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# POLYPROPYLENE PRODUCTION AND COLORECTAL CANCER

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# SUMMARY

Polypropylene has been produced for over 35 years. It has a wide variety of applications including industrial, food packaging and many domestic uses. High molecular weight substances such as polypropylene are considered chemically and biologically inert with little or no physiological or toxicological effects. The monomer, propylene has been examined in a two-year inhalation study in mice and rats and found to be without carcinogenic activity. No long-term cancer bioassay of polypropylene has been conducted. Subcutaneous implantation induces local tumour response, which is considered to be due to tissue displacement. With this exception there is no evidence that propylene or polypropylene has mutagenic or carcinogenic properties. No identifiable carcinogenic agent was found in the additives and process agents used in polypropylene manufacture.

In man colorectal cancer is a relatively common cancer. It increases markedly with age, particularly in North American, European, and other industrialised populations. Genetic and dietary factors are involved in its etiology. Although not considered an occupational cancer, an excess of colorectal cancer has been reported among workers exposed to asbestos as well as among automotive wood model and pattern makers. Screening, which may be an effective method for reducing the risk of colorectal cancer mortality, includes procedures such as digital rectal examination, faecal occult blood tests, sigmoidoscopy, and more recently, colonoscopy. The two endoscopic approaches are viewed as the most effective techniques.

Early epidemiologic studies of polypropylene production workers and carpet manufacturing employees who used polypropylene reported a significant excess of colorectal cancer. These studies were based on clusters of colorectal cancer. In one study, 5 of the 7 cases were diagnosed within a 5-month period and in the other study 5 cases were diagnosed within an 18-month period. Recent updates of these two original study populations have found no continuation of the excess of colorectal cancer, thereby indicating the chance nature of the clusters. Other investigations of polypropylene production workers in the United States, Germany, Australia and the United Kingdom found no link with colorectal cancer. As a whole, the combined weight of epidemiologic and toxicologic evidence do not support an association between polypropylene production and colorectal cancer.

Consequently medical surveillance programmes to detect colorectal cancer among polypropylene workers are not warranted.

# SECTION 1. INTRODUCTION

Following the publication of a study by Acquavella *et al* (1988) reporting a statistically significant increase of colorectal cancer incidence among the workers of a polypropylene production plant (Exxon Baytown Plant, Texas), discussions started among polypropylene producers about the significance of these results.

A workshop was organised by ECETOC in Brussels in May 1989 which reviewed the Exxon work in progress and which was subsequently been published (Acquavella *et al*, 1988, 1989a,b, 1990, 1991; Acquavella and Owen, 1990; Vernon *et al*, 1990; Owen *et al*, 1992).

European delegates from several companies also reported briefly on their experience. It appeared that no excess of colorectal cancer was observed in any of the European companies, although this was based on quick surveys rather than in-depth investigations. The polypropylene production processes differed among companies and in many cases the production technology employed had changed over time within an individual company. Although it was considered at the time of the ECETOC meeting that the results reported by Exxon were specific to a particular plant and not polypropylene production *per se*, it was considered desirable to evaluate the data in greater detail.

For the above reason a Task Force was established with the following terms of reference:

- gather information on past and current exposures in polypropylene plants and compare exposure in the Exxon Baytown plant with those in other plants;

- encourage and coordinate epidemiological investigations on mortality and morbidity (particularly associated with colorectal cancer) in polypropylene workers, and the publication of findings;

- if appropriate:

  recommend a medical surveillance programme aimed at early detection of colorectal cancer in exposed workers;

  prepare periodic reports to assist in provision of information to interested parties inside and outside industry;

recommend experimental animal studies and appropriate follow-up studies to investigate etiological factor(s) identified.

The above terms of reference reflected what was known at the time when the Task Force was formed in 1989 but during the tenure of the Task Force more information became available which led to modifications of planned activities.

The Task Force could not comply fully with the first term of reference (cf Section 2.3.9). Although historic information on the additives used in the process was available from most plants, these data were considered by many to be classified commercial information which the companies were not prepared to disclose unless a significant health hazard was demonstrated. The occupational hygienists involved with polypropylene production collectively expressed the view, that little information in fact was available, as the process was regarded as one which is relatively safe.

In order to address the second term of reference the Task Force explored possible epidemiological investigations to be made on the polypropylene manufacturing plants located in Europe. To this end it commissioned the Institute of Occupational Health, University of Birmingham, UK, to conduct a feasibility study for the investigation of colorectal cancer within these manufacturing units.

The feasibility study was based upon a visit to 6 polypropylene manufacturing plants by a team comprising an epidemiologist and an industrial hygienist. A detailed questionnaire was sent to 19 plants participating in the feasibility study. The questionnaire was aimed to assess the availability of:

- personnel and medical records for establishing a complete cohort;
- these together with process histories would be used for subdividing the population by exposure;
- results from exposure measurements (including the type of measurement and the rationale for sampling);
- information on the precautions used in various areas of the plant;
- regional or national cancer incidence registers and death certificates (with cause of death) for countries where the polypropylene production plants were located.

Having taken into account the respective availability of these elements, and the quality of the data they provided, it was concluded that the feasibility of conducting an epidemiological study was poor and enormously difficult to coordinate over several countries. A standardised protocol could only be applied to 9 of the 19 candidate plants thus providing insufficient power to detect a two-fold increase of the incidence of colorectal cancer in the cohort.

At the same time of the feasibility study new data were provided either by updates of previously investigated cohorts of workers or by cohorts of workers investigated for the first time. The data are reviewed in Section 5.

As the Task Force progressed with its work the original terms of reference became outdated and as new developments and new data became available the Task Force adapted its work to the changing situation.

# SECTION 2. MANUFACTURE OF POLYPROPYLENE

## 2.1 INTRODUCTION

The production of polypropylene by the polymerisation of propylene has resulted from the developments of Ziegler and Natta who invented a catalyst which revolutionised the field of polymer chemistry. These catalysts improved both linearity and stereochemistry. A polymerisation process was first reported in 1955, by Natta and co-workers, which produced commercially viable polypropylene. The benefits of polypropylene over other polymers include high tensile strength, hardness and stiffness, and are due in the main to the orientation of the methyl groups (see Section 2.2.1). Products incorporating polypropylene include: piping, packaging materials (boxes, industrial and food wrappings), medical appliances, electrical cable coating, garden furniture, toys, and carpet fibres.

In addition, the Ziegler-Natta catalyst is used in the production of copolymers. Two types of copolymer are produced with polypropylene, both utilise ethylene as the comonomer.

Polypropylene production is not a labour intensive activity. The maximum estimate of workers employed in its production in Western Europe is 4,500 since manufacturing started in 1955. European production of polypropylene in 1991 was 4.2m tonnes.

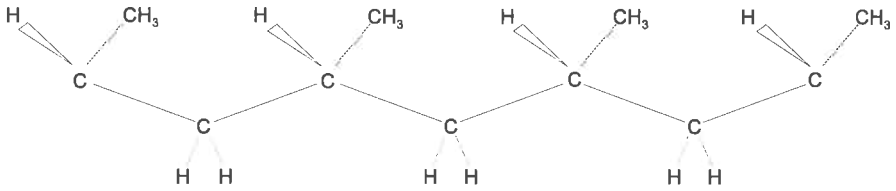
## 2.2 CHEMISTRY

### 2.2.1 Stereochemistry

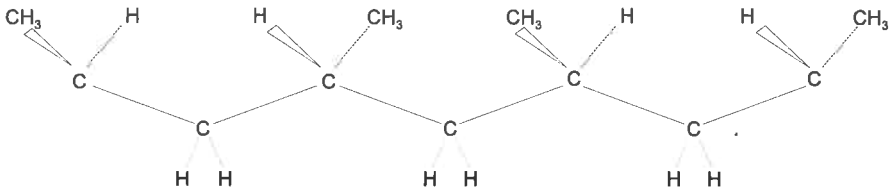
The orientation of the methyl groups is what provides polypropylene with its unique properties and hence value. The work by Natta showed that it was possible to create polypropylene with all of the methyl groups in the same orientation along the chain. This is called the isotactic isomer. If the methyl groups alternate their position with hydrogen atoms, then this is the syndiotactic isomer and if the methyl groups and hydrogen atoms are randomly sited along the chain, then this is the atactic isomer - see Figure 1 below

**Figure 1 Isotactic, Syndotactic and Atactic Isomers of Polypropylene**

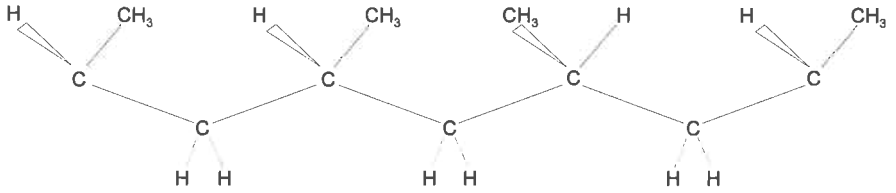
Isotactic
(methyl group in same position)



Syndiotactic
(methyl group in alternate position)



Atactic
(Methyl group in random position)



### 2.2.2 Chemical/Physical Homopolymer Properties

- CAS No. 9003-07-0 (for isotactic polypropylene)
- Empirical Formula $(C_3H_6)_n$ (where n > 1000)
- Average molecular weight 220,000 - 700,000
- Melting point
  - softens at approx. 155°C
  - melts at approx. 165°C
- Density
  - 0.90 - 0.92
- Ignition temperature
  - cloud 520°C
  - layer 250°C
- Minimum Cloud Ignition Energy
  - 0.240 joules
- Minimum Explosion Concentration
  - 0.055 kg/m$^3$

- Solubility — Insoluble in cold organic solvents, although swelling occurs; soluble in hot carbon tetrachloride and chloroform.

- Stability — Must be stabilised to prevent decomposition in sunlight. Heating in the presence of air or oxygen produces carbon dioxide, carbon monoxide, hydrogen, $C_1$ - $C_5$ saturated aliphatic hydrocarbons and polycyclic aromatic hydrocarbons.

- Reactivity — Resistant to acids and alkalis; attacked by strong oxidising agents.

## 2.3 PROCESS DESCRIPTIONS

There are at present three major types of manufacturing process; slurry, bulk (or liquid-pool) and the gas phase. A combination of these is also possible. Irrespective of the method of manufacture, the requirement to maximise the proportion of isotactic polypropylene is a common feature. The major danger in the process is inflammability and for this reason propylene release is rigorously controlled.

### 2.3.1 Slurry Process

This is often called the 'diluent' process and takes its name from the use of a polymerisation diluent. The latter is a liquid usually a $C_6$ - $C_7$ aliphatic alkane, typically hexane or heptane, although chain lengths up to $C_{11}$ are sometimes used. To ensure that no unsaturated compounds are present that would interfere with polymerisation, the diluents are hydrogenated. The catalyst ($TiCl_3$ and/or $TiCl_4/MgCl_2$), which is usually kept under nitrogen, and cocatalysts triethyl aluminium chloride, diethyl aluminium chloride and monoethyl aluminium chloride are added as a slurry in the polymerisation diluent contained in an agitated polymerisation vessel. Reaction conditions most often cited are 50-80°C and pressures of 5-30 atmospheres. Propylene is fed to the reactor at a controlled rate and pressure. The normally crystalline polymer formed under these conditions is insoluble and forms a finely divided granular solid enveloping the catalyst particles. Monomer addition is continued until the slurry reaches between 20 and 40% solids. The duration of residence varies from minutes to several hours depending on the catalyst concentration and activity as well as other reactor conditions. The chain length (molecular weight) can be altered by means of the addition of hydrogen, cocatalysts or higher temperatures; of these the addition of hydrogen is the preferred method.

The slurry is transferred to a stripping vessel where unreacted propylene is flashed off and is recycled to the reactor. The catalyst is then deactivated by the addition of an alcohol, usually isopropyl alcohol or butanol (methanol has also been used). The catalyst and alcohol are removed

from the diluent by extraction with alkali (pH=11). The polymer floats on the surface of the water. The majority of the diluent, including the atactic polymer, is removed from the isotactic polymer by centrifuging and the wet isotactic polymer is subsequently dried. This is usually performed under a nitrogen blanket. Extrusion and finishing are described later (section 2.3.5). Syndiotactic isomer requires the use of specific catalysts and polymerisation conditions. In normal processing the amount produced is negligible.

### 2.3.2 Bulk Process

A process utilising a liquid propylene monomer rather than a hydrocarbon diluent has been patented by Dart Industries and is called the bulk process. The benefits over the slurry process are twofold; firstly, the increased polymerisation activity due to the high concentration of monomer and secondly there is no need to purify the diluent. In order to keep the propylene in the liquid phase, the temperature is kept in the range of 45 - 80°C with the pressure of 17-37 atmospheres.

In this process liquid propylene is both the transport medium and source chemical. The same catalysts and cocatalysts are used as in the slurry process together with hydrogen to regulate chain length. The heat of polymerisation is removed from the reaction zone by removal of the propylene vapour, condensation of the vapour to a liquid and return of the liquid to the reactor. The polymer slurry, approximately 30-50% solids, is continuously removed from the reactor and taken to a vessel at approximately atmospheric pressure. The polypropylene solids are purified from catalyst residues and the non-isotactic polypropylene removed by washing with an alcohol (isopropanol) and aliphatic alkane (heptane). After separation by centrifuge the polymer is dried in an inert atmosphere (nitrogen). This step of purification is no longer required with the modern catalyst systems (third generation) where a cocatalyst (an electron donor) is used. Productivity and stereospecificity are such that no catalyst or atactic removal is necessary.

The widely licensed HIMONT Spheripol process is a variant of the bulk process in which polymerisation is operated in a loop without monomer vaporisation.

### 2.3.3 Gas Phase Process

This process is similar to the bulk process although the dispensing agent (propylene) is not present as a liquid but as a gas. Plant investment and operating costs are less than the other two processes as there is no diluent recycling and no drying other than flashing-off residual unreacted propylene. To obtain a high degree of activity it is necessary for the propylene to be of high purity. This is often achieved by passing the propylene at 50-100°C through a tower containing aluminium

and/or iron oxide. It is necessary to remove the heat of polymerisation from the reaction zone to optimise yield. This is commonly achieved by such means as condensing the evaporated unpolymerised propylene and returning it to the reaction zone with fresh propylene. It is of great importance to avoid over-heating as this decreases the average molecular weight (chain length). The same catalysts and cocatalysts are used as in the other processes with heptane and/or hexane used as a dispensing agent. Fluid bed processes like Union Carbide's UNIPOL process are an example of this type.

### 2.3.4 Purity Requirements

As a result of the extreme reactivity of the Ziegler-Natta catalyst, there is very stringent control of the purity of the chemicals used, especially the propylene monomer and diluents. Impurities of a polar nature destroy the catalyst, in particular, water. Other polar compounds which must be excluded for the process to operate at maximum efficiency include oxygen, carbon monoxide, carbon dioxide and hydrogen sulphide.

### 2.3.5 Powder Morphology

The polymerisation process produces a powder. The size of the powder particle depends upon the catalyst used. For first and second generation catalysts an average particle size for both the slurry and bulk process is between 400μm and 1,000μm, with highly active catalysts (third generation) being in the larger range from 500μm - 4,000μm. First generation catalysts, used mainly between 1950 - 1970's, of titanium and aluminium salts had poor productivity and stereospecificity. Second generation catalysts (1970 - 1990's) involved the addition of an electron donor which improves productivity and stereospecificity, thereby limiting the need for atactic removal. Third generation catalysts (1970's - present) use magnesium salts to improve the Ziegler-Natta catalyst; these can be left in the product. The shape of the particles depends on the morphology of the catalyst; both spherical and coarse shapes are used. The protrusions of the coarse polymer particles will tend to break off in the course of the process thereby a greater amount of "fines" are created than with spherical particles. The slurry and bulk process utilise both, although spherical particles are preferred in the loop reactors of the bulk process as otherwise an excessive amount of "fines" are formed due to the high shearing forces of the recirculation pumps. It is of benefit if the size distribution around the average size previously quoted is small although different catalysts control this to different degrees.

The gas phase process is somewhat different utilising fluidised beds which produce rough particles having a broad particle size distribution and consequently a high proportion of fines are produced.

The average particle size is similar to that of the third generation catalysts used in the slurry and bulk processes of about 500μm - 5,000μm. The production of smaller particles would limit the throughput capacity of polypropylene due to the risk of entrainment.

### 2.3.6 Extrusion and Finishing

In contrast to the earlier stages in the process described above, extrusion, finishing and packaging take place within closed buildings.

To ensure that the product is of uniform size and the various grades have the desired characteristics, the polypropylene from the reactors is mixed with a combination of the following: stabilisers, antioxidants, antistatics, ultra-violet stabilisers, acid scavengers (neutralisers), slip agents and other additives. This mixture then passes to the extruder which heats the mixture and forces it out of a number of fine holes. A rotating blade then cuts off the extruding polymer to a set length. Occasionally peroxides are also used to modulate the product chain length. In addition, fillers (and pigments) such as talc, calcium carbonate, titanium dioxide and carbon black can be used in compounding.

### 2.3.7 Packaging

The finished product is distributed to the various silos by pneumatic lines from where they are either delivered in bulk (road containers) to customers or packed into 25kg bags or 1 tonne big-bags. The majority of this is done automatically, with the smaller production runs being manually packed.

### 2.3.8 Chemicals Common to the Three Processes

The substances used in the production of polypropylene include:

- propylene,
- heptane/hexane (slurry process),
- $TiCl_3$, $TiCl_4/MgCl_2$,
- tri/di/monoethyl aluminium chloride,
- other solvents (benzene, toluene, xylene),
- alcohols (butanol, isopropanol, methanol),
- water (alkali),
- hydrogen,
- nitrogen,

- electron donors,
- UV stabilisers,
- anti-oxidants,
- anti-acids,
- anti-statics,
- fillers.

These materials appear to be common to all processes and their toxicological properties are evaluated in Section 3.

### 2.3.9 Occupational Hygiene

Subsequent to the observation of a colorectal cancer excess at the Exxon Baytown Plant, which used the slurry or diluent production process, an in-depth investigation was conducted by compiling a list of all substances used in the production process (some 300 substances) and examining occupational exposure (Acquavella *et al*, 1991; Owen *et al*, 1992). No obvious carcinogen was detected. No industrial hygiene data are available for assessing historic dust exposure. No similar evaluation has been published for other plants although it is the opinion of the engineers and industrial hygienists responsible for European-based production plants that the same situation prevails in their respective operations. In view of the absence of any significant toxicological observations (Section 3) the process has been regarded by occupational hygienists as one of low potential hazard for the workers. Without an in-depth investigation made by other companies no comparison can be made to the data generated by Exxon.

# SECTION 3. TOXICOLOGY

## 3.1 POLYPROPYLENE

Polypropylene is found in isotactic, syndiotactic and atactic forms, although the isotactic form accounts for 90-95% of commercial polymers. No information is available to differentiate these forms in terms of toxicity. Generally, such high molecular weight polymers are substances of great chemical inertness and the physiological and toxicological effects are slight or totally absent (Lefaux, 1968).

Polypropylene has very low acute oral toxicity, with an LD50 > 5 g/kg. Patch testing in human beings of polypropylene grades has indicated no apparent irritation or sensitisation potential (Montgomery, 1982). A 90-day inhalation study (6h/d, 5d/w) of polypropylene (0, 15, 30 or 60 mg/m$^3$) fibres (geometric mean diameter 1.6μm, 46% <1μm and a geometric mean length of 30.3μm)) found little evidence of pulmonary toxicity in rats (Hesterberg *et al*, 1992).

No cancer assay using polypropylene *per se* has been done. A two-year oral study in rats with the oligomeric material of molecular weight 800 was reported to have caused no effects when fed at the maximum dose tested of 20,000 mg/kg diet (Garvin, 1990). Likewise, a lifetime study in dogs fed up to 1,000 mg/kgbw/d showed no adverse effects (Garvin, 1990). No details of these studies can be presented as the source data for these latter experiments are no longer available for review and consequently no critique may be given upon the manner in which the studies were conducted or the nature of their outcome.

As with other polymeric materials, studies using polypropylene and involving tissue displacement and trauma have resulted in localised tumours (Oppenheimer *et al*, 1955). Subcutaneous implantation of polypropylene discs or powder has also produced local sarcomas at the site of implantation (Vollmar and Ott, 1961; IARC, 1979). These responses are likely due to the mechanical effects of tissue trauma and displacement rather than to any carcinogenic activity of the polymer itself (Moore, 1991).

## 3.2. MATERIALS ASSOCIATED WITH POLYPROPYLENE PRODUCTION PROCESSES

Most polypropylene production processes involve in excess of 300 process materials some of which are additives. A brief review of some of these materials is presented.