

Technical Report No. 57

POLYPROPYLENE PRODUCTION AND COLORECTAL CANCER

February 1994

ISSN-0773-8072-57

Brussels, February 1994
© ECETOC copyright 1994

ECETOC Technical Report No. 57

© Copyright - ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals), 4 Avenue E. Van Nieuwenhuyse (Bte 6), 1160 - Brussels, Belgium.

All rights reserved. No part of this publication may be reproduced, copied, stored in a retrieval system or transmitted in any form or by any means, electronic, mechanical, photocopying, recording or otherwise without the prior written permission of the copyright holder. Applications to reproduce, store, copy or translate should be made to the Director. ECETOC welcomes such applications. Reference to the document, its title and summary may be copied or abstracted in data retrieval systems without subsequent reference.

The content of this document has been prepared and reviewed by experts on behalf of ECETOC with all possible care and from the available scientific information. It is provided for information only. ECETOC cannot accept any responsibility or liability and does not provide a warranty for any use or interpretation of the material contained in the publication.

POLYPROPYLENE PRODUCTION AND COLORECTAL CANCER

CONTENTS

SUMMARY	1
SECTION 1. INTRODUCTION	2
SECTION 2. MANUFACTURE OF POLYPROPYLENE	5
2.1 INTRODUCTION	5
2.2 CHEMISTRY	5
2.3 PROCESS DESCRIPTIONS	7
SECTION 3. TOXICOLOGY	12
3.1 POLYPROPYLENE	12
3.2 MATERIALS ASSOCIATED WITH POLYPROPYLENE PRODUCTION PROCESSES	12
3.3 MUTAGENICITY STUDIES	15
3.4 AGENTS ASSOCIATED WITH DIGESTIVE TRACT CANCER	16
3.5 EVALUATION	16
SECTION 4. TUMOURS OF THE COLON AND RECTUM IN MAN	17
4.1 BACKGROUND	17
4.2 POLYPS	17
4.3 COLORECTAL CANCER	18
4.4 SCREENING	20
4.5 OTHER TESTS	22
4.6 EVALUATION	22
SECTION 5. EPIDEMIOLOGIC STUDIES	23
5.1. CANADIAN STUDIES	23
5.2 UNITED STATES STUDIES	25
5.3 GERMAN STUDY	27
5.4 OTHER STUDIES	27
5.5 DISCUSSION	28
5.6 EVALUATION	30
SECTION 6. CONCLUSIONS	32
BIBLIOGRAPHY	33
MEMBERS OF THE TASK FORCE	38
MEMBERS OF THE SCIENTIFIC COMMITTEE	40

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.

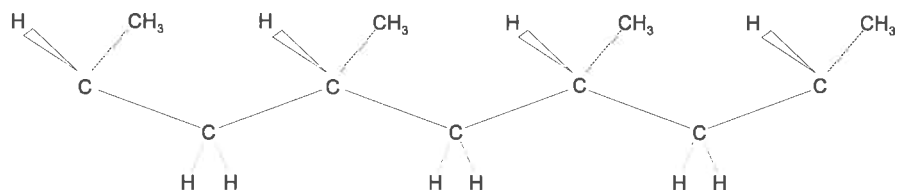
2.2 CHEMISTRY

2.2.1 Stereochemistry

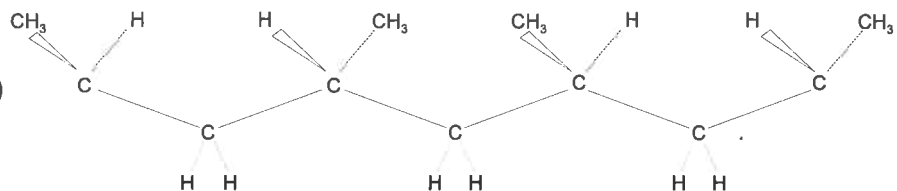
The orientation of the methyl groups is what provides polypropylene with its unique properties and hence value. The work by Natta showed that it was possible to create polypropylene with all of the methyl groups in the same orientation along the chain. This is called the isotactic isomer. If the methyl 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, Syndiotactic and Atactic Isomers of Polypropylene

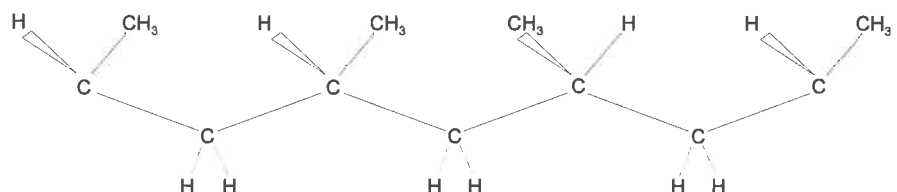
Isotactic
(methyl group in
same position)



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/m³

- 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 400 μm and 1,000 μm , with highly active catalysts (third generation) being in the larger range from 500 μm - 4,000 μm . 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 , $\text{TiCl}_4/\text{MgCl}_2$,
- 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/m³) 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.

Propylene: The monomer, propylene, has been the subject of a two-year inhalation cancer bioassay conducted in mice and rats at concentrations of 5,000 and 10,000 ppm and did not show any evidence of carcinogenicity (NTP, 1985). Similarly it was found to be without carcinogenic activity at exposures including the maximum tested of 5,000 ppm for 78 weeks and 104 weeks in mice and rats, respectively (Ciliberti *et al*, 1988).

Catalysts: There is no evidence in the toxicological literature that aluminium chloride, alkyl aluminium compounds (diethyl aluminium chloride, triethyl aluminium), or titanium chloride are associated with carcinogenic or mutagenic activity (NTP, 1992). The associated oxidation products, titanium dioxide and aluminum oxide, are formed spontaneously when Ziegler catalysts contact air. Lee *et al* (1985) exposed rats to titanium dioxide by inhalation exposure to concentrations of 10, 50 and 250 mg/m³ for two years. There was a dose-dependent pulmonary response (macrophage aggregation, alveolar hyperplasia) at doses ≥ 50 mg/m³ and local cystic keratinizing squamous cell carcinoma found primarily in high-dose females. The tumour type was well characterised as a unique type of experimentally induced tumour not usually seen in animals or man. These findings were attributed to excessive dust loading and overwhelmed clearance mechanisms. In a further study performed by the same group, rats were exposed to titanium tetrachloride hydrolysis products at aerosol concentrations of 0.1, 1.0 and 10 mg/m³ for two years. A similar response was observed only in the high-dose group, and the findings were likewise attributed to dust-overload and saturation of the clearance mechanism (Lee *et al*, 1986). Titanium dioxide has proved negative in an NTP feeding study bioassay, whereas aluminium oxide has not been subject to bioassay (NTP, 1992).

Sobota and Janas (1984) hypothesised that titanium chloride catalyst in the presence of a reducing agent such as diethyl aluminium chloride (as present in the slurry process) forms ammonia from nitrogen and hydrogen in the reactor vessel in this process. Under the right experimental conditions ammonia and propylene may possibly combine by ammoxidation to form acrylonitrile which could be entrained in the polymer. To our knowledge there has been no experimental confirmation of this hypothesis. Acrylonitrile is an animal carcinogen (NTP, 1992) and considered a likely human carcinogen (IARC, 1987b, Vainio and Wilbourn, 1992), although a recent study of acrylonitrile-exposed workers showed no increase in cancer risk (Swaen *et al*, 1992).

Solvents: None of the solvents commonly used in the polypropylene production process is known to have carcinogenic effects on the gastrointestinal tract in man or animals. Although high exposure to benzene is recognized as causing acute myelogenous leukaemia in man, there has been no association of benzene with cancer of the digestive tract (IARC, 1987b). Neither toluene nor mixed xylenes have produced evidence of activity in rodent cancer bioassays or in mutagenicity studies

(NTP, 1992). Alkylated xylenes, formed in polypropylene processes during occasional temperature elevations, have not undergone long-term testing (Vainio *et al*, 1985; NTP, 1992). Structural activity inspection does not suggest the presence of carcinogenic activity.

Killing Agents: There is no evidence of mutagenic or carcinogenic activity associated with methanol. Inhalation of methanol has been reported to cause characteristic pinpoint haemorrhages and congestion of the gastric mucosa in dogs. No chronic health-related data are available on sodium methylate (sodium salt of methanol). Ethanol has not caused mutations in bacteria or yeast but induces micronuclei in mice or rats; chromosomal aberrations have been reported in man. No carcinogenic effects have been seen in laboratory animals, although ethanol has been classified as a human carcinogen (IARC, 1988). n-Butanol was not found to cause mutations in bacteria (Rowe *et al*, 1982).

Neutralizers (anti-acids): No carcinogenic activity has been associated with sodium hydroxide, calcium oxide, calcium chloride, calcium hydroxide, or lithium chloride (NTP, 1992). In particulate form, such additives may result in localised irritation. Ingested calcium salts may decrease the mitogenesis of colonic epithelium (Wagovich *et al*, 1984).

Additives: Besides propylene, and the solvents and neutralizers which represent the major ingredients used in the process, a large number of additives have been used in small concentrations. When considering the amount of polypropylene produced on any individual plant site, the potential for exposure by a worker to an individual additive may be significant. The major groups of additives are antioxidants and fillers.

Antioxidants: Butylated hydroxytoluene (BHT) is used as an antioxidant in food, rubber, and plastic materials. BHT is not mutagenic (Bomhard *et al*, 1992); the understanding of the carcinogenic potential of BHT is complex and contradictory (IARC, 1986). The results of animal experiments provide evidence that BHT can initiate and inhibit tumour formation and in some cases it may act as a promoter. Thus 0.5% BHT has been shown to promote colon tumours in dimethylhydrazine treated mice (Lindenschmidt *et al*, 1986). Although BHT has been reported to produce hepatocellular tumours in rats (Olsen *et al*, 1986) and mice (Inai *et al*, 1988), other long-term studies in rodents have shown an absence of carcinogenic activity (Hirase *et al*, 1981; Williams *et al*, 1990). Overall, however, BHT is not considered an animal (NTP, 1992) or human carcinogen (IARC, 1986, 1987b; Vainio and Wilbourn, 1992).

Dilaurylthiodipropionate (DLTDP), distearylthiodipropionate (DSTDTP), which are used in the process are not mutagenic in *Salmonella* bacterial test systems (Exxon, 1989; American Cyanamid, 1990).

Metal dithiocarbamates (e.g., zinc dibutyldithiocarbamate), when used as stabilizers in rubber and ethylene propylenediene terpolymers, have been found to form the equivalent nitrosamine. This occurs both spontaneously in the additive *per se*, and when present in the polymer. The chemistry of formation is not known, but high temperatures are not required. To our knowledge no information exists on nitrosamine formation, either qualitatively or quantitatively, for the polypropylene process. Many n-nitroso compounds are carcinogenic in animals, but a direct relationship between human exposure to low levels of n-nitrosamines and the incidence of human cancers has not been demonstrated (Tomatis, 1990).

Fillers: Clays and talc are frequently used in polypropylene production. Long-term airborne exposure to these agents is associated with lung fibrosis and pleural sclerosis but not with carcinogenic activity (IARC, 1987a). Some talcs have been found to be contaminated with tremolite, a form of asbestos (IARC, 1987a).

3.3 MUTAGENICITY STUDIES

Until recently there has been no published information concerning the mutagenicity of polypropylene. Exxon, (1988, unpublished) studied the mutagenicity potential of various prepared samples based on the diluent production process. These consisted of a post-reactor polymer, a fume condensate from the polymer extruder, and a finished polymer containing the following additives: Nirez V2044, Polygard/Nugard P, Armostat 410, UV-cheran-104, BHT, DSTDP, DLTPD, and erucamide (cis-13-docosenamide). The polymer samples were extracted with dichloromethane. The residue remaining after dichloromethane extraction was suspended in dimethyl sulfoxide (DMSO). The fume condensate was collected in a liquid nitrogen trap and dissolved directly in DMSO. The materials were tested in *Salmonella* assays, with or without metabolic activation, and in *in vivo* mammalian bone marrow micronucleus assays. No mutagenic response was seen for any sample in any of the four *Salmonella* strains or systems used, nor did any activity occur in the mouse micronucleus assays. A small, but nonsignificant, elevation in reversion frequency was noted with the postreactor polymer extract in two bacterial test strains. It was concluded that no mutagenic activity is associated with either the chemicals used in the polypropylene heavy diluent production process or polypropylene samples derived during manufacture.

Recently, concentrated ethanol extracts were used derived from polypropylene in a variety of genotoxicity studies comprising the mouse lymphoma (ML), chromosomal aberrations in chinese hamster ovary cells assay (CHO), and unscheduled DNA synthesis (UDS) on rat hepatocytes. The ML and CHO assays were performed with and without S-9 metabolic activation. Results of all studies were negative (Mostrocco et al, 1994).

3.4 AGENTS ASSOCIATED WITH DIGESTIVE TRACT CANCER

Agents which initiate colorectal cancer in experimental animals e.g., 1,2-dimethyl hydrazine, nitrosomethyl urea, and nitrosomethyl nitroguanide (NTP, 1992) are not used in the production of polypropylene. The possibility of indirect action by bioactivation of an agent to become a carcinogen within the large bowel has been considered, but no material present in the polypropylene production process acting through this suggested mechanism has been identified.

3.5 EVALUATION

There is no evidence that polypropylene causes mutagenic or carcinogenic activity in isolated mammalian cells or experimental animals. Moreover an evaluation of the additives and process agents used in polypropylene manufacturing indicates no obvious carcinogenic agent.

SECTION 4. TUMOURS OF THE COLON AND RECTUM IN MAN

4.1 BACKGROUND

The colon and rectum are part of the gastrointestinal tract. The chief functions of the colon and rectum are to absorb water and to store and eliminate waste, although remaining material received from the small intestine may be converted by colonic bacteria into vitamins. Peristalsis moves the faecal matter through the colon and rectum. The colon and rectum, also known as the large bowel, are divided into a number of parts. It begins at the caecum, which connects the small intestine with the colon, followed by the ascending, transverse, descending and sigmoid sections of the colon. This last section connects to the rectum.

The large bowel is approximately 1.5 meters (5 feet) in length. The wall of the large bowel is composed of four layers of tissue: mucosa, submucosa, *muscularis externa*, and serosa. The mucosa produces mucus to lubricate and protect the inner surface of the bowel. The submucosa contains blood vessels, lymph vessels, nerves, and mucus-producing glands. The *muscularis externa* is composed of two layers of muscle fibres, one running lengthwise and one encircling the colon and rectum. The final layer, the serosa, contains cells which produce lubrication for the outer layer of the bowel (NCI, 1992).

4.2 POLYPS

Polyps are growths from the mucosa of the large bowel into the lumen. There are two major categories of polyps, hyperplastic and adenomatous (Fenoglio-Preiser, 1988). Hyperplastic polyps are non-neoplastic and assumed to be of no major clinical significance (Cohen *et al*, 1989). Adenomatous polyps, however, are believed to increase the risk of colorectal cancers (Cohen *et al*, 1989; Simons *et al*, 1992). There are three types of adenomatous polyps based on tissue structure: tubular, villous, and tubulovillous. Tubular adenomatous polyps are the most common and least likely to produce cancer; villous type polyps are the least common but most likely to produce cancer. Tubulovillous polyps have a risk and prevalence between that of the other two types (Cohen *et al*, 1989). Size of polyps appears to be an independent risk factor for all three types of adenomas, even large tubular adenomatous polyps have an increased likelihood of being cancerous (O'Brien *et al*, 1990).

Although rare in young people, the occurrence of polyps increases with age (Rex *et al*, 1991). It is estimated that between 30 to 40% of adults 50 years and older have polyps (Rex *et al*, 1991).

Autopsy studies have shown that the prevalence of polyps is correlated with the incidence of colorectal cancer (Clark *et al*, 1985). Although site distribution within the colon has been found to differ between polyps and cancers, when restricted to large polyps (diameter >7 mm), the site distributions more closely parallel each other (Clark *et al*, 1985). Polyps have been reported more often in men than women, but the incidence of colorectal cancer does not reflect large sex differences (Chow *et al*, 1991).

Since it is believed that most colorectal cancers arise from adenomatous polyps, removing such polyps presumably will reduce the occurrence of and mortality from colorectal cancer. Until recently, this view was a result of one study (Gilbertsen, 1974). For many the evidence supporting this view has not been convincing (Beck *et al*, 1991; Winawer *et al*, 1991a); however, recent studies have provided support for the view that eliminating adenomatous polyps reduces mortality from colorectal cancer (Atkin *et al*, 1992; Newcombe *et al*, 1992; Selby *et al*, 1992; Simons *et al*, 1992; Mandel *et al*, 1993). Although precise figures are not available, it has been estimated that up to 5 - 15% of adenomatous polyps become cancerous depending upon the tissue structure and size (Welin *et al*, 1963; Stryker *et al*, 1987; Murakami *et al*, 1990).

Although there has been limited research into environmental risk factors for adenomatous polyps, they appear to be similar to those identified for colorectal cancer (Winawer and Shike, 1992; Sandler *et al*, 1993). Diets low in fibre and high in saturated fat from meat and dairy products have been linked with increased risk of adenomatous polyps (Giovannucci *et al*, 1992; Winawer and Shike, 1992; Sandler *et al*, 1993).

One study has reported an association of polyps with asbestos exposure (Neugut *et al*, 1991). This may be of importance in this context since asbestos has been detected in some polypropylene manufacturing units (Acquavella *et al*, 1991) (cf Section 5.2).

4.3 COLORECTAL CANCER

The development of colorectal cancer is a complex multistage process starting with genetic and environmental factors that initiate and promote mucosal cell hyperproliferation to precursor adenomatous polyps, to malignant transformation, and finally to adenocarcinoma (Winawer *et al*, 1991b). Once developed, the cancer can grow through the bowel wall and extend into the surrounding organs. Virtually all colorectal cancers are adenocarcinomas, although a few originate from connective tissues (sarcomas) or lymphatic tissues (lymphomas) (Cohen *et al*, 1989).

Colorectal cancer is rare in people under the age of 50. The average age at diagnosis is over 60 (Ries *et al*, 1991). The five-year relative survival rate regardless of stage of disease is 57% for colon cancer and 53% for rectal cancer (Ries *et al*, 1991). The earlier the stage of disease at diagnosis, the better the survival. Localized colorectal cancers have a five-year relative survival rate of approximately 90% (Ries *et al*, 1991). There are a number of staging systems in use, all based on the degree to which the tumour has invaded the bowel wall starting with an *in situ* cancer and ending with distant metastasis (Cohen *et al*, 1989). The primary treatment for colorectal cancer is surgical removal of the tumour; if done at an early stage it is often curative (Cohen *et al*, 1989).

The highest incidence rates in the world for both colon and rectum cancer are found in the United States followed by the countries of Western Europe (Tomatis, 1990; Whelan *et al*, 1990). In industrialized nations, colorectal cancer ranks second in frequency among cancers (Tomatis, 1990; Boring *et al*, 1992). In the United States alone, 158,000 people developed colorectal cancer and 60,000 died from these tumours in 1991 (Boring *et al*, 1992). Rates for colorectal cancer are low in Africa, Asia, and Latin America. Colon cancer incidence rates in the United States have increased 15% between 1976 and 1987 among white men and 3% among white women (Chow *et al*, 1991). Rectal cancer rates have remained steady during the 1976 to 1987 period in the United States (Chow *et al*, 1991), but in Western European countries increases and decreases have been observed (Tomatis, 1990).

The known risk factors for colorectal cancer are primarily genetic or familial such as familial polyposis, a rare genetic disorder in which hundreds of polyps can appear relatively early in life; or Gardner's syndrome, another genetic condition which produces polyps in the colon and other parts of the body (Cohen *et al*, 1989; Winawer *et al* 1991b). Other definite risk factors are familial colorectal cancer syndrome, hereditary adenocarcinomatosis syndrome, and family history of colorectal cancer (Cohen *et al*, 1989; Winawer *et al*, 1991b). Inflammatory bowel disease such as ulcerative colitis and granulomatous colitis (Crohn's disease) are also high-risk conditions for this cancer.

Dietary factors such as increased fat and meat intake and decreased fibre consumption have been linked to elevated risks for these cancers, but the results of studies have not always been consistent (Willett, 1989; Nomura, 1990). There is mounting evidence that increased physical activity may reduce colorectal cancer risk (Bartram and Wynder 1989; Nomura, 1990). Recent work has also suggested a protective role for aspirin in both epidemiologic and animal studies (Thun *et al*, 1991; Marnett, 1992; Suh *et al*, 1993). Occupation is thought to contribute little to the etiology of colorectal cancer (Schottenfeld and Winawer, 1982; Neugut and Wylie, 1987; Willett, 1989), although elevated colorectal cancer risks have been reported for asbestos-exposed workers (Doll

and Peto, 1987), automotive wood model and pattern makers (Swanson *et al*, 1985) and, more recently, workers exposed to ethyl acrylate and methyl methacrylate (Walker *et al*, 1991).

4.4 SCREENING

The rationale for screening is predicated on the view that most colorectal cancers develop in a slow and orderly progression from normal colonic mucosa to adenomatous polyps, to early cancer (curable by surgery), and finally to advanced (incurable) cancer (Ransohoff and Lang, 1991). The point of screening is to identify and remove cancer in its early stages (and also adenomatous polyps larger than 1 cm in diameter) (Stryker *et al*, 1987). However, there is no consensus view on screening. Recommendations on time intervals for and methods of screening in the general population vary both within and between Western Europe and the United States (Ransohoff and Lang, 1991; Winawer *et al*, 1991a). There is agreement on the need for screening of high-risk individuals with genetic and familial conditions and inflammatory bowel disease (Cohen *et al*, 1989; Ransohoff and Lang, 1991; Winawer *et al*, 1991a). Recommendations from medical organizations vary for the general (asymptomatic) population because there is no convincing evidence from a randomized controlled trial that screening reduces mortality from colorectal cancer for such individuals (Ransohoff and Lang, 1991), although a recent randomised trial of a rehydrated faecal occult blood test did provide evidence for a reduction in colorectal cancer mortality (Mandel *et al*, 1993).

Most screening programs include one or more of the following procedures: digital rectal examination, faecal occult blood test, sigmoidoscopy and colonoscopy (NCI, 1991; Ransohoff and Lang, 1991; Winawer *et al*, 1991a).

4.4.1 Digital rectal examination

This simple procedure is often used in conjunction with other screening tests. Approximately 10% of all colorectal cancers develop within 10 cm from the anus and can be detected by this examination (Winawer *et al*, 1991a). It is inexpensive and easy to perform.

4.4.2 Faecal occult blood test

In most screening programs this test is recommended to be done every year in individuals starting at age 50. It should be kept in mind, however, this is a test for blood in the stool and not cancer. A number of diseases can produce a false positive result such as haemorrhoids, ulcers, and diverticulosis, along with certain foods (Ransohoff and Lang, 1991; Winawer *et al*, 1991a). False

positive rates are high, which is a significant problem if this test is used on large number of individuals, since a positive test must be followed-up by more expensive and invasive diagnostic tests. False negative results are also a problem, as some cancers bleed intermittently, little, or not at all (Cohen *et al*, 1989; Ahlquist *et al*, 1993). The recent reduction in risk of colorectal cancer mortality reported by Mandel *et al* (1993) using rehydrated slides indicates this method may be of use, although approximately 97 out of 100 positive slides were false positives.

4.4.3 Sigmoidoscopy

There are two types of sigmoidoscopies: rigid and flexible. The former is the older version which is less expensive, penetrates to only about 25 cm, and is less comfortable for the patient (Winawer *et al*, 1991a). The flexible sigmoidoscopy, although more expensive, can penetrate up to 60 cm (reaching the splenic flexure) and is better tolerated by patients (Winawer *et al*, 1991a; Ransohoff and Lang, 1993). Approximately 50 to 60% of the colorectal cancers occur in the area of the colon and rectum examined by the flexible sigmoidoscope (Cohen *et al*, 1989; Winawer *et al*, 1991a). Combining a sigmoidoscopy with a double-contrast barium enema is a reliable and relatively inexpensive method to examine the entire colon (Eddy, 1990).

4.4.4 Colonoscopy

Another endoscopic instrument, the colonoscope, is being used experimentally in some screening programs (Rex *et al*, 1991). This instrument can examine the entire length of the large bowel (1.5 meters) from the anus to the caecum. Colonoscopy, however, is primarily used for diagnostic purposes after a symptomatic individual has undergone a number of less invasive and expensive procedures. Cost is a serious consideration. In the United States, a colonoscopy can range from \$500 to \$1,000, since it requires a skilled endoscopist and intravenous sedation; whereas a sigmoidoscopy, which is conducted with the patient awake, ranges from \$50 to \$100 (Ransohoff and Lang, 1991). This procedure carries with it some risk of perforation, but in the hands of a skilled endoscopist it is very low (Wayne *et al*, 1990).

Colonoscopy (and flexible sigmoidoscopy) can be simultaneously diagnostic and therapeutic since adenomatous polyps and early stage cancers can be removed using this instrument (Cohen *et al*, 1989; Ransohoff and Lang, 1991, 1993; Winawer *et al*, 1991a). For patients at high risk of colorectal cancer, colonoscopy is used as a screening tool on a regular basis. When compared with other screening and diagnostic techniques colonoscopy has been demonstrated to be the most accurate and reliable method for identification of tumours in the colon (Dudley *et al*, 1987; Irvine *et al*, 1988; Cohen *et al*, 1989; Winawer *et al*, 1991a).

4.5 OTHER TESTS

A number of blood tests have been developed to detect colorectal cancer such as the carcinoembryonic antigen (CEA) test and the carbohydrate 19-9 (CA 19-9) test. Both these and other blood assays have been found unreliable as indicators of cancer and are used in conjunction with other tests primarily in monitoring for recurrence among patients who have had colorectal cancer (Cohen *et al*, 1989; NCI, 1992). Recently, the efficiency of the CEA test as a monitor for recurrence of colorectal cancer has been questioned (Moertel *et al*, 1993).

4.6 EVALUATION

Of all the screening and diagnostic techniques reviewed, faecal occult and other blood tests are not effective due to the relatively high rates of false positives and negatives. Colonoscopy is the most thorough and accurate method for the detection of colorectal cancer and polyps and is a useful method for high-risk groups; flexible sigmoidoscopy can also be effective, particularly when combined with a barium enema to examine the entire bowel, however, in a low-risk population it has not yet been shown that these methods are cost effective. Blood tests are still at the experimental phase.

SECTION 5. EPIDEMIOLOGIC STUDIES

Concern about the possibility of an increased risk of colorectal cancer in workers involved in the manufacture, processing, and use of polypropylene is mainly a result of two series of investigations, the first from a synthetic fibre production unit of a carpet manufacturing operation in Canada, which used polypropylene among other products, and the second from a polypropylene-producing plant in the United States. Recently, results from epidemiologic studies of polypropylene-producing plants in Germany and other countries have become available.

5.1. CANADIAN STUDIES

Vobecky and coworkers (1978) first identified a cluster of 5 workers with colorectal cancer employed in the same synthetic fibre unit of a carpet manufacturing plant in Quebec, Canada. All cases were diagnosed within an 18 month period from 1974 to 1975. Three of the 5 workers were under 50 years of age at diagnosis. After the initial identification of the cluster, the authors extended their study to include all new cases of colorectal cancer for the years 1965 to 1975 in the Eastern Townships of Quebec, where the plant is located. They interviewed the patients or their next of kin to obtain information on employment. A comparison was made of the proportion of male carpet factory workers with colorectal cancer to the proportion of men with this cancer from other occupations in the region. The proportion of male carpet factory workers with colorectal cancer was significantly greater than that of the other occupations for the period 1971 to 1975. No information was provided on the nature and the importance of the workers' exposures.

In an attempt to refine their initial observation, the authors conducted a case-control study of colorectal cancer in a 13-county region of Quebec for the years 1965 to 1976 (Vobecky *et al*, 1983). Two hundred seven patients (103 men and 104 women) with colorectal cancer were identified in the 24 communities that formed the likely labour pool for the carpet factory. A similar number of controls was chosen from the same 24 communities, matched on age, sex, and place of residence at time of diagnosis. The original cluster of 5 cases was included in the analysis. Among men there was a significant excess of cases having been employed at the carpet factory (relative risk (RR) = 2.33; $P < 0.01$ [calculated from the authors' Table 1]). There was no excess of colorectal cancer among women employed in the factory (RR = 0.55 [calculated from Table 1]). The risk for colorectal cancer was higher among men under age 60 than those aged 60 or over. Other potential risk factors for colorectal cancer were examined in the study such as family history, medical history, bowel habits and smoking. Family history of colorectal cancer was not a risk factor. The occurrence of appendectomy and haemorrhoidectomy was significantly higher among men, while

cholecystectomy was significantly lower among women. Long-term severe constipation was reported significantly more often by cases than controls. The association with employment in the carpet factory was not adjusted for these statistically significant non-occupational risk factors. In this report also no information was provided on workers' exposures.

In the third investigation Vobecky *et al* (1984) performed another case-control study, this time choosing cases and controls from the carpet plant employees. This allowed investigators to focus on particular plant processes or work areas that may relate to risk. The time period for case ascertainment was expanded (1965 to 1979), during which 37 male and 6 female carpet manufacturing employees were diagnosed with colorectal cancer. Each case was matched to three controls according to sex, age, date of employment start, and duration employment. Because of the small number of cases, women were excluded from analysis. Company records were used for the occupational data. The original 5 cases that made up the initial observation were not excluded from the analysis. When combined, workers involved in the extrusion D department (solubilisation of acetate), the extrusion TM department (extrusion of triacetate and polypropylene), and textiles (undefined) were at elevated risk (RR = 3.72; $P < 0.005$). Taken separately the RR in the extrusion D department was 1.75, for the extrusion TM department, 2.74, and for textiles, 2.95. Only the RR for work in textiles was statistically significant ($P < 0.03$). It was in the TM extrusion process that polypropylene was used along with cellulose triacetate (4 cases). Risks were also calculated for work in different plant buildings. The only statistically significant RR was for work in building 3 (RR = 4.13; $P < 0.02$) where extrusion D department was located (5 cases). The RR for building 4, where extrusion TM took place (and where polypropylene was used) was 2.28 and non-significant. In their discussion of the results, the authors suggest that polypropylene was a principal suspect since in their view many of the cancers occurred among individuals working in building 4, although no evidence was provided to link this building or polypropylene *per se* to the cases. Increased colorectal cancer risks were also observed for workers employed in other work sites and processes and in buildings not associated with polypropylene use.

A new retrospective cohort mortality study on the same plant of carpet manufacturing workers has recently been completed (Goldberg and Theriault, 1994a). The cohort consisted of 7,487 men and 2,624 women who worked at least one year at the plant from 1947 to 1977 with mortality follow-up through 1986. The standardized mortality ratio (SMR) for colorectal cancer among male employees was significantly lower than expected (SMR=0.69; 95% Confidence Interval (CI):0.52-0.92), among women employees mortality was close to expected (SMR=1.02; 95% CI:0.57-1.69). In a further refinement, Goldberg and Theriault performed a nested case-control study within the cohort of male carpet making workers adding the incidence data from the Quebec Tumour Registry for the years 1975 through 1987 to the deaths from colorectal cancer (Goldberg and Theriault, 1994b). This study

extends by 8 years the case ascertainment period of the final study by Vobecky and colleagues (1984). An excess risk of colorectal cancer associated with employment in the combined polypropylene and cellulose triacetate extrusion unit was observed, particularly for 5 years or longer (Odds Ratio (OR) = 5.81; 95% CI:0.98-34.46). However, of the 4 cases in this exposure category, 3 were from the original cluster identified earlier by Vobecky *et al* (1978). These original cancers were not excluded from the analysis. Hence, their study was not an independent test the hypothesis as it depended on the original index cases. In a strict statistical sense, when an unexpected finding is observed, further studies to check the association must exclude the index cases since it precludes a legitimate testing of the null-hypothesis (Doll, 1984; Fleming *et al*, 1991). The authors themselves conclude that their updated analysis does not provide an independent confirmation of Vobecky's finding, as it is primarily based on his original cases.

5.2 UNITED STATES STUDIES

In 1988, Acquavella and associates published the results of a cancer incidence follow-up study on a small cohort of workers employed in polypropylene production at an Exxon plant in Baytown, Texas (Acquavella *et al*, 1988). This study was initiated as a result of complaints by some workers of an excess of colorectal cancers. The study began in 1986 and included all employees who worked for 6 months or longer between January, 1960 and September, 1985. After reviewing personnel records and other sources, and restricting the analysis to workers with 10 or more years since first employment, a total of 335 male employees were identified for the incidence follow-up study. An increased number of colorectal cancer cases was observed (7 cases vs. 1.26 expected), with a standardized incidence ratio (SIR) of 5.6 (95% CI: 2.2-11.5). Of the 7 cases, 5 were diagnosed during a 5-month period in 1985 with 4 cases being between 55 and 60 years of age at diagnosis. The association was limited to mechanical (SIR=10.6; 95% CI: 3.4-24.7) and process workers (SIR=5.0; 95% CI: 0.6-17.8), and was not observed among office workers (0 cases vs. 0.39 expected). All 7 workers with colorectal cancer were diagnosed at least 20 years after starting work on the polypropylene unit.

In an attempt to further evaluate colorectal cancer excess among polypropylene manufacturing workers, Acquavella and Owen (1990) studied Exxon workers employed in polypropylene pilot plants in Louisiana and Texas. The cohort was comprised of 183 men who worked for 6 months or longer between 1956 and 1962 in the Louisiana plant or between 1959 and 1977 in the Texas plant. The workers were followed for colorectal cancer occurrence until December 31, 1985. No excess was observed. Three colorectal cancers were identified among the workers compared with 3.3 expected (SIR=0.9; 90% CI: 0.3-2.3). Further examination of cancer risk by type of job

(mechanic, process, and laboratory), duration of employment, and latency showed no association with risk.

As a result of the Baytown plant finding, Acquavella and colleagues (1989b) examined 213 volunteers among current and former employees of the polypropylene unit for colorectal polyps. After sigmoidoscopic examination, the Baytown workers were found to have a polyp prevalence rate 38% higher than a control group recruited from a gastroenterology clinic. Members of this control group may have been screened before, since 33% of the controls reported prior history of polyps. When analysis was restricted to larger polyps (greater than 0.5cm diameter) there was a 59% higher prevalence of polyps in the polypropylene unit group. Mechanical and process workers had a higher prevalence of polyps than white-collar workers at the plant. Use of 90% confidence intervals was unorthodox and allowed for a lower threshold to claim a statistically significant finding.

In the final paper of the series (Acquavella *et al*, 1991), polypropylene production workers from the Baytown plant found to have adenomatous polyps were studied using a nested case-control study design. Workers with polyps (N=24) were the cases and workers without polyps (N=72), the controls. Exposure assessment was based on detailed retrospective examination of industrial hygiene records and interviews of study subjects. The polyp cases had higher exposure scores than the controls for the pre-extrusion base plant polymer plus additives subgroup (OR=4.8; 90% CI: 1.5-15.3). Examination of case-control differences by job category or polypropylene plant area did not provide any additional information. The polyp cases also experienced greater exposure to asbestos (OR=2.7; 90% CI:0.9-8.7), but when exposures related to polypropylene production were controlled in the analysis a relationship between asbestos exposure and polyps was not observed. Again in this analysis the more liberal 90% confidence intervals were used.

Since the publication of the Acquavella studies, Exxon researchers have continued follow-up of the Baytown Plant cohort for colorectal cancer incidence (Lewis *et al*, 1994a). Results of the follow-up study, which now covers the time period 1960-1992, indicate that 9 colorectal cancers have been identified among the original cohort of Exxon polypropylene production workers compared with 3.8 expected based on Texas incidence rates and a 10-year latency period for a SIR of 2.4 (95% CI: 1.1-4.5). However, as a result of screening activities initiated by Exxon among these workers, 3 adenocarcinomas *in situ* were also identified. To take into consideration these 3 *in situ* cancers, 5 years of disease-free time was added to the time at risk for each screened worker in the Baytown cohort using the method of Hoar *et al* (1986) and Tilley *et al* (1990). This screening-adjusted SIR for colorectal cancer was 2.6 (95%CI: 1.4-4.6) based on 12 cancers. Seven of the 12 colorectal cancer cases were from the initial study that initiated the hypothesis (Acquavella *et al*, 1988).

If we eliminate these original cluster cases the excess risk is eliminated (SIR= 1.10; 95% CI:0.36-2.57). Of special note was the occurrence of colorectal cancer for the time period after the Acquavella study (1985 to 1992) where no elevation of risk (SIR = 0.8, 95% CI: 0.1-2.9) was observed. If the 3 *in situ* cancers that were identified in this period are included, the SIR is 1.5 (95% CI: 0.5-3.5). In brief, the new follow-up period (1985-1992), showed no statistically significant excess of colorectal cancer in the Baytown cohort (Lewis *et al*, 1994a).

A second screening study for polyps has recently been completed among Baytown polypropylene production workers, which attempted to remedy any possible shortcoming of the control group used in the first study (Lewis *et al*, 1994b). After having undergone a first screening with negative results, polypropylene production workers and control subjects were again screened approximately 3 years after the initial examination. Although the polypropylene workers had a higher prevalence of adenomatous polyps than their controls (adjusted RR=1.8;90% CI:0.7-4.8), the difference was not statistically significant. Moreover, engineers, chemists and administrative personnel at the plant had a higher RR (2.0;90% CI:0.6-7.3) than the process and mechanical workers, which is opposite of what was observed in the first polyp investigation (Acquavella *et al*, 1989b).

5.3 GERMAN STUDY

Results from an investigation of colorectal cancer among polypropylene production workers at three Hoechst plants in Germany have recently become available (Kaleja and Horbach, 1994). A total of 640 male workers employed from 1956 to 1991 were followed for colorectal cancer through 1992. All workers, employed or retired, were contacted by mail questionnaire with telephone follow-up. All reports of cancer were verified by the workers' physician. Three colorectal cancers were identified among the employees. To calculate the expected number of colorectal cancers, age- and calendar year-specific rates from the Saarland Cancer Registry were used as no cancer registry exists for the region where the plants are located. In this cohort of workers, 3 cases of colorectal cancer were observed compared with 4.0 expected for a standardized incidence ratio of 0.75 (95%CI:0.15-2.19).

5.4 OTHER STUDIES

Findings from a cohort study of polypropylene production workers at two Shell plants in the United Kingdom have recently been made available (Bouskill, 1994). Three hundred and eighty four employees were followed for colorectal cancer mortality from 1972 to 1992. There were no observed deaths from colorectal cancer in this cohort compared with 1.36 expected. One case of colorectal cancer (in a 72 year old man) has been observed compared with an expected incidence of 2.28 based on data supplied by the UK Office of Population Census and Surveys.

There are other epidemiologic studies, which although not initiated to evaluate the polypropylene and colorectal cancer hypothesis, provide relevant information. From Australia, data on polypropylene production workers are available from a large-scale follow-up study of that country's 15,000 petroleum workers (Christie *et al*, 1991). Of these employees, there were 128 polypropylene production workers who were followed for cancer incidence and mortality from 1980 to 1991. During the study period, one colorectal cancer case was identified compared with 0.5 expected (Bisby *et al*, 1992).

In a large-scale case-control study of risk factors for work-related cancers in the Montreal metropolitan area, 1979-1985, work exposure to 293 agents was evaluated, including polypropylene (Siemiatycki, 1991). The occupational histories of 754 patients with colorectal cancer and over 2,000 controls were examined by industrial hygienists for potential exposure to polypropylene and other factors. No colorectal cancer cases were found among the workers exposed to polypropylene compared with 5 exposed workers among the controls.

5.5 DISCUSSION

Of the three studies by Vobecky and his coworkers the initial study was little more than a cancer cluster report with relatively crude comparisons made between the carpet plant employees and other occupations for occurrence of colorectal cancer (Wen and Tsai, 1979). The second study, a case-control study, attempted to expand the study base to determine whether colorectal cancers from the region where the carpet plant was located were over-represented with employees from the carpet manufacturing plant and to evaluate other possible risk factors for colorectal cancer that may explain the excess risk. The handling of synthetic fibre was significantly more common among the cases than the controls, as were severe constipation, appendectomy, and haemorrhoidectomy, which were not adjusted for in the analysis. In the third study, they attempted to uncover processes or work areas that may be linked to increased risk. Of the work areas, only textiles was associated with a significantly increased risk. Employment in extrusion TM, which used polypropylene, was not significantly associated with risk. Risk was examined for employment by building with a significantly elevated RR associated with building 3, not building 4 where the extrusion TM process was located. It should be noted that after their initial report each study by Vobecky *et al* included the original cluster of cases and were not independent tests of the hypothesis that colorectal cancer was linked to polypropylene.

In the new analysis of the carpet plant employees (Goldberg and Theriault, 1994b) the cases originally identified by Vobecky also account for the excess risk. In the category of exposure associated with an increased risk, employment for 5 or more years in the polypropylene and

cellulose triacetate extrusion unit, 3 of the 4 cases were from the original Vobecky study. Thus, Goldberg and Theriault were forced to conclude that their findings are dependent on the original cluster of cases reported by Vobecky *et al.* In fact, since the end of the ascertainment period of the final Vobecky study, in 1979 (Vobecky *et al.*, 1984), only one additional colorectal cancer case was identified during the period 1980-1987 (Theriault and Goldberg, 1991). Hence, their study did not provide evidence for a continuation of risk among the carpet manufacturing workers. In the studies by Vobecky and colleagues (1978, 1983, 1984) and by Goldberg and Theriault (1994a,b) no results are presented to indicate that exposure to polypropylene was any more common than exposure to the other agents such as cellulose triacetate and cellulose acetate. Finally, none of the studies of the carpet factory workers adjusted for the potentially confounding effects of non-occupational risk factors for colorectal cancer such as diet, family history of colorectal diseases and cancer, and physical activity.

The initial report by Acquavella *et al.* (1988) used dated comparison rates (from 1969-1971) which did not reflect the increase over time in colon cancer rates in the United States (Ries *et al.*, 1991). Exxon researchers have since used the U.S. rates (adjusted for calendar year) from the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Program, which reduced the 5.6-fold risk ratio for colorectal cancer to 3.9-fold (95% CI:1.6-8.5), although the elevation remained statistically significant. More importantly, however, the initial Acquavella paper is dependent on a cluster of 5 cases diagnosed within a 5 month period, indicating a chance occurrence. In addition, the study of polypropylene pilot plant workers (Acquavella and Owen, 1990) in Texas and Louisiana showed no increased risk for colorectal cancer. Further follow-up of the Baytown cohort (1985-1992) showed no indication of the large initial excess risk first reported by Acquavella and is consistent with the hypothesis of no association between colorectal cancer and polypropylene production (Lewis *et al.*, 1994a). However, this lack of colorectal cancer risk for the new follow-up period must take into consideration the screening that the Baytown workers have undergone. To date, approximately 50% of the cohort have had colorectal screening using a combination of barium enema, flexible sigmoidoscopy or colonoscopy depending upon the clinical indications (Lewis *et al.*, 1994b). The effect of removing polyps is difficult to measure, but a possible influence on risk during the new follow-up period cannot be excluded. However, it should be noted that there was no similar screening process for the Canadian carpet plant workers.

The colorectal polyp screening study (Acquavella *et al.*, 1989b), which reported more and larger polyps among the Baytown Plant workers who volunteered to be screened, used a comparison group that appeared to have had previous screening. The authors may have made a comparison between the prevalence of polyps in the Baytown workers and the incidence of new polyps in the control group chosen from clinic patients. The physicians performing the sigmoidoscopies were not

blinded as to which patients were exposed workers and which were controls. These issues have been debated in the literature (Dougherty, 1990; Gibbs, 1990; Acquavella *et al*, 1990). The nested case-control study of workers with colorectal polyps at the Baytown Plant reported that exposure to the base plant polymer and to finishing additives was related to increased risk of polyps (Acquavella *et al*, 1991). Exposure to asbestos was also observed in this study but the levels apparently were low, and mortality reviews of the Baytown Plant cohort by Exxon researchers have revealed no deaths from asbestosis or mesothelioma (Lewis *et al*, personal communication). Although some talcs have been known to be contaminated with asbestos (IARC, 1987a), such talc was not apparently used at the Baytown plant. As in the Canadian studies, the potentially confounding effects of non-occupational risk factors such as diet, family history and previous medical conditions were not evaluated in any of the Exxon studies. Moreover, the recent polyp study of Baytown workers has failed to find a statistically significant excess among the polypropylene workers relative to controls (Lewis *et al*, 1994b).

The results for the Hoechst plants in Germany provide no evidence of an excess of colorectal cancer among polypropylene workers. Although a small study, the results support the findings from the Exxon pilot plants. The findings for Australian and British polypropylene production workers and for colorectal cancer cases from Montreal were also limited because of either few exposed subjects or limited follow-up, but they provided no evidence of an increased risk.

5.6 EVALUATION

The published and unpublished epidemiologic studies do not support a causal association between colorectal cancer and polypropylene production or use. In the Canadian studies by Vobecky a cluster of 5 cases diagnosed within 18 months initiated a series of investigations. No evidence was provided by Vobecky and colleagues to implicate polypropylene vis-à-vis the other agents used in the extrusion processes to which workers were exposed. The recent work by Goldberg and Theriault on this cohort of workers provides no evidence that initial excess of colorectal cancer among these workers is continuing, that is, their present finding depends entirely on the original Vobecky cluster of 5 cases and is not an independent test (as defined by Doll, 1984 and Fleming *et al*, 1991) of the hypothesis that polypropylene is related to colorectal cancer. For a test of a hypothesis to be independent it must exclude those observations that led to the hypothesis in the first place, to include those cases precludes a legitimate testing of the null-hypothesis.

In the first United States study, 5 of the 7 cases reported by Acquavella were diagnosed within a 5-month period, indicating, by the criteria of Fleming *et al* (1991), a frank cluster. The initial estimate of a 5.6-fold risk was inflated because of inappropriate comparison rates. After the initial Baytown

plant findings, a separate study of Exxon polypropylene production workers in two locations found no increase in risk (Acquavella and Owen 1990). The recent update of the Baytown cohort from 1985 through 1992 has reported no continuation of the excess of colorectal cancers initially observed by Acquavella (Lewis *et al*, 1994a). The first polyp screening study by Acquavella *et al* (1989b), which found an association among the polypropylene workers, especially mechanical and process workers, was potentially flawed by use of a control group with likely previous screening experience. This possible shortcoming was addressed in the new polyp screening study by Exxon investigators (Lewis *et al*, 1994b), which observed no significant increase of polyps among polypropylene workers. In fact, the white-collar workers had a higher prevalence of polyps than the mechanical and process employees, a finding opposite of the original screening study and not supportive of a work-related exposure.

Finally, the recent study of German polypropylene workers dating back to 1956 reported a lower risk of colorectal cancer than expected, and studies from Australia, the United Kingdom and Montreal showed no link with risk.

Taken as a whole, the epidemiologic studies do not provide evidence of a causal association, but rather of a cluster of a common cancer occurring in two separate plants, one in which polypropylene was manufactured and one in which polypropylene and a large number of other chemicals were used. Exclusion of the original cases that gave rise to the hypothesis eliminated the risk in recent update studies of these two employee populations. Further follow-up of the initial groups of workers has failed to provide any evidence of a continuation of the original colorectal cancer excesses, while other studies of polypropylene production workers have found no increase in risk.

SECTION 6. CONCLUSIONS

Polypropylene has been manufactured for more than 35 years. It is a widely used polymer with applications in food wrappings, medical packaging and appliances, building and automobile industries and in numerous consumer uses.

Polypropylene is a high molecular weight polymer that is chemically and biologically inert. There is no direct evidence that it causes mutagenic or carcinogenic activity in isolated mammalian cells or experimental animals. An evaluation of the additives and the process agents present in the manufacturing of polypropylene indicates no identifiable carcinogenic agent.

An excess of colorectal cancers initially observed at two plants located in North America represent space-time clusters of this common cancer. Recent updates of both the Canadian carpet manufacturing workers and the Baytown polypropylene production employees provide no evidence to indicate a continuation of risk after the initial clusters were reported. Other studies of polypropylene production workers in the United States, Germany, United Kingdom and Australia found no statistically significant increase in colorectal cancer incidence. A case-control study of work related cancers in Montreal (Canada) also observed no association between colorectal cancer and polypropylene.

The epidemiological and experimental data available to date do not support a causal relation between exposure to polypropylene and risk of colorectal cancer.

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

BIBLIOGRAPHY

- Acquavella J F, Douglass T S, and Philips S C. (1988). Evaluation of excess colorectal cancer incidence among workers in the manufacture of polypropylene. *J. Occup. Med.* 30, 438-442.
- Acquavella J F and Owen C V. (1990). Assessment of colorectal cancer incidence among polypropylene pilot plant employees. *J. Occup. Med.* 32, 127-130.
- Acquavella J F, Douglass T S and Hughes J I. (1989a). Factors associated with participation in an occupational program for colorectal cancer screening. *J. Occup. Med.* 31, 458-463.
- Acquavella J F, Douglass T S, Vernon S, Hughes J I and Thar W E. (1989b). Assessment of colorectal cancer screening outcomes among workers involved in polypropylene manufacture. *J. Occup. Med.* 31, 785-791.
- Acquavella J F, Vernon S W, Thar W E, Douglass T S, and Hughes J I. (1990). The authors reply (a letter). *J. Occup. Med.* 32, 1143-1144.
- Acquavella J F, Owen C V, Bird M G, Yarborough C M and Lynch J (1991). An adenomatous polyp case-control study to assess occupational risk factors following a workplace colorectal cancer cluster. *Am. J. Epidemiol.* 133, 357-367.
- Ahlquist D A, Wienand H S, Moertel C G, McGill D B, Loprinzi C L, O'Connell M J, Mailliard J A, Gerster J B, Pandya K and Ellefson R D. (1993). Accuracy of fecal occult blood screening for colorectal neoplasia. *JAMA*, 269, 1262-1267.
- American Cyanamid. (1990). Personal Communication to M G Bird, Exxon Biomedical Sciences, Inc.
- Atkin W S, Morson B C and Cuzick J. (1992). Long-term risk of colorectal cancer after excision of rectosigmoid adenomas. *N. Engl. J. Med.* 326, 658-662.
- Bartram H P and Wynder E L. (1989). Physical activity and colon cancer risk? Physiological considerations. *Am. J. Gastroenterol.* 84, 109-112.
- Beck K, Kronberg O and Fenger C. (1991). Adenomas and hyperplastic polyps in screening studies. *World J. Surg.* 15, 7-13.
- Bisby, J A, Adams G, Roberts M, Botham L, and Baade A. (1992). Health Watch, Ninth Annual Report. The Australian Institute of Petroleum Health Surveillance Program. Department of Public Health and Community Medicine, University of Melbourne.
- Bomhard E, Bremmer J N and Herbold B A. (1992). Review of the mutagenicity and genotoxicity of BHT. *Mutat. Res.* 227, 187-200.
- Boring C C, Squires T S and Tong T. (1992). *Cancer Statistics 1992*. American Cancer Society.
- Bouskill J. (1994). Absence of colorectal cancer risk among workers at a UK polypropylene production plant. (submitted for publication).
- Chow W-H, Devesa S S and Blot W J. (1991). Recent colon cancer incidence trends in the United States. *Cancer Causes Control* 2, 419-425.
- Ciliberti A, Maltoni C and Perino G. (1988). Long-Term carcinogenicity bioassays on propylene administered by inhalation to Sprague-Dawley rats and Swiss mice. *Ann. N. Y. Acad. Sci.* 534, 235-245.
- Clark J C, Collan Y, Eide T J, Estevar J, Ewen S, Gibbs N M, Jensen O M, Koskela E, MacLennan R, Simpson J G, Stalsberg H and Zaridze D G. (1985). Prevalence of polyps in an autopsy series from areas with varying incidence of large bowel cancer. *Int. J. Cancer* 36, 179-186.
- Christie D, Robinson K, Bordon I and Bisby J. (1991). A prospective study in the Australian petroleum industry. II. Incidence of cancer. *Br. J. Ind. Med.* 48, 511-514.
- Cohen A M, Shank B and Friedman M A. (1989). Colorectal cancer. In: DeVita VT Jr, Hellman S, Rosenberg S A (eds). *Cancer. Principles and Practice of Oncology*. 3rd ed. Lippincott: Philadelphia, 895-964.
- Doll R. (1984). Occupational Cancer: Problems in interpreting human evidence. *Ann. Occup. Hyg.*, 28, 291-305.
- Doll R and Peto J. (1987). Other asbestos-related neoplasms. In: Antman K, Aisner J (eds). *Asbestos-Related Malignancy*. Grune & Stratton, Inc: New York, 81-96.
- Dougherty J. (1990). Polypropylene and colorectal adenomas: searching for prevalence. *J. Occup. Med.* 32, 1141-1143.
- Dudley P, Weston P M T, and Williams N S. (1987). Colonoscopy or barium enema as initial investigation of colonic disease. *Lancet* ii, 549-551.
- Eddy D M. (1990). Screening for colorectal cancer. *Ann. Int. Med.*, 113, 373-384.
- Exxon (1988). POU-Colorectal Cancer, Toxicology Program, Technical Report MR.3DOX.88, Exxon Biomedical Sciences internal report.
- Exxon (1989). Technical Report 89MRL 125, Exxon Biomedical Sciences internal report.

- Fenoglio-Preiser C M. (1988). Hyperplastic polyps and mixed hyperplastic adenomatous polyps of the colon: Definitions. In: Steele G Jr, Winawer S J, Karr JP (eds). *Basic Clinical Perspectives of Colorectal Polyps and Cancer*. Alan R. Liss: New York, 3-12.
- Flemming L E, Ducatman A M and Shalat S L. (1991). Disease clusters: A central and ongoing role in occupational health. *J Occup. Med.* 33, 818-825.
- Garvin P J. (1990). Personal Communication, Amoco Corp., Chicago, Ill. (tests conducted at Industrial Bio-Test Laboratories by Standard Oil Co. 1964-1966).
- Gibbs G W. (1990). Colorectal cancer and polypropylene exposure: how good is the evidence? *J Occup. Med* 32, 1143.
- Gilbertsen V A. (1974). Proctosigmoidoscopy and polypectomy in reducing the incidence of rectal cancer. *Cancer* 34, 936-939.
- Giovannucci E, Stampfer M J, Colditz G, Rimm E B and Willett W C. (1992). Relationship of diet to risk of colorectal adenoma in men. *J. Natl. Cancer Inst.* 84, 91-98.
- Goldberg M S and Theriault G (1994a). A retrospective cohort of workers of a synthetic textile plant in Quebec. I. General Mortality. *Am. J. Ind. Med.* (in press).
- Goldberg M S and Theriault G (1994b). A retrospective cohort of workers of a synthetic textile plant in Quebec. II. Colorectal cancer mortality and incidence. *Am. J. Ind. Med.* (in press).
- Grasso P and Sharratt M. (1991). Role of persistent non-genotoxic damage in rodent cancer and relevance to humans. *Ann. Rev. Pharmacol. Toxicol.*, 31, 253-287.
- Hesterberg T W, McConnell E E, Miller W C, Hamilton R and Bunn W B. (1992). Pulmonary toxicity of inhaled polypropylene fibres in rats. *Fundam. Appl. Toxicol.* 19, 358-366.
- Hirase M, Shibata M, Hagiwara A, Imaida K and Ito N. (1981). Chronic toxicity of butylated hydroxytoluene in Wistar rats. *Fed. Cosmet. Toxicol.* 19, 147-151.
- Hoar S K, Bang K M, Tillett S, Rodriguez M, Cantor K F and Blair A. (1986). A screening for colorectal cancer and polyps among pattern makers. *J. Occup. Med.* 28, 704-708.
- IARC (International Agency for Research on Cancer). (1979). Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Monomers, Plastics, and Synthetic Elastomers, and Acrolein. IARC Monogr. Eval. Carcinog. Risk 19, 218-230.
- IARC (International Agency for Research on Cancer). (1986). Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some naturally occurring and synthetic food components, furocoumarins and ultraviolet radiation. IARC Monogr. Eval. Carcinog. Risk 40, 101-206.
- IARC (International Agency for Research on Cancer). (1987a). Evaluation of the Carcinogenic Risk of Chemicals to Humans: Silica and some silicates. IARC Monogr. Eval. Carcinog. Risk 42, 185-224.
- IARC (International Agency for Research on Cancer). (1987b). Evaluation of the Carcinogenic Risk of Chemicals to Humans: Overall evaluation of carcinogenicity. IARC Monogr. Eval. Carcinog. Risk, Supplement 7.
- IARC (International Agency for Research on Cancer). (1988). Evaluation of the Carcinogenic Risk of Chemicals to Humans: Alcohol drinking. IARC Monogr. Eval. Carcinog. Risk 44, 101-259.
- Inai K, Kobuke T, Nambu S, Takemoto T, Kou E, Nishina H, Fajihara M, Yonehara S, Suehiro S, Tsuya T, Horiuchi K and Tokuoka S. (1988). Hepatocellular tumorigenicity of butylated hydroxytoluene administered orally to B6C3F1 mice. *Jap. J. Cancer Res.* 79, 49-58.
- Irvine E J, O'Connor J, Frost R A, Shorvon P, Somers S, Stevenson G W and Hunt R H. (1988). Prospective comparison of double-contrast barium enema plus flexible sigmoidoscopy vs. colonoscopy in rectal bleeding: barium enema vs. colonoscopy in rectal bleeding. *Gut* 29, 1188-1193.
- Kaleja R and Horbach L. (1994). Colorectal cancer among polypropylene workers. (submitted for publication).
- Lee K P, Trochimowicz H J, and Reinhardt C V. (1985). Pulmonary responses of rats exposed to titanium dioxide (TiO₂) by inhalation for two years. *Tox. Appl. Pharmacol.* 79, 179 - 192.
- Lee K P, Kelly D P, Schneider P W and Trochimowicz H J. (1986). Inhalation toxicity study on rats exposed to titanium tetrachloride atmospheric hydrolysis products for two years. *Tox. Appl. Pharmacol.* 83, 305.
- Lefaux R. (1968). *Practical Toxicology of Plastics*, English Ed., CRC Press, Cleveland, Ohio.
- Lewis R J, Schnatter A R and Lerman S E (1994a). Colorectal incidence among polypropylene manufacturing workers: an update. *J Occup Med* (in press).
- Lewis R J, Lerman S E, Schnatter A R, Hughes J I and Vernon S. (1994b). Colorectal polyp incidence among polypropylene manufacturing workers. *J Occup Med* (in press).
- Mandel J S, Bond J H, Church T R, Snoven D C, Bradley M, Schuman L M and Ederer F. (1993). Reducing mortality from colorectal cancer by screening for faecal occult blood. *N. Eng. J. Med.* 328, 1365-1371.
- Marnett L J. (1992). Aspirin and the potential role of prostaglandins in colon cancer. *Cancer Res.* 52, 5575-5589.
- Moertel J S, Flemming T R, Macdonald J S, Hadler D G, Laurie J A and Tangen C. (1993). An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with rectal colon cancer. *JAMA* 270, 943-947.

- Montgomery R R. (1982). Polymers. In: Clayton G D, Clayton F E (eds). *Patty's Industrial Hygiene and Toxicology*, Vol 2c, 3rd rev ed. New York: John Wiley & Sons, 4252-4554.
- Moore G E. (1991). Foreign body carcinogenesis. *Cancer* 67, 2731-2732.
- Mastrocco F J, Przygoda R T, Bird M G, Myhr B C and Stringer D A. (1994). Evaluation of an ethanol extract of polypropylene in an *in vitro* genotoxicity battery. *Environ Mutagen Soc, Ann Mtg*, 7-12 May, Poster Presentation.
- Murakami R, Tsukuma H, Kanamori S, Imanishi K, Otani T, Nakanishi K, Fujimoto I and Oshima A. (1990). Natural history of colorectal polyps and the effect of polypectomy on the occurrence of subsequent cancer. *Int. J. Cancer*, 46, 154 - 164.
- Natta G, Pino P, Corradini O, Danusso F, Mantica E, Mazzanti G and Moraglio G. (1955). Crystalline high polymers of α -olefins. *J Amer Chem Soc* 77, 1708-1710.
- NCI (National Cancer Institute). (1992). Research Report: Cancer of the Colon and Rectum. National Cancer Institute NIH Pub No. 92-95.
- Neugut A I and Wylie P. (1987). Occupational cancers of the gastrointestinal tract. I. Colon, stomach, and esophagus. *State Art. Rev. Occup. Med.* 2, 109-135.
- Neugat A I, Murray T I, Garbowski G C, Treat M R, Forde K A, Wayne J D and Fenoglio-Preiser C. (1991). Association of asbestos exposure with colorectal adenomatous polyps and cancer. *J. Natl. Cancer Inst.* 83, 1827-1828.
- Newcombe P A, Norfleet R G, Storer B E, Swrawicz T S and Marcus P M. (1992). Screening sigmoidoscopy and colorectal cancer mortality. *J Natl. Cancer Inst.*, 84, 1572-1575.
- Nomura A. (1990). An international search for causative factors of colorectal cancer. *J. Natl. Cancer Inst.* 82, 894-895.
- NTP (National Toxicology Program) (1985). TR-272. Toxicology and Carcinogenesis studies of propylene (CAS n° 115-07-1) in F 344/N Rats and B6C3F₁ mice (Inhalation studies). Public Health Service, National Toxicology Program, National Institute for Environmental Health Sciences, Research Triangle Park, North Carolina.
- NTP (National Toxicology Program) (1992). Seventh Annual Report on Carcinogens, 1992. 2 vols. Public Health Service, National Toxicology Program, National Institute for Environmental Health Sciences, Research Triangle Park, North Carolina.
- O'Brien M J, Winawer S J, Zauber A G, Gottlieb L S *et al* (1990). The National polyps study: Patient and polyp characteristics associated with high-grade dysplasia in colorectal adenomas. *Gastroenterol.* 98, 371-379.
- Olsen P, Meyer O, Bille N and Wurtzen G. (1986). Carcinogenicity study on butylated hydroxytoluene (BHT) in Wistar rats exposed in utero. *Fed. Chem. Toxic.* 24, 1-12.
- Oohashi Y, Ishioka T, Wakabaya K and Kuwabara N. (1981). A study on carcinogenesis induced by degraded carageenan arising from squamous metaplasia of rat colorectum. *Cancer Lett.*, 14, 262-272.
- Oppenheimer B S, Oppenheimer E T, Danishefsky I, Stout A P and Eirich F R. (1955). Further studies of polymers as carcinogenic agents in animals. *Cancer Res.* 15, 333-340.
- Owen C V, Acquavella J A, Lynch J and Bird M G. (1992). An industrial hygiene methodology developed in support of a retrospective morbidity case-control study. *Amer. J. Hyg. Assoc.* 53, 540-547.
- Ransohoff D F and Lang C A. (1991). Current concepts: Screening for colorectal cancer. *N. Engl. J. Med.* 325, 37-41.
- Ransohoff D F and Lang C A. (1993). Sigmoidoscopic screening in the 1990's. *JAMA*, 269, 1278-1281.
- Rex D K, Lehman G A, Hawes R H, Ulbright T M and Smith J J. (1991). Screening colonoscopy in asymptomatic average-risk persons with negative faecal occult blood tests. *Gastroenterol.* 100, 64-67.
- Ries L A G, Hankey B F, Miller B A, Hartman A M and Edward B K. (1991). Cancer Statistics Review 1973-88. National Cancer Institute. NIH Pub. No. 91-2789.
- Rowe V K and McCollister S B. (1982). Alcohols. In: Clayton GD, Clayton FE (eds). *Patty's Industrial Hygiene and Toxicology*, Vol 2c, 3rd rev ed. New York: John Wiley & Sons, 4523-4708.
- Sandler R S, Lyles C M, Peipins L A, McAuliffe C A, Wools J T and Kupper L L. (1993). Diet and risk of colorectal adenomas: Macronutrients, cholesterol and fibres. *J. Nat. Cancer Inst.* 85, 887-891.
- Schottenfeld D and Winawer S J. (1982). Large intestine. In: Schottenfeld D, Fraumeni JF, Jr (eds). *Cancer Epidemiology and Prevention*. Philadelphia: W B Saunders, 703-727.
- Selby J V, Friedman G D, Queensberry C P and Weiss N S. (1992). A case-control study of screening sigmoidoscopy and mortality for colorectal cancer. *N. Eng. J. Med.*, 326, 653-657.
- Siemiatycki J. (1991). Risk factors for cancer in the workplace. Boca Raton, Florida, CRC Press.
- Simons B D, Morrison A J, Lev R and Yerholk-Oftedahl W. (1992). Relationship of polyps to cancer of the large intestine. *J. Natl. Cancer Inst.* 84, 962-966.
- Sobota P and Janas Z. (1984). Formation of a nitrogen-carbon bond from N₂ and CO: Influence of MgCl₂ on the N₂ reduction process in the system TiCl₄/Mg. *J. Organometallic Chem.* 276, 171-176.

- Stryker S J, Wolff B G, Culp C E, Libbe S D, Ilstrup D M and MacCarty R L. (1987). Natural history of untreated colonic polyps. *Gastroenterol.* 93, 1009-1013.
- Suh O, Mettlin C and Petrelli N J. (1993). Aspirin use, cancer and polyps of the large bowel. *Cancer* 72, 1171-1177.
- Swaen G M H, Bloemen, L J N, Twisk J, Scheffers T, Slangen J J M and Sturmans F. (1992). Mortality of workers exposed to acrylonitrile. *J. Occup. Med.* 34, 801-809.
- Swanson G M, Belle S H and Burrows R W. (1985). Colon cancer incidence among model makers and pattern makers in the automotive manufacturing industry. *J. Occup. Med.* 27, 567-569.
- Theriault G and Goldberg M S. (1991). Cancer mortality and the incidence of colorectal cancer among workers of the Celanese Drummondville, Quebec, synthetic textiles plant. Montreal, Quebec: School of Occupational Health, McGill University, Technical Report.
- Thun M J, Namboodiri M M and Heath C W Jr. (1991). Aspirin use and reduced risk of fatal colon cancer. *N. Engl. J. Med.* 325, 1593-1596.
- Tilley, B C, Johnson, C C, Schultz, L R, Buffler, P A and Joseph C L M. (1990). Risk of colorectal cancer among automotive pattern and model makers. *J Occup Med.*, 32, 541-546.
- Tomatis L. (1990). Cancer: Causes, Occurrence and Control. IARC Sci. Pub. No. 100, 57-59.
- Vainio H and Wilbourn J. (1992). Identification of carcinogens within the IARC monograph program. *Scand. J. Work Environ. Health* 18, Suppl. 1, 64-73.
- Vainio H, Waters M D and Norppa H. (1985). Mutagenicity of related organic solvents. *Scan. J. Work Environ. Health*, 11, 75-82.
- Vernon S W, Acquavella J F, Yarborough C M, Hughes J I and Thar W E. (1990). Reasons for participation and nonparticipation in a colorectal cancer screening program for a cohort of high risk polypropylene workers. *J. Occup. Med.* 32, 46-51.
- Vobecky J, Devroede G, Lacaille J and Watier A. (1978). An occupational group with a high risk of large bowel cancer. *Gastroenterol.* 75, 221-223.
- Vobecky J, Caro J and Devroede G. (1983). A case-control study of risk factors for large bowel carcinoma. *Cancer* 51, 1958-1963.
- Vobecky J, Devroede G and Caro J. (1984). Risk of large bowel cancer in synthetic fibre manufacture. *Cancer* 54, 2537-2542.
- Vollmar J and Ott G. (1961). Experimental tumour formation by surgical plastics. *Arch. Klin. Ghir.* 298, 729-736.
- Wagovich M J, Eng, V W S and Newmark H L. (1984). Calcium inhibits the damaging and compensatory proliferative effects of fatty acids on mouse colonic epithelium. *Cancer Lett.* 23, 253-258.
- Walker A M, Cohen A J, Laughlin J E, Rothman K J and DeFonso L R. (1991). Mortality from cancer of the colon or rectum among workers exposed to ethyl acrylate and methyl methacrylate. *Scand. J. Work Environ. Health* 17, 7-19.
- Wayne J, Lewis B and Yessayan S. (1990). Colonoscopy, a prospective report of complications. *Gastroentest. Endosc.* 36 (Suppl) A226.
- Welin S, Youker J, Spratt J S, Linnell F, Spjut H J, Johnson R E and Ackerman L V. (1963). The rates of pattern of growth of 375 tumours of the large intestine and rectum observed serially by double contrast enema study (Malmo technique). *Am J Roentgenol.*, 90, 673 - 687.
- Wen C-P and Tsai S-P. (1979). Doubts about carpet factory-induced colonic cancer (letter). *Gastroenterol.* 76, 656-657.
- Williams G M, Wang C X and Iatropoulos M F. (1990). Toxicity studies of butylated hydroxy anisole and butylated hydroxytoluene, II. Chronic feeding studies. *Fed. Cosmet. Toxicol.* 28 (12), 799-806.
- Winawer S J, Schottenfeld D and Flehinger B J. (1991a). Colorectal cancer screening. *J. Natl. Cancer Inst.* 83, 243-253.
- Winawer S J, Zauber A G, Stewart E and O'Brien M J. (1991b). The natural history of colorectal cancer. *Cancer* 67, 1143-1149.
- Winawer S J and Shike M. (1992). Dietary factors in colorectal cancer and their possible effects on earlier stages of hyperproliferation and adenoma formation. *J. Natl. Cancer Inst.* 84, 74-75.
- Whelan S L, Parkin D M and Masuyer E. (1990). Patterns of cancer in five continents. IARC Sci Pub No. 102, 17-18.
- Willett W. (1989). The search for the causes of breast and colon cancer. *Nature* 338, 389-394.

MEMBERS OF THE TASK FORCE

H. Lagast ¹ (Chairman)	SOLVAY B - Brussels
A. W. Ahlberg	NESTE OY SF - Espoo
G. Briatico-Vangosa	HIMONT I - Milano
J. C. Contassot ¹	ELF-ATOCHEM F - St Fons
J. Ph. Gennart	PETROFINA B - Brussels
B. Huisman	SHELL NL - Den Haag
R. J. Lewis ¹	EXXON BIOMEDICAL SCIENCES USA - East Millstone, NJ
V. J. Marchesani	HIMONT USA - Wilmington, DE
O. Roeyneiland	STATOIL N - Bamble
T. M. L. Scheffers	DSM NL - Geleen
J. Tomenson ¹	ICI GB - Macclesfield
D.A. Stringer (Secretary)	ECETOC B - Brussels

¹ Indicates Task Force Members mainly concerned with preparation of the Task Force Report.

Acknowledgement

In addition the Task Force wishes to acknowledge the help received from:

M. Bird	EXXON USA - East Millstone, NJ
J. de Gerlache	SOLVAY B - Brussels
K. Gardiner	INST. OF OCCUPATIONAL HEALTH, GB - University of Birmingham

together with comment and advice from the following on occupational hygiene:

M.J. Evans (EXXON, GB, Southampton), D. Akselsen (STATOIL, N, Stathelle), B. Fenton (SHELL CHEMICALS, GB, Carrington), P. Boureleau (SHELL FRANCE, F, Ferre-l'Etang), P.S.J. Rocchi (SHELL NEDERLAND, NL, Rotterdam), A. Espagnach (APPRYL, F, Puteaux), W. Asnong (SOLVAY, B, Brussels) and Dr. Granieri (HIMONT, I, Terni).

MEMBERS OF THE SCIENTIFIC COMMITTEE

W. F. Tordoir ¹ (Chairman), Head, Occupational Health and Toxicology Division	SHELL NL - Den Haag
H. Verschuuren (Vice-Chairman), Head, Toxicology Department	DOW EUROPE CH - Horgen
O. C. Bøckman, Scientific Advisor	NORSK HYDRO N - Porsgrunn
N. G. Carmichael, Toxicology Director Worldwide	RHONE-POULENC F - Lyon
H. De Henau, European Technical Centre Professional and Regulatory Services	PROCTER AND GAMBLE B - Brussels
A. de Morsier, Head Ecotoxicology	CIBA-GEIGY CH - Basel
P. A. Gilbert, Head, Environment Division	UNILEVER GB - Port Sunlight
I. J. Graham-Bryce, Head Environmental Affairs	SHELL NL - Den Haag
B. Hildebrand, Director Experimental Toxicology	BASF D - Ludwigshafen
J. R. Jackson ¹ , Director Medicine and Health Science	MONSANTO EUROPE B - Brussels
K. Künstler, Head, Biological Research	HENKEL D - Düsseldorf
H. Lagast, Chief Medical Officer	SOLVAY B - Brussels
E. Löser, Head, Institute of Industrial Toxicology	BAYER D - Wuppertal
R. Millischer ¹ , Chief Toxicologist	ELF ATOCHEM F - Paris
I. F. H. Purchase, Director, Central Toxicology Laboratory	ZENECA GB - Macclesfield

¹ Stewards responsible for the Primary Peer review