



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 7/16	A1	(11) International Publication Number: WO 91/13608 (43) International Publication Date: 19 September 1991 (19.09.91)
(21) International Application Number: PCT/NO91/00032 (22) International Filing Date: 4 March 1991 (04.03.91) (30) Priority data: 901031 5 March 1990 (05.03.90) NO (71)(72) Applicants and Inventors: RÖLLA, Gunnar [NO/NO]; Kragstveit 13, N-0391 Oslo 3 (NO). ELLINGSEN, Jan, Eirik [NO/NO]; Skogbrynet 17b, N-0283 Oslo 2 (NO). (74) Agent: GØRBITZ, Johan, H.; Bryn & Aarflot A/S, P.O. Box 449, Sentrum, N-0104 Oslo 1 (NO). (81) Designated States: AT, AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH, CH (European patent), CM (OAPI patent), DE, DE (European patent), DK, DK (European patent), ES, ES (European patent), FI, FR (European patent), GA (OAPI patent), GB, GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL, NL (European patent), NO, PL, RO, SD, SE, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.		Published <i>With international search report.</i>
(54) Title: DENTIFRICE INHIBITING DENTAL PLAQUE (57) Abstract Dentifrice comprising a liquid silicone oil and a fat-soluble antibacterial agent dissolved therein either directly or indirectly after dissolution of the antibacterial agent in an organic solvent. The dentifrice is useful for protection of teeth against plaque formation due to a slow release of the antibacterial agent into the saliva.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	ES	Spain	MG	Madagascar
AU	Australia	FI	Finland	ML	Mali
BB	Barbados	FR	France	MN	Mongolia
BE	Belgium	GA	Gabon	MR	Mauritania
BF	Burkina Faso	GB	United Kingdom	MW	Malawi
BG	Bulgaria	GN	Guinea	NL	Netherlands
BJ	Benin	GR	Greece	NO	Norway
BR	Brazil	HU	Hungary	PL	Poland
CA	Canada	IT	Italy	RO	Romania
CF	Central African Republic	JP	Japan	SD	Sudan
CG	Congo	KP	Democratic People's Republic of Korea	SE	Sweden
CH	Switzerland	KR	Republic of Korea	SN	Senegal
CI	Côte d'Ivoire	LI	Liechtenstein	SU	Soviet Union
CM	Cameroon	LK	Sri Lanka	TD	Chad
CS	Czechoslovakia	LU	Luxembourg	TG	Togo
DE	Germany	MC	Monaco	US	United States of America
DK	Denmark				

"DENTIFRICE INHIBITING DENTAL PLAQUE".

The present invention relates to dentifrices having an improved effect against the growth of plaque on teeth. The dentifrices may be in the form of powders, tooth pastes, chewing gums etc., but tooth pastes are normally preferred. An important constituent of the dentifrices of the invention is organopolysiloxanes.

From British Patent No. 686.429 it is known to incorporate organopolysiloxanes in dentifrices to prevent the adhesion of or facilitate the removal of tars, stains, tartar and the like from teeth.

British Patent No. 789.851 discloses oral hygiene compositions containing an organopolysiloxane and a higher aliphatic acyl amide of an amino carboxylic acid compound which is preferably a water-soluble carboxylate salt. British Patent No. 1.194.885 describes the addition of a quaternised tertiary cyclic amine in which a C₈₋₂₂ aliphatic radical is attached to the quaternary nitrogen atom, to a dimethyl polysiloxane to improve the adherence of the silicone film to the teeth.

A similar solution is suggested in US patent 4.161.518 where quaternary ammonium groups are incorporated in an organosiloxane molecule.

EP patent application, publication No. 0376363 discloses the use of aminoalkyl silicones and sarcosinate surfactants to prevent staining of teeth and in preventing caries, particularly in conjunction with antimicrobials which have a tendency to stain teeth.

Bacterial growth on teeth is a well known problem. The two major dental diseases, caries and periodontitis, are initiated and develop only in the presence of dental plaque. Dental plaque consists of dense aggregates of bacteria which attach to the tooth enamel, mainly in the interproximal area, or along the gingival margin. The enamel disintegrates when sucrose or other fermentable carbohydrates are consumed; the plaque bacteria produce organic acids (mainly lactate) in this situation which cause dissolution of the hydroxyapatite of which enamel mainly consists. Dental plaque may also produce

enzymes, toxins or antigens which may cause inflammation of the gingival tissue. A chronic inflammation under certain conditions lead to loss of the alveolar bone which supports the teeth, and subsequent toothloss.

Inhibition of adsorption of bacteria to dental enamel will thus have the potential to prevent both dental caries and periodontal disease. The mechanism by which the bacteria bind to enamel is not well understood. The inhibition of plaque formation obtained up to now has been caused by antibacterial agents with a longterm effect in the mouth. These substances interfere with bacterial growth rather than with the adsorption of bacteria to enamel. Such substances have untoward side effects like staining of teeth and tongue, and unpleasant taste, and they cause a general decrease of the number of bacteria in the oral cavity. Substances which solely reduce the growth of plaque on the teeth by interference with their binding mechanisms have not yet been found.

As it will appear from the above it is previously known that silicone oil binds to the enamel surfaces of teeth, and provides a hydrophobic surface thereon by forming a thin layer of oil which covers the surface for several hours after a single application. We have now surprisingly found that this layer of silicone oil can serve as a reservoir of certain antibacterial agents which are soluble in silicone oil directly, or indirectly, after an initial step where the antibacterial agent is dissolved in another organic solvent, and the resulting solution is then dissolved in silicone oil.

Thus, the invention provides a dentifrice which comprises silicone oil and a fat-soluble antibacterial agent dissolved therein, either directly or after dissolution of the antibacterial agent in an organic solvent.

Suitable silicone oils are e.g. the fluid organopolysiloxanes described in the above mentioned British Patent No. 789.851. A preferred class comprises the diphenyl or di(C₁₋₄)alkyl polysiloxanes, in particular liquid dimethylpolysiloxane.

Suitable antibacterial agents are antiseptic phenols, in particular triclosan (also called irgasan) (5-chloro-2-

(2,4-dichlorophenoxy)phenol), which may be used in amounts varying from 0.01%, based on the silicone oil, to the maximum amount soluble in the silicone oil.

If the antibacterial agent is insoluble in the silicone oil, it may first be dissolved in a suitable organic solvent such as ethanol, and the resulting solution is then dissolved in the silicone oil.

It is important that the antibacterial agent is non-toxic and is soluble in the silicone oil used and of very limited solubility in water. Triclosan is such an agent and is also known to decrease plaque formation (but not dissolved in polysiloxanes), see e.g. C.A. vol 81(1974) no 20897y. Similarly it is important that the polysiloxane is non-toxic, such as Dow Corning® 200 which has been used in the examples.

When the dentifrice is applied to the teeth, the silicone oil forms a hydrophobic layer which serves as a reservoir for the antibacterial agent. As known in the art, the silicone oil in itself will provide some protection due to its hydrophobic character. However we have now found that the protection will be much better when the antibacterial agent is dissolved therein and subsequently slowly released into the environment. The treatment furthermore inhibits calculus formation, probably due to the smooth silicone oil-covered surface which prevents the fixation of calculus to the teeth, and triclosan which inhibits plaque formation. Calculus constitutes in fact calcified plaque.

Experimental

Six students painted their teeth 2 x daily with Q-tips moistened with either water, silicone oil (dimethylpolysiloxane) alone, 0.3 % triclosan in water or silicone oil + 0.3% triclosan. Their teeth were pumiced at the start of the study and plaque was scored on each surface of all the teeth after 4 days. No other form of oral hygiene was allowed. The test persons chewed six pieces of chewing gum containing 75% sucrose per day to increase plaque formation. The results are shown in Fig. 1-4. Score 0 is given to surfaces with no plaque. Score 1 is given to surfaces where visible plaque is seen on the probe

after running the point of the probe along the gingival margin of each tooth. Score 2 indicates visible plaque, and score 3 plaque up to 2 mm above the gingival margin.

Fig. 1 illustrates the score for each of the six test persons after painting their teeth with water only.

Fig. 2 illustrates the score for the same persons after treatment with dimethylpolysiloxane.

Fig. 3 illustrates the score for the same person (-1) after treatment with 0.3 % of triclosan suspended in water.

Fig. 4 illustrates the score after treatment with dimethylpolysiloxane containing 0.3% triclosan.

The pairs of letters of the right hand side of the graph represent the initials of the test persons, and the subsequent number is the experiment involved. The abscissa indicates the score distribution, and the ordinate represents the number of surfaces having the indicated score for each test person. While triclosan alone gives no improvement, it will be seen that the silicone oil results in an increased number of scores 0 and 1 compared with the control. Silicone oil + 0.3% triclosan gives a marked improvement in plaque scores compared with the control (Fig.1) and the silicone oil treated teeth (Fig.2).

The teeth of the group treated with silicone oil + triclosan were shiny clean. Small amounts of plaque occasionally present was easily removed with a compressed air syringe.

Five individuals who were selected on the basis that they produced high amounts of calculus in their mouths were selected for the study. They used a toothpaste which contained 0,3 % triclosan and silicone oil, and calculus was again scored after one month. The amounts of calculus formed were markedly reduced and the small amount present was easily removed since the calculus was only loosely attached to the teeth.

In an in vitro experiment glass test tubes were treated with either water, silicone oil or silicone oil + 0.3% triclosan. 0.5 ml of a 1 day old culture of Strep. mutans and 5 ml of glucose broth medium + 5% sucrose was then added to the tubes. Abundant growth and bacteria sticking to the glass wall was seen in the water treated tubes. The tubes treated with silicone oil alone showed reduced growth, only a few bacteria

adhering to the glass surface. However, the test tube which had been pretreated with silicone oil containing 0.5% triclosan showed only negligible growth and no bacteria on the glass surface.

These experiments considered together indicate that the teeth and the glasstubes acquire a hydrophobic surface layer with antibacterial activity which inhibit adsorption of bacteria when treated with silicone oil and triclosan. This is a unique effect which is not obtained by any previously known clinical procedure in preventive dentistry. It is caused by the fact that the polysiloxane acts as a reservoir for the antibacterial agent (triclosan) dissolved therein. Small amounts of the antibacterial agent are slowly released from the polysiloxane film adhering to the teeth and will therefore effectively inhibit the formation of plaque due to the limited solubility in water.

C l a i m s

1. Dentifrice comprising a silicone oil,
c h a r a c t e r i z e d i n that it comprises a liquid
silicone oil and a fat-soluble antibacterial agent dissolved
therein either directly or indirectly after dissolution of the
antibacterial agent in an organic solvent.
2. Dentifrice according to claim 1,
c h a r a c t e r i z e d i n that the liquid silicone oil is
a diphenyl or di(C₁₋₄)alkyl-polysiloxane.
3. Dentifrice according to any of claims 1 and 2,
c h a r a c t e r i z e d i n that the antibacterial agent is
selected from antiseptic phenols.
4. Dentifrice according to any of claims 1-3,
c h a r a c t e r i z e d i n that the silicone oil is a
di-methylpolysiloxane.
5. Dentifrice according to any of claims 1-4,
c h a r a c t e r i z e d i n that the antibacterial agent
is triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol).

1/2

Fig. 1

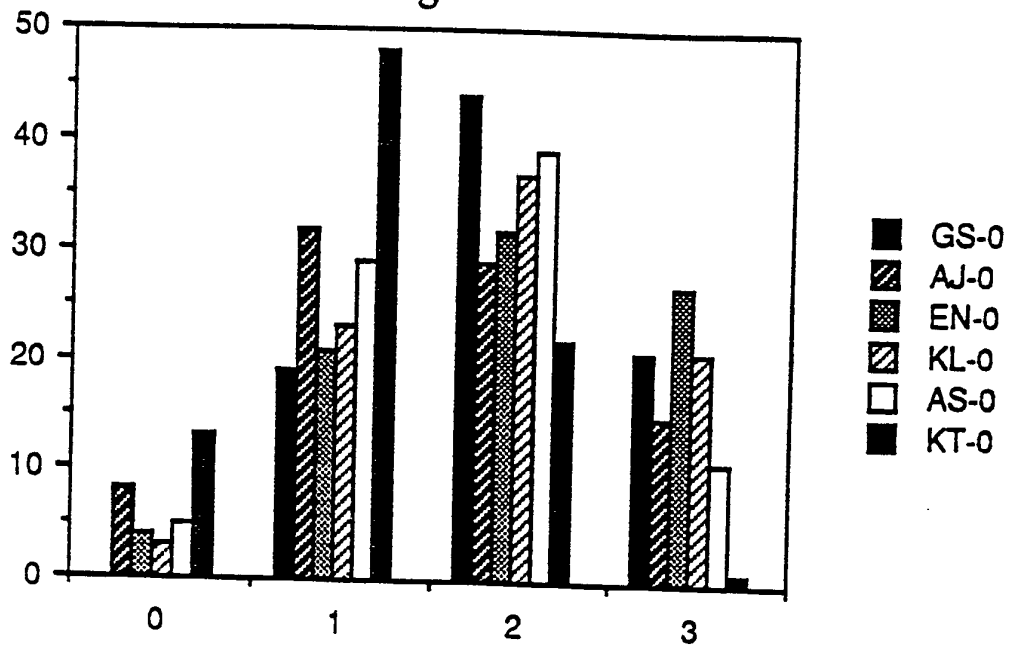


Fig. 2

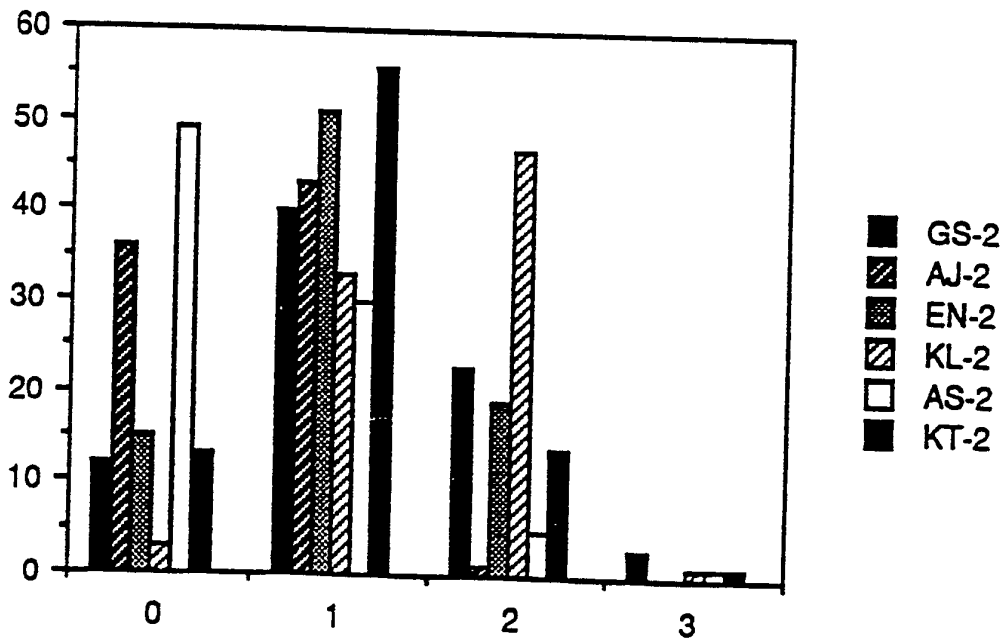


Fig. 3

2/2

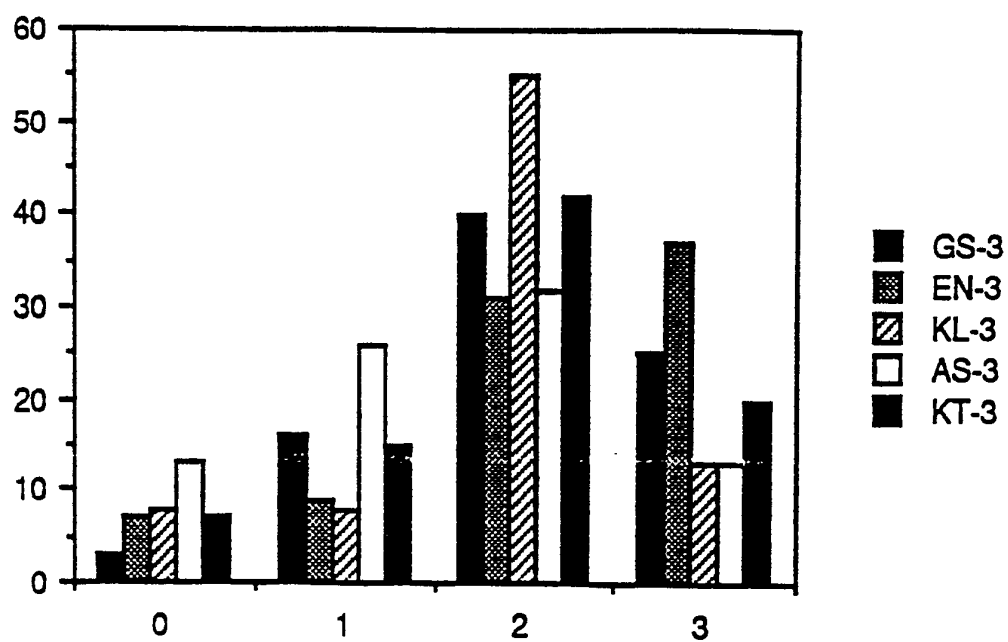
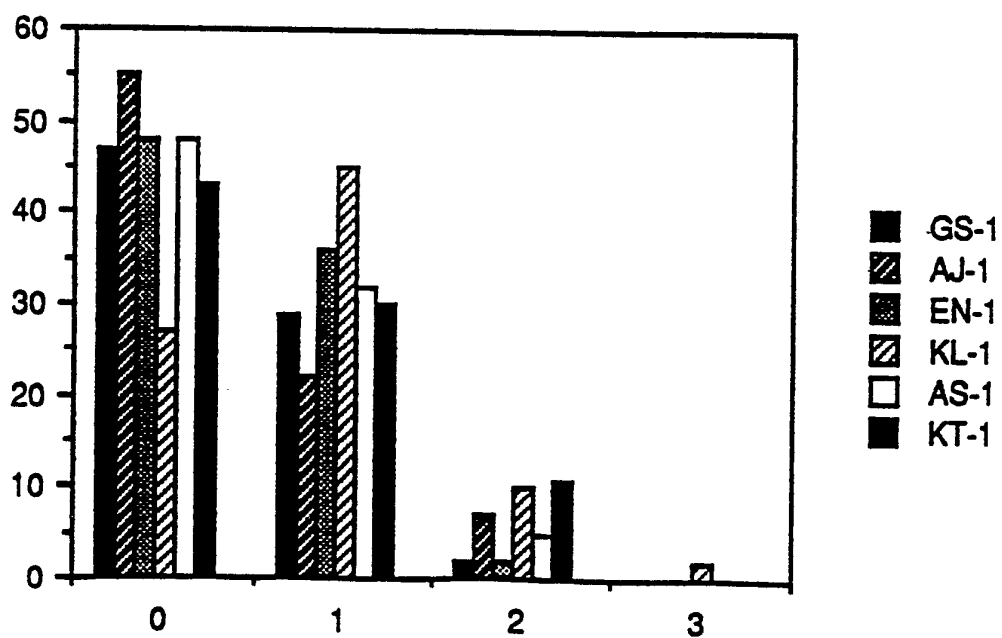
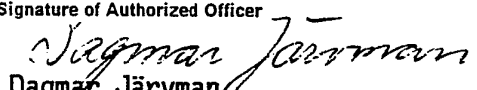


Fig. 4



INTERNATIONAL SEARCH REPORT

International Application No PCT/NO 91/00032

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC5: A 61 K 7/16		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
IPC5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched ⁸		
SE,DK,FI,NO classes as above		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category *	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X	GB, A, 686429 (DOW CORNING LIMITED) 21 January 1953, see the claims 1-3 and 5; description, page 2, lines 23-30 --	1,4
P,X	EP, A2, 0371551 (UNILEVER NV) 6 June 1990, see the description, page 7, lines 10-19 --	1-5
P,X	EP, A2, 0373688 (UNILEVER NV) 20 June 1990, see the description, page 4, lines 15-27 --	1-5
P,X	EP, A1, 0376363 (UNILEVER NV) 4 July 1990, see the description, page 4, lines 28-38 --	1-5
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>* Special categories of cited documents:¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
10th June 1991	1991 -06- 1 2	
International Searching Authority	Signature of Authorized Officer	
SWEDISH PATENT OFFICE	 Dagmar Järvmä	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
A	GB, A, 789851 (COLGATE-PALMOLIVE COMPANY) 29 January 1958, see the whole document --	1-5
A	US, A, 4022880 (VINSON ET AL) 10 May 1977, see the description, column 2, lines 10-15, 41-44; column 7, lines 11-60 and claim 7 --	1-5
A	EP, A2, 0220890 (BEECHAM GROUP PLC) 6 May 1987, see the whole document --	1-5
A	EP, A2, 0161899 (UNILEVER PLC) 21 November 1985, see the whole document -- -----	1-5

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.PCT/NO 91/00032**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the Swedish Patent Office EDP file on **91-04-30**. The Swedish Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 686429	53-01-21	NONE	
EP-A2- 0371551	90-06-06	JP-A- 2200618	90-08-08
EP-A2- 0373688	90-06-20	JP-A- 2223512	90-09-05
EP-A1- 0376363	90-07-04	JP-A- 2209805	90-08-21
GB-A- 789851	58-01-29	NONE	
US-A- 4022880	77-05-10	NONE	
EP-A2- 0220890	87-05-06	AU-B- 596123 AU-D- 6421986 JP-A- 62126116	90-04-26 87-04-30 87-06-08
EP-A2- 0161899	85-11-21	AU-B- 571330 AU-D- 4204585 CA-A- 1256035 JP-B- 1010489 JP-C- 1527555 JP-A- 60239410	88-04-14 85-11-14 89-06-20 89-02-22 89-10-30 85-11-28