a) Biologische Methode: s. unter 3.2 2.3., S. 40.

b) Blasenmethode: Die Filterkerze ist in Ordnung (bakteriendicht), wenn in angefeuchtetem Zustand bei einem Luftdruck von 0,5 atm keine Luftblasen auftreten (HOCK, H. Chem. Fabrik 3 [1930], 249).

33. Die Entfernung pyrogener Stoffe durch Filtration

Pyrogene sind in der Hauptsache mikrobielle Zellwandbestandteile, die bis zu etwa 90% an die Zelle gebunden sind. Sie sind nur im Tierversuch nachweisbar (s. S. 491). Bei Temperaturen über 200° C werden sie nach etwa 30 min zerstört.

Ihre Abtrennung durch Filtration setzt zunächst die Entfernung aller Bakterienzellen, auch der durch die Hitzesterilisation abgetöteten, voraus. Ferner sollte vorbeugend stets darauf geachtet werden, daß es in mikrobiell anfälligen Injektionslösungen nicht zu einer Keimvermehrung und damit Pyrogenanhäufung kommt. Die stärksten Pyrogenbildner sind gramnegative Bakterien, Pseudomonas-Arten, E. coli usw., aber auch grampositive Keime und Viren spielen hier eine Rolle.

Während die „echten" Pyrogene im Tierversuch bereits nach 30 min eine Temperaturerhöhung zeigen (Standardsubstanz: das Lipopolysaccharid Pyrexal der Firma ASTA, das am Kaninchen in einer Konzentration von 0,25 γ Wirkstoff/0,5 ml Aqua dest. innerhalb 30 min eine Temperaturerhöhung um 0,8–1,5° C hervorruft), hinken die Viruspyrogene nach und zeigen erst nach 1–2 Stunden eine deutliche Fieberwirkung. Nach SIEGERT u. Mitarb. (S.-B. Ges. Förd. ges. Naturwiss. [Marburg] 83, 1/2; 84, 1 [1961/62], 255) bestehen zwischen den Bakterien- und Viruspyrogenen eindeutige Unterschiede. Während die ersteren von der Zellwand abtrennbar (löslich) sind und erst nach längerer Zeit (30 min) bei einem Erhitzen auf 200° C zerstört werden, lassen sich die letzteren nicht von den Viruspartikeln abtrennen, werden aber durch Hitze leichter inaktiviert und sind durch Antikörper neutralisierbar. Die Bakterienpyrogene sind *nicht* wasserdampfflüchtig, trotzdem gehen bei der Destillation oft Stoffe mit über, die gleichfalls eine um mehrere Stunden verzögerte Fieberreaktion hervorrufen. Hierbei handelt es sich wahrscheinlich ebenfalls um bakterielle Abbauprodukte, wie Amine und andere stickstoffhaltige Verbindungen.

Die Entfernung der an die Bakterienzelle oder deren gröbere Bruchstücke gebundenen Pyrogene geschieht durch Filtration mittels Membranfilter (maximale Porenweite 250 mμ) (SCHMIDT, B., V. BLASS, Z. Hyg. 142 [1955/56], 183, 298), oder Seitz-Filterschichten (WILKE, H., u. E. VOSS, Arzneimittel-Forsch. 1 [1951], 8; K. D. RUDAT, Zbl. Bakt., I. Abt. Orig. 164 [1955], 370). Weit schwieriger gestaltet sich die Beseitigung der „freien", teilweise gelösten Pyrogene. Diese können nur mit adsorptiv wirkenden Filtern, wenn nötig während mehrerer Filtrationsvorgänge, entfernt werden. Auch hierbei spielt die Belastungsgrenze (die verfügbare Adsorptionsfläche beträgt nach WILKE und VOSS für 1000 cm² Filterfläche [EKS] etwa 2000 m²) der Filterschichten, die Zusammensetzung (besonders der Proteingehalt) der zu behandelnden Lösung sowie deren Py-

rogengehalt eine entscheidende Rolle. Wird diese Belastungsgrenze überschritten, so kommt es zu einem Durchbruch der Pyrogene. In jedem Falle sollten Vorversuche die jeweiligen Verhältnisse klären. Im allgemeinen kann man sagen, daß sich aus wäßrigen, nicht allzu viele hochmolekulare Stoffe enthaltenden Lösungen alle Pyrogene (bis zu 1 mg/l) im Verlauf der Entkeimungsfiltration entfernen lassen. Kolloide (Serum, Proteine usw.), hochviskose Lösungen (Plasmaexpander) sowie oberflächenaktive Stoffe (Saponine, zugesetzte Konservierungsmittel usw.) hemmen den Pyrogenadsorptionsprozeß ganz entscheidend. Mit oberflächenaktiven Stoffen lassen sich darüber hinaus sogar die geringen Mengen der von der Fertigung her in den Filterschichten enthaltenen Pyrogene eluieren. Diese geringen Pyrogenmengen können wegen der hohen adsorptiven Wirkung der Filterschichten normalerweise vernachlässigt werden. Größte Sicherheit bietet in jedem Falle die Verwendung einer möglichst großen Filterfläche, und davon sollte man, besonders bei Infusionslösungen, stets Gebrauch machen.

Dextranlösungen (MG ca. 50000) lassen sich mit EKS bei einer Belastung von 500 l/m² ausreichend entpyrogenisieren. Schwieriger ist es bei Eiweißhydrolysaten. Während die durch Säuren gewonnenen Hydrolysate durch eine Doppelfiltration mit EKS II ausreichend von Pyrogenen befreit werden können, gelingt dies bei den hochmolekularen enzymatischen Eiweißspaltprodukten nicht. Hier hilft unter Umständen eine Vorbehandlung mit Ionenaustauschern (z. B. Amberlite der Firma Rohm & Haas) weiter. In diesem Falle überlagert man die EKS-Filterschicht mit einer etwa 5 bis 10 cm dicken Austauscherschicht.

Nach KUNTSCHER, H., W. FAHRIG lassen sich gelöste Pyrogene bei einer Konzentration von 10 bis 100 γ/100 ml durch eine Filterschicht (Seitz-EK) von 100 cm² und einem Durchlauf von 25 l in ausreichendem Maße entfernen.

Neuerdings hat sich nach Angaben der Seitz-Werke bei der Entpyrogenisierung einer 16%igen Gammaglobulinlösung auch eine Vorfiltration mit 5 Schichten 40×40 AKS 4 (die etwa 5 mm dicken Schichten enthalten neben Zellstoffen und Asbestfasern als Gerüstsubstanzen zur Steigerung des Filtereffektes noch einen sehr hohen Anteil an feinstteiliger Aktivkohle und sind zum Schutze der Ablösung von Kohleteilchen mit kohledichtem Filtrierpapier hinterlegt) und eine nachfolgende Entkeimung mit 15 EKS-Schichten bewährt.

Die Untersuchungen von KIENHOLZ, M. (Arzneimittel-Forsch. 14 [1964], 1259) haben gezeigt, daß 1 m² Seitz-EKS-Filterfläche ausreicht, um ca. 90 m³ Wasser (mit einem Pyrogengehalt von etwa 500 mg; zugesetztes E. coli-Lipopolysaccharid) pyrogenfrei zu filtrieren.

TRANSLATION

Section 3.3. Pages 41/42 from Sterilisation - Desinfektion - Konservierung - Chemotherapie by Dr. K.H. Wallhaeusser (Frankfurt/M. - Hoechst) and Professor Dr. H. Schmidt (Wabern b. Bern)

WITHOUT COMMITTMENT

3.3. The Removal of Pyrogens by Filtration.

Pyrogens are, in the main, constituents of the cell walls of bacteria, of which something towards 90% are bound to the cells. They can only be detected by animal experiments (see page 491). At temperatures over 200°C they are destroyed in approximately 30 minutes.

A pre-condition of their separation by filtration is the removal of all bacterial cells including those that have been killed by heat sterilisation. Further, steps must be taken with injection solutions that are sensitive to microbial infection to prevent bacterial reproduction and combined therewith, accumulation of pyrogens. The strongest pyrogen formers are the gram-negative bacteria, Pseudomonas types, E. coli and so on although gram-positive bacteria and viruses can also play a part.

Although the "genuine" pyrogens can induce temperature increases within 3o minutes in animal experiments, the virus pyrogens lag behind somewhat and only show a significant fever effect after 1 - 2 hours. (The standard for control - Lipopolysaccharide Pyrexal prepared by the ASTA Company causes in rabbits when used in a concentration of 0.25% effective substance in 0.5 ml of distilled water a temperature rise of 0.8 - 1.5°C within 30 minutes.)

According to Siegert and collaborators (S.-B. Ges. Ford. ges. Naturwiss. (Marburg) 83, 1/2; 84, 1 (1961/62), 255) there are significant differences between bacterial and virus pyrogens. Whereas the former can be separated from the cell wall (soluble) and are only destroyed after heating for a longer time (30 minutes) at 200°C, the latter cannot be separated from the virus particles, they are more readily inactivated by heating and can be neutralised by anti-bodies. The bacterial pyrogens are not volatile in steam but, nevertheless, substances are carried over on distillation which do result in a fever reaction, although only after several hours. It is probable that the products carried over are bacterial breakdown products such as amines and other nitrogenous based compounds.

Continued .....

The removal of the pyrogens bound to the bacterial cells or fragments thereof can be effected by filtration through a membrane filter (maximum pore size 250 m micron) (Schmidt, B., V. Blass; Z. Hyg. 142 (1955/56), 183, 298), or Seitz filter sheets (Wilke, H., H.E. Voss: Arzneimittel-Forsch. 4 (1954), 8; K.D. Rudat; Zbl. Bakt., I.Abt. Orig. 164 (1955), 370). The removal of the "free" partly solubl e pyrogens is far more difficult. These can only be eliminated by means of adsorptive action filters and, when necessary, by repeated filtration processes. The loading limit (the available adsorptive surface) is, according to Wilke and Voss for 1000 cm^2 filter surface (EKS) some 2000m^2 , the composition (and particularly the protein content) of the solution to be processed and the pyrogen content all play significant roles. If the loading limit is exceeded then the pyrogens will pass through. In any case proving experiments should be used to clarify the corresponding relationships. In general it can be said that with watery solutions which do not contain too much high molecular weight substances all pyrogens (up to 1 mg/l) will be removed in the course of the sterilising filtratinn. Colloids (serum, proteins etc.), high viscosity solutions (plasma substitute) as well as surface active agents substances (Saponins, preservation additives etc.) hinder quite significantly the pyrogen adsorption process. With surface active substances the small amounts of pyrogens remaining in the filter sheets after manufacture can even be eluted out. These small amounts of pyrogens can normally be disregarded owing to the high adsorptive action of the filter sheets. The best safety measure is, in any case, to use the greatest possible filtering surface and this should always be done, especially with infusion solutions.

Dextran solutions (molecular weight approximately 50,000) can be satisfactorily depyrogenised through EKS sheets at a loading of 500 litres per square metre. Albumen hydrolysates are more difficult and whereas hydrolysates prepared by acid hydrolysis can be adequately depyrogenised by double filtration through EKS², this is not adequate for the high molecular weight products obtained by the enzymatic splitting of albumen. A pretreatment with ion exchange resins (e.g. Amberlite of Roehm & Haas) is of assistance. IN this case the EKS filter sheet is covered with a 5/10 cm thick layer of the ion exchange resin.

According to Kuntscher, H., W. Fahrig, the soluble pyrogens in concentrations ranging from 10 to 100 λ100/ml can be adequately removed by filtration through a single sheet (Seitz-EK) of 100 cm^2 surface and a volume of 25 litres.

Continued .....

According to a recent report from the Seitz-Werke a 16% gammaglobulin solution a prefiltration through five sheets 40 x 40cm Grade AKS4 (these sheets which are some 5 mm thick contain in addition to cellulose and asbestos fibres as the basic structure a high content of very fine activated carbon to increase the filtration effect and to prevent the washing through of the activated carbon carry on the outlet side a suitable filter paper that will hold it up) and a finishing sterilisation with 15 EKS sheets proved satisfactory.

Investigations of Kienholz, M. (Arzneimittel-Forsch. 14 (1964), 1259) have shown that 1 m^2 of Seitz EKS shdet is adequate to depyrogenise approximately 90 m^3 water with a pyrogen content of some 500 mg from added E. coli-Lipopolysaccharide.

GO/DMD
5.12.1973.

A BRIEF HISTORY OF THE USE OF ASBESTOS BEARING FILTER MEDIA FOR THE CLARIFICATION AND STERILISATION OF BEVERAGES AND DRUGS

INTRODUCTION

The clarification and/or sterilisation of beverages and drugs by means of filtration is a process that has long been established in both industries. The main types of filter media that carry a content of asbestos and which are used for these operations are:-

(a) Filter pulp.

This material is prepared from cotton or wood cellulose and normally carries up to 5% of asbestos. This filter medium is utilised in what are classified as pulp filters.

(b) Fibrous materials.

Here there are two types. One is based on cellulose and asbestos, the cellulosic portion being derived from either cotton or wood pulp, with the asbestos content ranging from 0 to 100% according to grade. The other is based on kieselguhr and asbestos, the maximum asbestos content being 50%. The first type is utilised in what are classified as alluvial filters and precoat or pressure leaf filters, whereas the second type only finds usage in pressure leaf or precoat filters.

(c) Filter Sheets.

These are based on cellulose, kieselguhr and asbestos, the cellulosic portion being derived from either cotton or wood pulp. The asbestos content ranges from 0 to 50%, according to grade. This type of filter medium is used in what are referred to as sheet filters and which are generically, flush plate or plate and frame filter presses.

FILTER PULP

This material, which may contain up to 5% asbestos, is used in cake form. The basic pulp is supplied by the manufacturers in blocks and to form into cakes, suitable for use in the particular type of pulp filter in use, these blocks are disintegrated in water in a disintegrating/washing unit. The blocks supplied by the manufacturers are pure cellulose and it is customary to add the requisite amount of asbestos after disintegration in water. The usual addition

is $2\frac{1}{2}\%$, the normal maximum 5% and, for certain special applications, up to $12\frac{1}{2}\%$. When the two components - cellulose and asbestos - have been thoroughly mixed in the disintegrating/washing unit, the requisite volume of suspension is drawn off into a forming press, the water drained off by gravity and pressure, thus forming a filter pulp cake some 2 inches thick and in a format to suit the specific pulp filter in which it is to be utilised. At the end of each cycle the exhausted cakes are removed from the pulp filter, broken up and washed in the disintegrating/washing unit, during which period the material is freed from the impurities that it has filtered out from the product that was filtered. Additionally there is some loss of asbestos fibres and it is standard practice at the end of each washing cycle, to add $\frac{1}{2}/1\%$ of asbestos, to maintain the asbestos content at the desired level.

Developed towards the end of the 19th century, with first patents being taken out in the 1890's, pulp filters rapidly achieved popularity in the brewing trade and, by the first decade of the 20th century, were referred to in text books on brewing as standard items of equipment for beer filtration.

During the first two decades of the 20th century the use of filtration for bottled beers and, for the filtration of draught lager beers presented in cask, became standard practice in the brewing industry throughout the world, with the exception that certain types of bottled beer that traditionally underwent a secondary fermentation in bottle continued to be bottled without recourse to filtration and, in the United Kingdom, draught beers continued to be presented to the public in an unfiltered condition, clarification being effected by fining with isinglass. In other words, by the 1920's, for practical purposes all the beers produced and consumed, with the exception of a small percentage of bottled beer and the cask beers presented in the United Kingdom, were clarified by passage through this asbestos bearing filter pulp.

In the 1930's following the introduction of pressure leaf or precoat filters and sheet filters there were new developments for the processing of beers, all based on two stage filtration, the alternatives being:-

(a) First filtration through pulp filter and second filtration through sheet filter.

(b) First filtration through precoat or pressure leaf filter and second filtration through sheet filter.

(c) Both first and second filtration through sheet filters.

In the United Kingdom there was another development which also resulted in an increase in the volume of beer filtered i.e. the introduction of metal casks

to replace the older wooden casks - now generally referred to as kegs - and which were used for the presentation to the public of carbonated filtered beers. Such beers were filtered by one of the systems specified above. It is therefore reasonable to suggest that by the end of the 1930's the bulk of beers produced throughout the world were filtered through asbestos bearing filter pulp with a relatively small percentage going through precoat or pressure leaf filters and with a fair percentage receiving their second filtration through filter sheets, also an asbestos bearing filter medium.

Pulp filtration also found applications in the production of spirits and more especially, Scotch whisky, where it became one of two generally accepted methods of clarification by filtration, the other being the use of alluvial filters using fibrous materials. There is still limited usage of both methods in the production of Scotch whisky today, although the bulk - as with other spirits such as brandy, eau-de-vie, vodka and so on - are now clarified with the use of filter sheets.

Pulp filtration found but little use in the preparation of drugs.

FIBROUS MATERIALS

The fibrous materials based on a mixture of cellulose and asbestos were developed in Germany towards the end of the 19th century, and were first used in that country on a commercial scale in 1887.

The alluvial filters in which they were used were readily accepted by the wine and spirit trade, fruit juice and soft drink producers as well as by drug manufacturers.

By the turn of the century they were in use on an appreciable scale in all wine and spirit producing countries and this development continued at an accelerating pace. The 1920's saw a vast expansion of usage and a similar technical development to that described for pulp filters - the introduction of two stage filtration, following the development of filter sheets and sheet filters, so that coming into the 1930's, it is reasonable to say that wines were being processed, at the filtration stage, by one or other of the following methods:-

(a) Alluvial filter using fibrous material followed by sheet filter, using filter sheets.

(b) Centrifuge followed by a sheet filter dressed with filter sheets.

(c) Two stage sheet filtration, using coarse and fine grade clarifying sheets or, as an alternative to the latter, sterilising sheets.

There were similar developments in fruit juice, but more detail is given in the next section.

Over the past 20 years there has been a fall off in the use of alluvial filters, although two stage filtration has been maintained, the alluvial filters being replaced by precoat or pressure leaf filters.

The fibrous materials based on cellulose/asbestos mixtures were also used on a considerable scale for the clarification of drug preparations, typical products processed being simple syrup, tinctures, extracts, medicaments and lotions and, although perhaps a little bit outside the drug field, cosmetic preparations such as perfume, eau de colognes, hair washes, shampoos and so on.

The second type of fibrous material referred to - based on kieselguhr and asbestos - finds its application in precoat or pressure leaf filters. It has come into general usage in these filters over the past 15 years and their main application is in the brewing industry, where particularly in America, they are used on a considerable scale. They also find application for clarification of drugs.

FILTER SHEETS

This type of filtering medium, supplied ready made by the manufacturers, is based on cellulose, asbestos and kieselguhr. For special applications additives may be used to achieve a specific effect, typical examples being activated carbon to clean up the palate and colour of sugar syrup solutions used in the manufacture of soft drinks and nylon or polyvinylpyrrolidone powders, used where it is desired to reduce the anthocyanogen content of a beer and so improve its shelf life. The asbestos content ranges from 0 to 50%.

This class of filtering material and the filters in which used - sheet filters - were both developed in Germany well over 50 years ago, the first major application being for the clarification and sterilisation of water for use by armed forces in the field, the initial supplies being made in 1917. Today filter sheets are manufactured not only in Germany but also in the United

States of America, Great Britain, Mexico, Argentine, Australia, India, South Africa, U.S.S.R., Poland, East Germany, Austria, France and Spain. The sheet filters in which they are used are made in all these countries and in a number of others as well.

Filter sheets, the filtering effect of which can be varied by changes in composition and in the methods of working up the constituent raw materials, are available in a wide range of porosities. The coarsest, when treated with wet strength agents to give washing characteristics, are used purely and simply as support for a filter aid such as kieselguhr. Then come a whole range of clarifying filter sheets, varying from coarse to fine clarification and finally sterilising sheets which are suitable for the sterilisation by the simple process of filtration of the most varied liquids. Indeed, there is one very specialised application in the drug field which is of considerable importance - depyrogenisation by filtration.

Although originally developed for the production of potable water for the German fighting forces, sheet filters and filter sheets gained rapidly in popularity for many filtration tasks in the decade following the conclusion of World War I. In the production of drugs they offered certain technical advantages and came into general use for clarification of the most varied products - a far wider range than that given under the previous heading - and, even more important, for the sterilisation of drugs, especially those of a thermolabile character where heat sterilisation cannot be used as it causes undesirable changes in the product itself. Apart from preparations for oral or external application such as already specified, filter sheets found ready application for both clarification and sterilisation of intravenous and intramuscular injections, vaccines, antitoxines and salines.

Continuing in the drug field, the standard process for the sterilisation of "synthetic" blood plasma based on dextran as well as blood plasma itself was based on the use of filter sheets and it continues to be a standard method of sterilising these products. In the years following World War II there have been further developments in this area e.g. the separation of blood protein fractions and again, the process has been based on the use of filter sheets and it continues to be a standard method of production of such preparations.

Another major area in the drug field where sheet filters have been used on a major scale is in the production of antibiotics, where the use of filter sheets for both clarifying and sterilisation may almost be described as

"axiomatic".

To summarize with regard to the use of sheet filters in drug manufacture, it is reasonable to say that filter sheets have now been in commercial use on an ever increasing scale for the sterile filtration of intravenous and intramuscular injection preparations for something over 50 years and that blood plasmas and antibiotics, which have come into general use in the past 25 years are, for the most part, passed through sheet filters for the essential operation of sterile filtration.

In the production of wines, these filter sheets, which first became available after World War I, gained rapidly in popularity for two major filtration tasks - clarifying filtration during the course of maturation and polishing and/or sterilising filtration at the bottling stage. By the late 1930's the system had become accepted as a modern method and its use was wide spread, as can be judged from the list of countries in which filter sheets are manufactured, throughout the world. Post World War II the use of filter sheets for the final filtration of wines and spirits at the bottling stage has become standard practice. Indeed, there was a time when the same comment could be made with regard to clarification of wines during their maturation but here there have been technical changes, for the necessary clarification at this stage in the development of a wine is now generally carried out on precoat or pressure leaf filters. It is no exaggeration to say that in Europe and in many other wine producing areas, that the final filtration of wines and spirits at the bottling stage is an operation that is almost universally carried out on sheet filters dressed with filter sheets, this position gradually having been attained over the past 50 years.

The decade after World War I saw a major development in the methods of producing non-alcoholic fruit juices. This was the introduction of two systems, both hinging on the use of filters, for the clarification and then the sterilising filtration of the product. These systems, known as the "Seitz cold process" and the "Seitz-Boehi" process make use of alluvial filters using fibrous materials for the clarifying filtration and sheet filters using filter sheets for the sterilising filtration. Major installations based on these systems were made in Germany, Switzerland and South Africa, to mention but three countries where production runs into many millions of gallons annually. In other words, non-alcoholic fruit juices produced by the methods just specified and both using asbestos bearing filtering media, have been on the market on an ever increasing scale for some 50 years.

The introduction of filter sheets some 50 years ago also resulted in changes in the methods of handling the basic raw materials used in soft drink manufacture - water, syrup and essences or extracts. During the various stages of water treatment associated with the production of many soft drinks, filtration is an important, indeed, essential operation. Clarification is in the main, through filter sheets whereas sterilisation is sometimes achieved by chemical means i.e. chlorination or alternatively, by sheet filtration. When chlorination is used it is customary to pass the processed water to a carbon filter to eliminate excess chlorine and finally through a trap filter - usually a sheet filter - to eliminate any carbon that may have become dis_entrained from the carbon filter. It has long been standard practice to filter the syrups according to the particular type of soft drink and the quality of the sugar. Dependant on the nature of the requirement filtration will be through a filter paper, a clarifying filter sheet or a special type of filter sheet carrying carbon as an additive, where it is essential to remove all colour and any off flavours. It is not unknown to resort to sheet filtration for the sterilisation of the syrup if it is produced by the "hot" system. The essences and extracts, where clarification is required, are normally processed through filter sheets. All these filtration tasks in the soft drinks industry have been practiced and continue to be practiced on an ever increasing scale over the past 25 years, with some of them - such as the clarification and sterilisation of water and the clarification of syrups, being used on quite an appreciable scale since the 1920's.

In the brewing trade the availability of filter sheets after World War I revolutionised the methods of beer filtration. The pulp filters that had previously been used were either replaced by two stage sheet filtration or augmented by single stage sheet filtration, so that by the late 1930's, a high proportion of the beers produced in Europe, to mention but one major beer producing area, were passing through filter sheets. Post World War II the use of sheet filtration for the final polishing of beer, be it for presentation in bottle, in cask or in keg, became standard practice, the exception to this generalisation being the United States of America where they found only limited application, mainly due to the fact that at that time there were not sheet filters available with adequate flowrates to meet the demands of the high production packaging units in use in the American brewing industry. Techniques have indeed changed over the past 25 years for pulp filters have now been more or less completely disgarded, being replaced either by sheet filters or, alternatively, precoat or pressure leaf filters. This latter

development has been followed on a considerable scale in the United States of America.

To sum up, it can be said that with the exception of the U.S.A. where sheet filtration has never been used on a major scale, the greater portion of the filtered beer offered to the consumer has for the past 25 years and to a lesser extent for the 25 years prior to that, received its final filtration through filter sheets.

Turning briefly to spirits there has in the post World War II period, been a major change, as for practical purposes, pulp filters and alluvial filters have been completely replaced by sheet filters, with a relatively small usage of precoat or pressure leaf filters.

ASBESTOS TYPE

It is well worth recording that, as far as is known, all manufacturers of the various asbestos bearing filter media to which reference has now been made do not make use of the crocidolite type which has been specifically referred to in technical publications as a possible cause of gut cancers such as mesothelomias. Only the chrysotile type is used which has relatively low resistance to acid media and which, in contact with gastric juices, is subject to leaching out of its megnesium resulting in the degradation of the fibre itself into something approaching a hydrated silica gel.

PARTICLE MIGRATION

It is acknowledged that with all the filter media described there can and will be some migration of particulate matter from the medium itself into the filtered product. For this reason it has become standard practice to use some form of trap filter after the main filter, to ameliorate the position. Such trap filters range from simple equipment making use of fine silk as the straining medium, through ceramic candles to sintered glass or sintered stainless steel cartridges and they certainly eliminate visible particulate matter. Indeed, in some countries, the use of such trap filters is incorporated in the codes covering production of drugs and pharmaceutics. Also, for the past 15/20 years, leading sheet manufacturers have been applying a bonding agent to the outlet side of such filter sheets which effectively stop migration of visible particulate matter.

STATISTICS.

In view of the long history of asbestos bearing filter media in the production of beverages and drugs, the following tables set out statistics covering on a world and country basis, the production figures under various headings - wines, spirits, fruit juices, soft drinks and beer - for consideration in relation to the incidence of cancers and the consumption of beverages.

STATISTICS TO FOLLOW WHEN AVAILABLE

GO/DMD
4.1.1973

B E E R - ANNUAL PRODUCTION

WORLD WIDE	Year	Total (1,000 hectolitres)
	1953	308,800
	1963	450,700
	1971	657,669
U. S. A.		
	1953	106,111
	1963	114,943
	1971	149,462
United Kingdom		
	1953	40,888
	1963	46,315
	1971	56,694
German Federal Republic		
	1953	26,677
	1963	59,156
	1971	90,029

W I N E - ANNUAL PRODUCTION

WORLD WIDE	Year	Total (1,000 hectolitres)
Average	1934/1938	202,600
Average	1949/1951	193,413
Average	1959/1961	236,573
	1970	289,227

F R U I T J U I C E S - ANNUAL PRODUCTION

WORLD WIDE	Year	Total (1,000 hectolitres)
Average	1956/1960	21,415
	1965	27,859
	1970	35,400

S O F T D R I N K S - ANNUAL PRODUCTION

UNITED KINGDOM

YEAR	Concentrated Soft Drinks	Unconcentrated Soft Drinks	Ready to Drink Equivalent
	(Thousand Gallons)		
1958	27,599	193,831	331,826
1959	38,786	227,382	421,312
1960	40,103	215,136	415,651
1961	43,400	230,100	448,300
1962	39,800	209,100	409,000
1963	42,600	210,300	423,000
1964	51,400	237,800	495,000
1965	50,700	236,300	490,000
1966	54,700	244,100	518,000
1967	61,500	249,000	556,000
1968	60,400	253,000	555,000
1969	66,400	262,200	594,000
1970	72,100	267,800	629,000
1971	69,800	274,000	623,000

EUROPEAN COUNTRIES

	1966	1967	1968	1969	1970	1971
	(Million litres)					
Austria	161	176	188	210	270	298
Belgium	435	466	447	505	489	530
Denmark	179	187	190	201	208	220
Finland	107	120	119	142	183	183
France	640	697	716	833	890	960
Germany	1983	2147	2244	2540	2859	3250
Holland	462	523	526	632	694	771
Italy	1005	958	1200	1400	1200	1260
Norway	102	109	130	146	157	175
Portugal	30	33	57	63	87	100
Spain	1544	1621	1734	-	1490	-
Sweden	259	257	280	293	294	293
Switzerland	203	224	229	245	242	281

POTABLE SPIRIT - PRODUCTION

(Expressed in original proof gallons)

UNITED KINGDOM

Year	Total
1938/1939	29,223,556
1948/1949	30,872,270
1959/1960	74,208,667
1969/1970	152,273,000

POTABLE SPIRIT - CONSUMPTION

(Expressed in original proof gallons)

UNITED KINGDOM

Year	Total
1938/1939	17,394,079
1948/1949	14,508,756
1959/1960	33,432,180
1969/1970	76,895,752

GO/DMD
9.1.1973