yellow liquid, bp_{0.1} 130°. d_{25}^{25} 1.16. n_{D}^{30} 1.5883. Practically insol in water. Miscible with organic solvents. LD₅₀ orally in rats: 3 mg/kg, *Toxic Substances List*, H. E. Christensen, Ed. (1974) p 602.

Caution: Cholinesterase inhibitor.

USE: Soil insecticide.

2374. Ciprofloxacin.

1-Cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid; Bay q 3939. C₁₇H₁₈FN₃O₃; mol wt 331.35. C 61.62%, H 5.48%, F 5.73%, N 12.68%, O 14.49%. Fluorinated quinolone antibacterial. Prepn: K, Groheet al., Ger. pat. 3,142,854; eidem, U.S. pat. 4,670,444 (1983, 1987 both to Bayer AG); K, Grohe, H, Heitzer, Ann. 1987, 29. Antibacterial spectrum in vitro: B, Watt, F, V, Brown, J. Antimicrob. Chemother. 17, 605 (1986); C, M, Bassey et al., ibid. 623. HPLC determin in biological fluids: W, Gau et al., J, Liq. Chromatog. 8, 485 (1985). Pharmacokinetics: G, Hoffkenet al., Antimicrob. Ag. Chemother. 27, 375 (1985). Clinical trials: C, A, Ramirez et al., ibid. 28, 128 (1985); B. E. Scully et al., Lancet 1, 819 (1986). Symposia on antibacterial spectrum and clinical use: Am. J, Med. 82, Suppl. 4A, 1-404 (1987); J. Antimicrob. Chemother. 26, Suppl. F, 3-193 (1990). Review of clinical safety and efficacy in children: R. Kubin, Infection 21, 413-421 (1993). Dec 255-257°.

Monohydrochloride monohydrate, C₁₇H₁₈FN₃O₃.HCl.H₂O, Bay o 9867. Baycip (Bayer), Ciflox (Bayer), Ciloxan (Alcon), Cipro (Bayer), Ciprobay (Bayer), Ciproxan (Bayer), Ciproxin (Bayer), Flociprin (IBI), Septicide (Bago), Uniflox (Bayer), Velmonit (Esteve). Light yellow crystalline powder. mp 318-320.

THERAP CAT: Antibacterial.

3630. Enrofloxacin.

I-Cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid; CFPQ; Bay Vp 2674; Baytril (Mobay). C₁₉H₂₂FN₃O₃; mol wt 359.40. C 63.50%, H 6.17%, F 5.29%, N 11.69%, O 13.36%. Fluorinated quinolone antibacterial. Prepn: K. Grohe et al., Ger. pat. 3,142,854; eidem, U.S. pat. 4,670,444 (1983, 1987 both to Bayer AG); K. Grohe, H. Heitzer, Ann. 1987, 29. Use as plant fungicide: K. Grohe et al., U.S. pat. 4,563,459 (1986 to Bayer AG). Pharmacokinetics in calves: J. N. Davidson et al., Proc. West. Pharmacol. Soc. 29, 129 (1986); in chickens: G. M. Conzelmaner al., ibid. 30, 393 (1987). Spectrofluorometric determn of residues in poultry tissues: T. B. Waggoner, M. C. Bowman, J. Assoc. Offic. Anal. Chem. 70, 813 (1987). Toxicology and physical properties: P. Altreuther, Vet. Med. Rev. 2, 87 (1987). Series of articles on pharmacology, in vitro antibacterial activity and field trials: ibid. 90-140.

Pale yellow crystals, mp 219-221°. Slightly sol in water at pH 7. LD₅₀ in male, female mice (mg/kg): >5000, 4336 orally; -200, -200 i.v.; in male rats, male rabbits (mg/kg): >5000, 500-800 orally (Altreuther).

THERAP CAT (VET): Antibacterial.

6805. Normethandrone.

(17β)-17-Hydroxy-17-methylestr-4-en-3-one; 17α-methyl-19-nortestosterone; methylestrenolone; normethandrolone; normethandrone; methylnortestosterone; Orgasteron (Organon); Metalutin (Parke, Davis); Methalutin, C₁₉H₂₈O₂; mol wt 288.43. C 79.12%, H 9.78%, O 11.09%. Prepn: Djerassi *et al.*, U.S. pats. 2,744,122 and 2,774,777 (1956 to Syntex); J. Am. Chem. Soc. 76, 4092 (1956); De Ruggieri, U.S. pats. 2,849,461 (1958).

Crystals from ether-hexane, mp 156-158 (Kofler). $[\alpha]_D$ +33°. uv max (ethanol): 240 nm ($\log_8 4.23$).

THERAP CAT: Androgen.

7892. Prasterone.

(3p)-3-Hydroxyandrost-5-en-17-one; dehydroepiandrosterone; dehydroisoandrosterone; trans-dehydroandrosterone; Δ5-androster-3β-ol-17-one; DHEA. C₁₉H₂₈O₂; mol wt 288.43. C 79.12%, H 9.78%, O 11.09%. Major secretory steroidal product of the adrenal gland; secretion progressively declines with aging. Occurs in serum unconjugated or as the sulfate. May have estrogen-or androgen-like effects depending on the hormonal milieu. Isoln from male urine: Butenandt, TschemingZ. Physiol. Chem. 229, 167 (1934); Butenandt, Dannenbaum, Ibid. 192. Prepn from cholesterol: Butenandtet al., ibid. 237, 57 (1935); Ruzicka, Wettstein, Helv. Chim. Acta 18, 986 (1935); Wallis, Fernholz, J. Am. Chem. Soc. 57, 1379, 1504 (1935); Schoelleret al., Naturwiss. 23, 337 (1935); from sitosterol: Oppenauer, Nature 135, 1039 (1935). High yield prepn: H. Hosodaet al., J. Org. Chem. 38, 4209 (1973). Metabolism study: P. Knapsteinet al. Acta Endocrinol. 58, 261 (1968). Toxicity study of the sulfate: M. Yahara et al., J. Toxicol. Sci. 2, 161 (1977). Clinical evaluation in hormone replacement therapy: A. J. Moraleset al., J. Clin. Endocrinol. Metab. 78, 1360 (1994); in systemic lupus erythematosus: R. F. van Vollenhovenet al., Arthritis Rheum. 38, 1826 (1995). Review of physiological importance: P. Ebeling, V. A. Koivisto, Lancet 343, 1479-1481 (1994). Symposium on role in aging: Ann. N. Y. Acad. Sci. 774, 1-350 (1995).

Dimorphous, needles, mp 140-141°; leaflets, mp 152-153°. $[a]_{D}^{18}+10.9^{\circ}$ (c = 0.4 in alc). Pptd by digitonin. Sol in benzene, alcohol, ether; sparingly sol in chloroform, petr ether.

Sulfate, C19H28O5S, DHEAS.

Sodium sulfate, C₁₉H₂₇NaO₅S, sodium dehydroepiandrosterone sulfate, Astenile (Recordati), Mylis (Kanebo). White cryst powder, mp 154 (dec). Sol in methanol, slightly sol in water, abs ethanol. Practically insol in acetone, chloroform, benzene.

THERAP CAT: In treatment of menopausal syndrome.

5535. Liothyronine.

O-(4-Hydroxy-3-iodophenyl)-3,5-diiodo-1-tyrosine; 1-3-[4-(4-hydroxy-3-iodophenoxyl)-3,5-diiodophenyl]alanine; 4-(3-iodo-4-hydroxyphenoxyl)-3,5-diiodophenyl]alanine; 3,5,3'-triiodothyronine; T-3.C₁₅H₁₂I₃NO₄; mol wt 650.98. C 27.68%, H 1.86%, 1 58.48%, N 2.15%, O 9.83%. Amino acid found in human plasma and thyroid gland, similar to thyroxine.4. Gross, Pitt-Rivers, Lancet 1952, I, 439. Formation from diiodothyronine: Rocheet al., Biochem. Biophys. Acta 11, 215 (1953). Isoln from thyroid gland and synthesis: Gross, Pitt-Rivers, Biochem. J. 53, 645 (1953). Rocheet al., Bull. Soc. Chim. France 4, 462 (1957); Plati, Wenner, U.S. pat. 2,784,222 (1957 to Hoffmann-La Roche): Pitt-Rivers, Gross, U.S. pat. 2,823,164 (1958 to Nat. Res. Dev. Corp.); Razdan, Wetherill, U.S. pat. 2,993,928 (1961 to Glaxo). Elevated levels of T-3 in victims of sudden infant death syndrome: G. Kocsard-Varo, Med. J. Aust. 2, 789 (1973); M. A. Chacon, J. T. Tildon, J. Pediatr. 99, 758 (1981). Monograph: Pitt-Rivers, R. Tata, The Thyroid Hormones (Pergamon Press, 1959).

Crystals, dec 236-237. [a]695+21.50 (c = 4.75 in a mixture of 1 part N HCI + 2 parts ethanol). Possesses 5 times the activity of L-thyroxine (goiter prevention test in rats). Insol in water, alc, propylene glycol. Sol in dil alkalies with the formation of a brownish, water-soluble, sodium salt.

Sodium salt, C₁₅H₁₁I₃NNaO₄, liothyronine sodium, sodium _L-triiodothyronine, Cyomel (SKB), Cytobin (Norden), Cytomine (Darby), Cytomel (SKB), Cynomel (SK & F), Tertroxin (Glaxo), Triothyrone.

Hydrochloride, $C_{15}H_{12}I_3NO_4$.HCl, *Thybon (Hoechst)*. Long birefringent needles, decomp 202-203. [α] $_D^{29.5}$ +21.5 $^{\circ}$ (c = 4.75 in a mixture of 1 vol N HCl and 2 vols ethanol).

DL-Triiodothyronine hydrochloride, Trionine.

THERAP CAT: Thyroid hormone. THERAP CAT (VET): Thyroid hormone.

2844. Cyproterone.

CI
(1g,2g)-6-Chloro-1,2-dihydro-17-hydroxy-3'H-cyclopropal1,2|pregna-1,4,6-triene-3,20-dione; 6-chloro-17-hydroxy-1₀,2_α-methyleneprogesterone; 6-chloro-1,2_α-methyleneprogesterone; 6-chloro-1,2_α-methylene-4,6-pregnadien-17_α-01-3,20-dione; SH-881; SH-80881. C₂₂H₂₇ClO₃: mol wt 374.91. C 70.48%, H 7.26%, Cl 9.46%, O 12.80%. Prepn of free alcohol: Wiechert, Neumann, Ger. pat. 1,189,991, C.A. 63, 1842e (1965); Wiechert, U.S. pat. 3,234,093 (1965, 1966 both to Schering AG). Biodynamics in man: Gerhardset al., Arzneimittel-Forsch. 23, 1550 (1973). The free alcohol is an anti-androgen; the acetate is both an anti-androgen and a progestogen. Effect on hormone secretion and on spermatogenesis in man: L. Moltz et al., Contraception 21, 393 (1980). Review of pharmacology and clinical studies (acetate) on acne and hirsutism in women: J. Hammerstein et al., J. Steroid Biochem. 19, 591 (1983).

Crystals from ethyl acetate, mp 237.5-240.

Acetate, C₂₄H₂₉ClO₄, CPA, SH-714, Androcur (Schering AG), Cyprostat (Schering AG). Crystals from diisopropyl ether, mp 200-201≈, uv max (methanol): 281 nm (∈ 17280).

Mixture of acetate with ethinyl estradiol, Diane 35 (Schering AG), Dianette (Schering AG).

THERAP CAT: The acetate as antiandrogen; combination with estrogen in treatment of acne.

9566. Tibolone.

CH₃
(7₀,17₀)-17-Hydroxy-7-methyl-19-norpregn-5(10)-en-20-yn-3-one; 7₀-methyl-17₀-ethynyl-17_β-hydroxy-19-norandrost-5(10)-en-3-one; 7₀-methyl-17₀-ethynyl-17_β-hydroxyestr-5(10)-en-3-one; Org-OD-14; Livial (Organon). C₂₁H₂₈O₂; mol wt 312.45. C 80.73%, H 9.03%, O 10.24%. Synthetic steroid with weak estrogenic, androgenic and progestogenic activity. Prepn: Neth. pat. Appl. 6,406,797; H. P. de Jongh, N. P. van Vliet, U.S. pat. 3,340,279 (1965, 1967 both to Organon). Improved process: M. S. de Winter, E. A. Harryvan, U.S. pat. 3,475,465 (1969 to Organon). Endocrinological profile: J. de Visseret al., Arzneimittel-Forsch, 34, 1010 (1984). Series of articles on pharmacology and clinical efficacy in post-menopausal women: Maturitas Suppl 1, 1-72 (1987). Clinical effect in osteoporosis: P. Geusenset al., ibid. 13, 155 (1991). Crystals, mp 165-169.

THERAP CAT: In treatment of menopausal syndrome.

3504. Dromostanolone.

(2_G,5_G,17g)-17-Hydroxy-2-methyl-androstan-3-one; 17β-hydroxy-2_G-methyl-5_G-androstan-3-one; 2_G-methyl-androstan-17β-ol-3-one; 2_G-methyl-dihydrotestosterone; drostanolone; C₂₀H₃₂O₂; mol wt 304.47. C 78.90%, H 10.59%, O 10.51%. Synthetic estrogen antagonist. Prepn: H. J. Ringold*et al., J. Am. Chem. Soc.* 81, 427 (1959); H. J. Ringold, G. Rosenkranz, U.S. pat. 3,118, 915 (1964 to Syntex). GC-MS determn of urinary metabolites: D. DeBoer*et al., J. Steroid Biochem. Molec. Biol.* 42, 411 (1992). Crystals from acetone/hexane, mp 149-153°. [α]_D +32° (ethanol).

Note: This is a controlled substance (anabolic steroid) in the U.S. Code of Federal Regulations, Title 21 Part 1308.13, as defined in Part 1308.02 (1995).

Propionate, C₂₃H₃₆O₃, NSC-12198, Drolban (Lilly), Emdisterone, Masterid (Grunenthal), Masteril (Syntex), Masterone (Syntex), Permastril (Cassenne). Crystals from hexane, mp 126-130. [α]_D +24°.

THERAP CAT: Antineoplastic.

Annex I to Doc. NS0022E1 (SSC/16/Jan. 01)

9544. Thymopentin.

Arg-Lys-Asp-Val-Tyr

N-(N-(N-(N-1-arginyl-1-lysyl)-1-0;-aspartyl)-1-tyrosine; thymopoietin pentapeptide; TP-5; ORF-15244; Immunox (Citag); Sintomodulina (Italfarmaco); Timunox (Citag), C₁₀H₂₀N₂O₀; mol wt 679.77. C 53.01%, H 7.27%, N 18.54%, O 21.18%. Thymic hormone analog corresponding to residues 32-36 of thymopoietinq.v., which exhibits the full biological activity of the natural hormone. Synthesis: G. Goldstein.et al., Science 204, 1309 (1979); eidem, U.S. pat. 4,190,646 (1980 to Sloan-Kettering). Bioavailability: T. Audhya, G. Goldstein.Int. J. Pept. Protein Res. 22, 187 (1983). Pharmacology: K. Bollaet al., Int. J. Clin. Pharmacol. Res. 4, 431 (1984). Comparison of biological activity with thymopoietin and splenin: T. Audhyaet al., Proc. Nat. Acad. Sci. USA 81, 2847 (1984). Clinical study in treatment of primary immunodeficiencies: F. Aituiet al., Lancet 1, 551 (1983); in AIDS: N. Clumeck et al., Int. J. Clin. Pharmacol. Res. 4, 459 (1984); in rheumatoid arthritis: M. G. Malaiseet al., Lancet 1, 832 (1985). Review: E. A. Boyse, Surv. Immunol. Res. 4, 6-10 (1985).

THERAP CAT: Immunoregulator.

9548. Thymostimulin.

TP-1. Biological response modifier; partially purified extract of calf thymus composed of a mixture of bovine thymic peptides. Extraction and purification: G. Bergesi, R. Falchetti, Folia Allergol. Immunol. Clin. 24, 204 (1977). Pharmacology and biological properties: R. Falchetti et al., Drugs Exp. Clin. Res. 3, 39 (1977). Clinical studies in combination with antimicrobial therapy: P. Periti et al., J. Chemother. 5, 37 (1993); as an adjunct to cancer chemotherapy: M. Federicoet al., Am J. Clin Oncol. 18, 8 (1995); with zidovudine, q.v., vs HIV infection: G. Barbaro et al. Curr. Ther. Res. 56, 369 (1995). Review of pharmacology and therapeutic use: K. L. Dechant, H. M. Bryson, Clin. Immunother. 1, 378-398 (1994).

THERAP CAT: Immunomodulator.

Hormone	Classification as appeared in the HSCDB	Proposed classification (1996 version)	Proposed classification (2002 version)	Remarks
Normethandrone	2937.92	2937.99	2937.29	Indicated as an androgen. See Annex 1.
Prasterone	2937.99	[2937.92] [2937.99]	[2937.23] [2937.29]	May have estrogen- or androgen-like effect depending on the hormonal milieu.
Liothyronine	2937.99	2937.99	[2937.40] [2937.90]	An amino acid. The subheading text of 2002 version refers to amino-acid derivatives.
Liothyronine sodium	2937.99	2937.99	[2937.40] [2937.90]	A salt of an amino acid. Subheading text of 2002 version refers to amino-acid derivatives.
Cypreterone	2937.99	[2937.92] [2937.99]	[2937.23] [2937.29]	The acetate is both an anti-androgen and a progestogen.
Tibolone	2937.99	[2937.92] [2937.99] [2914.40]	[2937.23] [2937.29] [2914.40]	Synthetic steroid with weak estrogenic, androgenic and progestogenic activity.
Dromostanolone	2937.99	[2937.92] [2937.99] [2914.40]	[2937.23] [2937.29] [2914.40]	Synthetic estrogen antagonist.
Thymopoietin pentapeptide (Thymopentin)	2937.99	[2937.99] [2924.10]	2937.19	Thymic hormone analogue.
Thymostimuline (INN)	2937.99	[2937.99] [3504.00]	[2937.19] [3504.00]	Indicated as an Immunomodulator and as a mixture of bovine thymic peptides.