PF TOX
VINYL CHLORIDE
HUMAN

A P M E

ASSOCIATION OF PLASTICS
MANUFACTURERS IN EUROPE

Brussels, 12 August 1996

Dear Sir/Madam,

As part of its Responsible Care Programme the Association of Plastics Manufacturers of Europe maintain a register of cases of angiosarcoma of the liver associated with exposure to vinyl chloride monomer.

In the past this has relied on spontaneous reporting of cases, usually from medical officers associated with the plants concerned. Reports to date have mainly been from plants in Western Europe and North America.

The previous custodian Dr Francoise Drion did attempt a more proactive approach and we acknowledge her valuable contribution to improving the quality of the Register.

A further review lead to the preparation of a formal protocol which included a requirement for me to directly mail plants each year and this is the purpose of this letter.

Please could you look at the attached protocol and decide who the most appropriate person in your organisation is to deal with this matter. If you have had any actual or suspected cases of angiosarcoma of the liver then I would be most interested to hear the details as requested in the protocol. If you have not had any cases then confirmation of this would be equally valuable. I have enclosed an addressed envelope for your convenience.

I will acknowledge all replies. If you do reply you will receive a copy of the next publication of the Register free of charge.

If you have any queries relating to possible health problems associated with exposure to Vinyl Chloride Monomer I will do my best to provide you with further information on request. The Association has for some years collected information in this area and has the benefit of regular advice from the Medical Officers and other Safety, Health and Environment specialists from its member companies.

Yours sincerely

Dr J C Paterson Bsc., FFOM
Occupational Physician

UCC 105824

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APME

ASSOCIATION OF PLASTICS MANUFACTURERS IN EUROPE

Protocol for the maintenance of a register of cases of angiosarcoma related to PVC production.

Association of Plastics Manufacturers of Europe

ABOUT APME

The Association of Plastics Manufacturers of Europe

represents the interests of the industry at European level and promotes the benefits of plastics in every aspect of life. It co-operates with other industry sectors to provide effective solutions to plastics-related issues through scientific fact and environmental and economic data.

The Association has a full time secretariat with a range of steering and working groups made up of experts from member companies.

The APME Vinyls Medical and Toxicological Working Group

monitors and advises the Vinyls Committee of APME and its other working groups on medical and toxicological aspects of vinyls materials and substances used in the production of vinyl materials and initiates and co-ordinates any studies or submissions required on medical and toxicological aspects of the materials of interest.

UCC 105825

Revision 1 August 9, 1996

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Introduction

The knowledge of the toxicity of Vinyl Chloride Monomer (VCM) developed during three well defined periods:

In the first, between the 30's and 40's the acute effects on man, above all on the Central Nervous System, with euphoria, dizziness, headaches, narcosis, due to the inhalation of high concentrations of VCM were pointed out. However the substance was considered moderately toxic.

The effects, both experimental and human, of repeated exposure to VCM were described following the great industrial development of the 50's, in the production of VCM and its derivatives, mostly polymers (Polyvinyl Chloride - PVC). These effects, characterised by s a specific alterations of the liver, digestive and respiratory systems, and Raynaud like phenomenon to the hands with sclerodermic lesions and osteolytic bone alterations of distal phalanges, are part of the so-called "Vinyl Chloride Illness".

At the beginning of the 70's, following the experimental studies begun by Prof. Viola and continued by Prof Maltoni, the carcinogenic effect of VCM was discovered. In particular, Prof. Maltoni's studies indicated that VCM was responsible for a very rare tumour of the liver, the angiosarcoma. At the same time, the clinical confirmation on man of this effect came from the United States.

VCM has probably been the only case, in environmental toxicology, in which the experimental evidence on animals, was confirmed, almost at the same time, by clinical data on man. The measures taken by Industry following these discoveries, show that it is possible to continue the production of chemical substances, even carcinogenic, using such technologies as to minimise the risk for workers and users.

Regarding the possibility that VCM is the cause, even in man, of other tumours, the studies carried out up to now do not give certain results.

The International Agency for Research on Cancer (IARC) has recently published the results of a multi-centric collaborative European study on workers of different industries producers of VCM/PVC which indicate:

- an important increase in liver cancer and above all angiosarcoma.
- no significant excess of mortality for cancer of other sites, although there is a slight increase in the incidence of lung and brain cancer and lymphosarcoma.

- an increased risk of bladder cancer and melanoma of the skin not related to exposure.

- no increased mortality has been observed for the other main causes of death

The following sentence appeared in the important magazine 'The Lancet" in June of 1974:

"Vinyl Chloride is a milestone in Occupational Hygiene"

DR P Bonetti - Solvay S.A.

Purpose

To as far as reasonably practical maintain and make available a register of cases of angiosarcoma associated with the production of vinyl chloride and polyvinyl chloride world-wide in order to:

- Assess the impact of the technological, organisational and hygiene improvements on the occurrence of angiosarcoma of the liver.
- Collect data for the epidemiological investigation of cases.
- Maximise our understanding of the disease with a view to its eradication.

Scope

This protocol applies to the Custodian and the APME secretariat responsible for the maintenance of the register and associated files.

Definitions

APME - The Association of Plastic Manufacturers of Europe

ASL Register - A register of cases of angiosarcoma of the liver known to have occurred world-wide.

Secretariat - The secretary of the APME Vinyls Committee Medical and Toxicological Work Group and their supporting staff within APME.

Angiosarcoma - A malignant tumour composed of spindle or pleomorphic cells with inconspicuous nuclei that line, or grow into, the lumina of preexisting vascular spaces, such as liver sinusoids and small veins (from - "Histological Typing of Tumours of the Liver" by K.G Ishak, P.P. Anthony, and L.H. Sobin in collaboration with Pathologists in 6 countries, WHO, 1994)

Case - A histologically confirmed case of angiosarcoma of the liver occurring in a patient who has previously been employed in the manufacture of vinyl chloride monomer or polyvinyl chloride for more than 6 months and more 1 year after starting work

Vinyls Medical and Toxicological Working Group - A working group consisting of medical officers representing member companies of the APME as well as other professionals who may from time to time be co-opted for the consideration of particular problems.

Custodian - The Occupational Physician appointed by the Medical and Toxicological Working Group to be responsible on their behalf for all aspects of management of the Register and in particular to ensure confidentiality of the clinical data and ethical operation of the Protocol. The Custodian shall normally be a member of the Group. At all times the Custodian is acting as an

agent of the Vinyls Medical and Toxicological Working Group.

Security undertaking - The Secretary of the Medical Working Group shall ensure that all staff who may work with or have access to the files associated with the register prior to its publication sign the security undertaking laid out in appendix 1.

General Administrative Arrangements

APME regards the security and confidentiality of any clinical information related to the maintenance of the register as the single most important feature of its operation and has made the following arrangements to address this issue. Accordingly ONLY the Chairperson of the Medical and Toxicological Working Group, the Custodian and the Secretariat will have access to any information used in the preparation of the Register within APME.

The Chairperson, the Custodian and all staff in the Secretariat shall be required to sign the security undertaking in appendix 1 *before* they start any work related to the Register.

All files associated with the maintenance of the Register and its publication will be kept at the APME's offices in Brussels under the day to day charge of the Secretariat. Files not actually in use will be kept in locked storage at all times.

The published Register shall **not** contain personal identifiers of each case including Name, initials, or exact date of birth. This information will only be sent out for checking to those making the initial case report.

Arrangements will be maintained by the Secretariat that at least one copy is maintained by the Custodian of all papers relating to the Register at a location remote from APME. The Custodian shall ensure that all these copies are kept in locked storage when not in use. Archival of documents will be arranged by the Secretariat and will involve the scanning of documents onto CD-ROM. Copies will be strictly controlled with two copies being held by the Secretariat and one by the Custodian. In the event of a change in Custodian all papers, copies and computer media related to the register shall be returned by the Custodian to APME for use by the new Custodian.

No disclosure of data other than that specified in the Protocol shall be made by the Custodian without the authority of the Vinyls Medical and Toxicological Working Group. This would require a formal written agreement as to the purpose of the study and include adequate security undertakings.

In the event that the Register is wound up all documentation relating to the register will be lodged with a suitable Academic Unit identified by the Medical and Toxicological Working Group and no copies retained in APME.

The System

Once per year the Custodian and the Secretariat will arrange a search of a suitable Commercial Database in order to establish as far as reasonably practicable a list all sites involved in the manufacture of vinyl chloride monomer or polyvinyl chloride world-wide.

This list will be used to update the list of existing and previous manufacturing sites already identified. This list will form the basis for an annual mailing to explain the Register and solicit the further identification of cases.

The updated list shall be reviewed by the Vinyls Committee of APME to further check its accuracy. A note will be kept of any changes suggested by the Vinyls Committee.

The Custodian and the Secretariat will then arrange the mailing of each site on the list. The mailing shall include this protocol together with a request for the notification of new cases, a case input form, and a request will also be included to check the record of production dates at that plant. A nil return will be requested. **Contact details for any Occupational Physician attending the plant will also be requested.** One follow up mailing shall be made to each plant not responding within two calendar months.

Details of previous European cases will be circulated to the APME Vinyls Medical Work Group for checking. Where plants outside Europe identify Occupational Physicians then details of cases previously notified from those plants will be sent to the relevant Occupational Physician for checking.

It is anticipated that general correspondence relating to cases or plant records will continue to arrive at other times during the year.

The Custodian and the Secretariat shall meet on a regular basis at the APME in Brussels. At these meetings all correspondence will be reviewed and arising actions agreed and minuted.

The Register itself shall be maintained by the Custodian and Secretariat as an appropriate computerised database copies of which shall exist on one personal computer at APME and the personal computer of the Custodian. Alterations to the database shall only be made in the presence of both the Secretariat and the Custodian and a record of EVERY amendment will be kept in a paper amendment record and as an appendix to the computer file.

The Secretariat shall establish the following files for correspondence related to the Register.

1) A file for each case

2) A file for each plant

3) A database amendment file

4) A general correspondence file.

5) A file for cases that have been notified but not included in the Register.

6) A review file to contain the annual security and epidemiological reviews.

7) A pending file for information received and not yet evaluated for inclusion in Register

A key word index shall be established for the general correspondence file.

Amendments to the plant records shall only be made at the discretion of the Custodian *and* the Secretariat based on correspondence received.

Amendments to the case file shall be made by the Custodian when the criteria are met which are:

- Patient worked at least *six months* on vinyl chloride monomer **or** polyvinyl chloride production *starting more than one year previously.*

- There is histological confirmation of the diagnosis.

When the custodian does not feel that the above criteria have not been met, he will inform the person who notified the case.

For surviving cases the Custodian shall establish the progress of the case by letter each three months.

A panel of pathologists has been established to help with advice on diagnosis. The Custodian shall establish and update the pathological criteria for diagnosis.

The Custodian and the Secretariat shall establish with the agreement of the Vinyls Medical Work Group the routine analyses of the data to be included in the Register. These will be checked with an independent epidemiologist to ensure that they are appropriate and valid on this database.

The Custodian shall present a review of all matters relating to the Register at each meeting of the Medical and Toxicological Working Group.

The Register shall be published at intervals determined by the volume of cases notified but not normally less than once every three years.

The Custodian and Secretariat shall arrange for a triennial review by an independent.

Revision 1, August 9, 1996
Ensures case details only released to relevant Occupational Physicians for checking
Ensures notifier told where criteria not met

epidemiologist, approved by the Medical and Toxicological Working Group, of the data collection and analyses, as well as the security aspects of the system. Each such review will be included as an appendix to the next edition of the Register.

Revision 1, August 9, 1996
Ensures case details only released to relevant Occupational Physicians for checking
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Appendix 1

Security undertaking

It has been explained to me that during the course of my employment with APME either directly or under contract that I may gain knowledge of or be entrusted with sensitive, personal or medical information. I understand that APME regards such medical information as the most confidential and expects me to take all practical steps to prevent its untimely disclosure.

Signature of staff member/contractor Date

Signature of APME supervisor Date

APME