PART 3 – AROMA CHEMICALS from PETROCHEMICAL FEEDSTOCKS

8 INTELLECTUAL PROPERTY ISSUES

8.1 Para Hydroxy Benzaldehyde

In 1998 AECI identified the general status of the cresol oxidation process in terms of existing patented processes as an area that needed further clarification. This was approached from two angles:

- Whether the process infringed upon other processes, and
- Whether the AECI process could be patented

A literature search was undertaken. This resulted in four patents which described processes or steps bearing a resemblance to aspects of the oxidation step of the AECI route, and which could therefore be considered a potential threat. The four patents were: European patents EP 012939 and EP 725052 and Japanese patents JP 6124535 and JP 63301843. These four patents are discussed below.

EP 012939

This patent is by Sumitomo and expired in Europe in 1999 and the US equivalent (US 4,429,163) in 2001. The patent described an oxidation process marginally different to the AECI process. The invention was described as a "process for the production of 4-hydroxybenzaldehyde derivatives by oxidising a p-cresol derivative with oxygen or a free oxygen-containing gas, in the presence of a base and a cobalt compound or metallic cobalt. The patent also makes specific reference to the possibility of selectively oxidising p-cresol in the presence of m-cresol and gives an experimental example of this.

The most significant difference between the Sumitomo patent and the AECI process is that the patent does not mention the use of a mixed oxidation catalyst. Conversions and selectivities to pHB seem to be lower than that was achieved by the AECI process. It was therefore concluded by AECI that although the Sumitomo patent describes a process very similar to the AECI process, the latter's use of a mixed or possibly specifically designed co-precipitated catalyst system, and the better use of selectivities and yields that were obtained by the process, can possibly be seen as process improvements which will allow for the circumvention of patent EP012939.

EP 725052

The patent, which was believed to still be under examination in 1998, was filed by Bayer. The patent was primarily concerned with the downstream processing of the post-oxidation reaction, but does include some reference to an oxidation process similar to the AECI process. There is however no mention of oxidations of mixed cresol streams. The downstream processing procedure described involves adjustment of the post-oxidation mixture to pH 11 using sulphuric acid, followed by filtration of the resulting insoluble salt. The AECI downstream process does not involve removal of an insoluble salt in this fashion. It was therefore concluded that patent EP 725052 is not a threat.

JP 6124535

This patent was only granted in Japan, apparently as JP 9314696 to Kansai Co., and describes an oxidation reaction, which is very similar to the AECI process, including the use of a mixed catalyst system. The ratio of catalysts recommended varies between 0.2:1 and 4:1 on an atomic basis. The conclusion reached by AECI was that the AECI process must be developed to use a higher ratio in order to circumvent the patent. In addition, the patent does not seem to include any reference to the oxidation of a mixed m/p-cresol feed stream similar to that proposed in the AECI process.

JP 63301843

This patent was granted to Sumitomo as JP95064777, and describes a p-cresol oxidation methodology similar to the AECI process, including oxidation of a mixed m/p-cresol stream, but using only cobalt containing catalysts. The main purpose of the patent relates to the downstream processing procedure involved. The sequence is very similar to the AECI downstream processing route. It appeared however that this patent was only granted in Japan.

Advice was obtained by AECI with a patent lawyer from its Patents and Trade Marks Group to review the current patent situation regarding the m/p-cresol oxidation step of the pHB process, especially in terms of potential infringements of the process on other patents. The following is a summary of the comments, conclusions and recommendations made.

Possible patent infringements:

- Patents JP 6124535 and JP 63301843 were only granted in Japan. As this was not seen as a target market for the products, these patents would not affect it. The former patent could be circumvented by a higher ratio use of the mixed catalysts.
- Patent EP 012939 expired in 1999 in Europe and the US equivalent in 2001. This patent is therefore not a threat.
- Patent EP 725052 is sufficiently different to the AECI process to not pose a threat.

Advice on the potential patentability of the AECI process was also given. The factors which may enable the process to be patented are the fact that the process at the time was based on a 50:50 m/p-cresol feed stream, that it uses a mixed catalyst[27] and that the selectivity and conversions are higher than those described in the other patents (i.e. process improvements).

[27] The identity of the components of the catalyst stream cannot be divulged due to reasons of protecting the process's competitive advantage.

The CSIR has chosen not to patent the process, choosing instead to trademark the two unique reaction vessels used in the process. These reaction vessels are the oxidation reactor, SAFOX ™, and the vessel that extracts the m-cresol from the reaction, VIPEX ™.

8.2 p-Anisaldehyde

The methylation of pHB using methyl chloride or dimethyl sulphate has been operated by a number of companies, most importantly Bayer and the majority of the Chinese producers. Koffolk also used to manufacture pAA from pHB using dimethyl sulphate and caustic soda but changed processes in the early 1980's when Dow ceased producing pHB by the Reimer-Tiemann process, leading to a 2 – 3 fold increase in the price of pHB.

The CSIR technology is a step-change improvement on a similar technology used by Bayer in its pAA production plant until 1997. The Bayer process consisted of the oxidation of pure p-cresol to pHB using a proprietary catalyst, followed by the methylation of pHB to pAA using methyl chloride. The CSIR process is differentiated in that mixed cresols can be used as the feedstock in the oxidation step, as well as pure p-cresol. The technology is based on the selective oxidation of p-cresol in a p- and m-cresol mixture (called MP99) to form pHB, leaving the m-cresol unreacted.

The CSIR performed a patent search for the production of pAA from pHB in May 2004.[28] This search indicates that the patents are older than 1978/1981 and have therefore expired.

The route to pAA from pHB by methylation with dimethyl sulphate or iodomethane in an alkaline environment is published in a paper:

- Ploadus N.N, Translated by Liu Shuwen.; Perfumery Chemistry. Beijing, Qinggongy Chubanshe, 1984, 224.

8.3 Vanillin/Ethyl Vanillin

The CSIR performed a patent search in May 2004.[29] Most patents for the production of vanillin and ethyl vanillin are in China only, and do not describe the CSIR process exactly. The solvents used are different e.g. dimethyl formamide and not as environmentally friendly as the CSIR process solvent. There does not appear to be any patent cover in South Africa.

8.4 Octylmethoxycinnamate

Most of the routes to OMC involve the synthesis of p-methoxycinnamic acid followed by esterification. The methods, which have been reported in open literature to synthesise

[28] Documents: F. Marais CSIR Bio/Chemtek
[29] Documents: F. Marais CSIR Bio/Chemtek

derivatives of cinnamic acid, are discussed in a literature review conducted by AECI in 1998.[30]

Patent protection exists for a number of processes:

- US 4609756, 1985, Bayer, Process for the Preparation of Optionally Substituted Cinnamic Acid in the Presence of a Catalyst, and
- US 5527974, 1996, ISP Van Dyke, Process for Preparation of Cinnamate Sunscreen Agents.
- US 5334750, 1993, Bayer, Process for the preparation of cinnamic acid derivatives

In 1998, in the early stages of the technology development for pHB and pAA, it was felt that a conflict would exist if both pAA and OMC were produced, as AECI would be in direct competition with its customers. It was subsequently decided that AECI would enter into the pAA market; OMC technology development was therefore suspended. The CSIR has investigated a number of different synthetic routes to the manufacture of OMC, including non-pAA based technologies, however, the CSIR does not have any OMC technology.

The commercial routes to the production of OMC therefore appear still to be covered by patent.

8.5 Menthol

Thymol serves as the starting material for the production of menthol *via* m-cresol. Thymol is manufactured by isopropylating m-cresol with propylene or another isopropylating agent.[31] Hydrogenation of thymol produces a mixture of menthol stereoisomers directly. The menthol isomers are equilibrated to increase the (±) menthol content.[32, 33, 34] The equilibrium mixture obtained contains approximately 62 wt % (±) menthol, 23 % wt neomenthol, 12 wt % (±) isomenthol and 3 wt % (±) neoisomenthol. The (±) menthol isomers can be separated by high efficiency distillation and the remaining isomers recycled to equilibration. The required (-) menthol can be produced by resolution of the (±) menthol isomers. Symrise (ex Haarmann and Reimer) patented a process whereby a supersaturated solution of a benzoic derivative of (±) menthol is seeded with the (-) form of the derivative to induce selective crystallisation.[35] See Appendix 5 for the Flowsheet.

[30] A literature review on the synthesis of cinnamic acid and derivatives: SJ Heggie, 1998
[31] Bull. Chem. Soc., Jpn. 47,2360 (1974)
[32] Chem. Ind. (London), 236 (1964)
[33] Agric. Biol. Chem. 29 (9), 824 (1965)
[34] US Patent 2,827,499 (Mar 19 1958) to the Glidden Corporation
[35] US Patent 3,943,181 (Mar 9 1976) to Haarmann and Reimer

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The competitive advantage of the CSIR process over the Symrise commercialised process is the novel biocatalysis step in which menthol is generated as a single isomer.[36] The menthol mixture resulting from the hydrogenation of thymol is submitted to enzymatic acylation, whereby the desired acylated menthol is generated with an excess greater than 95%. Acylation of the other isomers is insignificant. The process is completed by separating (+)-menthyl acetate from the 7 other menthol isomers through distillation. This distillation is significantly less demanding than the distillation separating (±)-menthol from the other diastereomers in the Symrise process. Hydrolysis generates (+)-menthol and finally, crystallisation provides (+)-menthol of the required purity. The seven non-commercially attractive isomers are submitted to an isomerisation/racemisation, regenerating the original mixture of isomers containing 56% (±)-menthol, which can be re-introduced to the resolution reaction with the overall result (over multiple cycles) being substantially full conversion of thymol to (+)-menthol

The CSIR has patented its menthol process in two patents WO 02/04384 A2 (January 2002) and WO 02/36795 (May 2002). Furthermore, concept patents have been applied for in the following countries: Australia, Brazil, China, Czechoslovakia, Europe, Indonesia, India, Japan Mexico, Russian Federation, Singapore, Slovakia, South African and the United States. Process patents have been applied for in China, Germany, India, Japan, South Africa and the United States. For a description of the CSIR process technology for menthol see Appendix 6.

The other company producing synthetic menthol, Takasago, uses a completely different process based on beta-pinene, which is converted to myrcene, and then further converted to d-citronellal and subsequently to menthol. As their feedstock is already optically active, there is no need to resolve a racemic mixture, as is the case in the Symrise process.

8.6 Raspberry Ketone

A comprehensive literature and patent search was conducted by AECI in 1998.[37] It was concluded that the AECI route is distinguishable in part from commercial routes in literature through the isolation of the intermediate in sodium salt form, followed by hydrogenation of this sodium salt in water, as distinct from hydrogenation of the phenolic form of the compound.

[36] CSIR Bio/Chemtek website
[37] "Synthesis of Raspberry Ketone": M Portwig, CJ Parkinson, September 1998

