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February 12, 1976

THE U.S.A. VINYL CHLORIDE (VCM) STUDIES

We attach a glossary of terms to this summary, which may be useful in understanding the language of the toxicologists and epidemiologists. As noted, it is selected for brevity.

Today I am joining thousands of self-styled experts on the vinyl chloride health problem. Over 98% of us were made after the January 1974 news that B.F.Goodrich had identified three cases of death by angiosarcoma of the liver in workers at its Louisville, KY PVC production plant. The outcry of Monday morning quarterbacks was unbelievable.

First, it is important to note that the very rare human disease of angiosarcoma (of the bloodvessels) was previously related primarily to Thorotrast (thorium oxide) blood injections for X-ray and less so to arsenic exposures in Vinter's disease from Paris Green and other insecticides. There are, however, animal experiments recording angiosarcoma due to other organic chemicals such as nitrosoamines and urethane.

However, during 1973[1] Prof. Cesare Maltoni of Bologna Oncogenic Research Institute had in progress a long-term VCM inhalation experiment on rats, funded by a European chemical group of four companies, in which he had observed angiosarcoma of the liver among other types of cancers after a year of exposure to a VCM concentration as low as 250 ppm. This made it logical for B.F.Goodrich medical authorities to suspect VCM as an occupational factor in its rare human angiosarcoma cases.

The peculiar nature of suspension polymerization of PVC for electrical grades of resin had historically exposed U.S.A. and some European PVC polymerization workers to high VCM vapor concentrations during the physically demanding job of scraping polymerizer walls between charges.

This type of work had already been correlated in the mid-1960's with an unusual disease, called acroosteolysis, or decalcification of the bone in the finger tips of a small percentage of PVC reactor cleaners. An active international industry sponsored university study was made of this health problem in the mid 1960's, including an epidemiology study (mortality and morbidity) of the X-ray identified affected and non-affected workers. It was concluded that the problem was primarily caused by physical trauma, but that VCM exposure levels should also be reduced as an added precaution. High pressure water cleaning systems were developed, to implement this decision. These are finding use in synthetic rubber production plants, to reduce the necessity of human vessel entry.

[1] The acroosteolysis problem had stimulated Prof. Viola of the University of Rome to initiate inhalation studies of rats, exposed to VCM concentrations approaching the explosive limit at 30,000 ppm. This did not result in acroosteolysis, but after 8 months' exposure he did observe a very high incidence of cancer of the ear canal, common in rats, called zymbal gland tumor. Publication of this work stimulated concern in both European and U.S.A. industries to initiate further long term studies at lower VCM exposure concentrations. Because of the interest of Prof. Maltoni and his establish d inhalation exposure capabilities, the European work was underway within a year or so. He selected a strain of rats with a very low incidence of spontaneous cancer.

In the U.S.A. work was delayed until the protocols of the European work could be reviewed, to avoid unnecessary duplication of the costly long-term studies. Proper inhalation exposure facilities had to be prepared by the selected contractor, Industrial Bio-Test Laboratories of Chicago. In addition, the U.S.A. group of sponsoring companies (initially 17, ultimately over 30) initiated an epidemiology[2] study of North American VCM/PVC production workers with Tabershaw/Cooper Associates. This is relatively easy in the U.S.A. with its National Center for Vital Statistics publications of cause of death by date, age, race, and now - geographical location. However, it was expensive, time-consuming and required ready access to company personnel records at the production plant level. This study showed a unique increase in deaths from angiosarcoma of the liver, as well as a suggested increase in deaths from brain, lung and lymphomatic cancers.

There is another technique for epidemiology that was undertaken at three VCM/PVC production plants in the U.S.A. - current morbidity. This involves a one-time physical examination of all employed in the selected plant, with their permission and that of their elected representatives. The difficulty with this type of study is that of identifying an adequate control group[3]. National morbidity tables are less scientifically accepted than mortality tables, although both are questioned by some experts. No new evidence of VCM health problems were disclosed by these tests, except for the observation of "increased" chromosome breaks and possibly increased fetal wastage. These questions require further study.

The VCM/PVC producers group, working in all cases through the administration of the Manufacturing Chemists Association, also initiated metabolic, mutagenic and teratogenic studies on VCM, to search for possible mechanisms to help interpret the toxicology and epidemiology results. This work was performed under contract to the Dow Chemical Biological Research Laboratories at Midland, Michigan. This study has indicated slight increases in birth defects in some animals at relatively high exposure concentrations. The mutagenic response of selected mutant strains of bacteria was also slight, and this was confirmed by Prof. Ames Laboratories at Berkeley, California. The metabolic work todate has shown that there may be more than one route to metabolism in the body of a rat, when exposed to relatively high concentrations of VCM. At low exposure levels the metabolic route is related to that for ethyl alcohol. Further studies will be needed, to follow these leads to a logical conclusion.

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[2] Epidemiology results can be analyzed in different ways. If accountability is very high (over 90%) of all workers selected for the study, direct comparison with the HEW statistical tables for Standard Mortality Rates is acceptable. This type of study is reported as Standard Mortality Ratio (SMR). However, if the group is restricted to current employees and retirees, and employee terminations are not followed up, epidemiologists prefer to use Proportional Mortality Ratios (PMR), which simply compare relative cause of death of the group with relative ratios from the date, age and sex specified statistical tables. PMR does not include the absolute risk of dying from any specific cause.

[3] A more precise, but more difficult technique for morbidity is the matched pair study, in which a control population is selected in the same geographical area and of similar individual characteristics as the workers. This type of study has not been done, to my knowledge, for any VCM/PVC worker group.

The total cost for these many U.S.A. VCM toxicity and epidemiology studies has not been released, but it already exceeds 1 million in 1974 U.S.A. dollars.

So, what have we learned from this escalated vinyl chloride toxicity problem?

1. <u>The long latency period for cancer requires long term animal testing in the future</u>.

   The facts are that VCM was seriously considered in the 1920's and 1930's by the medical profession as an anaesthetic for human surgery. It was superior to diethyl ether and chloroform, because extensive acute animal and human testing showed it to be generally less dangerous and with less post-anaesthetic after effects. It was ruled out because of undesirable reactions on cardiac-deficient patients.

   Many subsequent acute and longer-term VCM inhalation toxicity studies were performed on both animals and humans by the best protocols available at the time. The first cloud that emerged for long-term chronic harm was the report, in 1961, by Dow workers with rats exposed for six months to VCM concentrations as low as 200 ppm. No effect was noted at 100 ppm inhalation levels. A peer group of Government Industrial Hygienists felt this data was insufficient to warrant more than a reduction of the ceiling exposure level to 500 ppm.

2. <u>Lifetime animal testing results have correlated with human high level VCM exposure history</u>.

   In March 1976 we have recorded around the world about 50 cases of confirmed angiosarcoma of the liver (by qualified histologists), related to VCM vapor exposure in VCM/PVC production plants or in use of VCM in the laboratory or filling aerosol cans. Because of the long latency period (average 17 years, but as long as 27 from first exposure) more cases will be reported in the coming years. The animal work has shown positive angiosarcoma at as low an exposure level as 50 ppm. We believe, exposure to the current 1 ppm TWA insures no development of cancer due to VCM in our production plants.

   It is important to note that vinyl chloride is a unique case of industrial toxicology. Had the disease not been so unusual, we could still have been arguing the relative merits of expert opinions. For example, an increased incidence of lung cancer has been noted in workers in many industries, especially with dusty atmospheres. However, epidemiology data invariably prove a higher degree of correlation with cigarette smokers and, therefore, the relative importance of industrial exposure is in question.

   No one yet believes that it is possible to set allowable exposure limits from animal experiments because of the many cases in food and drug toxicology where large differences in response occur between animal species - often due to differences in metabolism and the toxicity of the metabolites, rather than the original chemical. There is also unresolved controversy among experts on cancer with respect to the existence of a reasonable threshold limit or the "one hit" by one molecule theory. Reason tells us

2. - cont'd

that life expectancy has an inherent statistical probability, and that there is no risk-free environment. U.S.A. politicians often find themselves being pressured to vote otherwise.

3. <u>After a suspected industrial chemical exposure hazard is identified, industry can expect to be castigated as callous, unresponsive and negligent to published dangers</u>.

In the case of VCM, the weight of published data on relative safety was ignored or discounted. <u>Industry</u>, not Government, academia or labor, should have had the omniscience to foresee that VCM could cause cancer, and that ACGIH (American Conference of Governmental Industrial Hygienists) standards should have been ignored. For example, East European articles were identified which had shown "observation of liver damage in PVC workers" as early as 1949. Actually, to anyone who had the article translated and studied, the PVC workers were making coated fabrics with solvents and polychlorinated biphenyl plasticizers. Their exposure to VCM must have been minimal. Yet even today you will find this referred to as evidence of "PVC industry lack of concern for the health of its employees".

4. <u>All industries, including synthetic rubber producers, ask: "Is there another VCM lurking?"</u>

Your IISRP Toxicology Committees from around the world doubt that such a unique case will emerge from synthetic rubber operations. However, this does <u>not</u> mean that we <u>may</u> not have toxicological problems that require more vigilance. And it certainly does not mean, in the future, that the industry may not be subjected to the same kind of criticism or allegations that have beset the VCM/PVC industry during the last two years.

There are uncomfortable parallels between VCM and butadiene:

- both are gases at ambient temperature, and both require pressure containers;

- both have relatively high odor detection levels. Without measuring with instruments more sensitive than an explosion meter, we don't know what the potential exposure levels are now, or were then;

- both are heavier than air and hence tend to stay in open vessels, stream towards ventilation outlets and flow to lower levels in the plant;

- both had been given relatively clean acute and sub-acute toxicity ratings and, therefore, had enjoyed relatively little attention by industrial hygienists;

- both are highly reactive monomers and form peroxides on exposure t air (and blood haemoglobin?);

4. - cont'd

- neither had been subjected to lifetime animal exposure testing until recently with VCM. Such studies on butadiene have y t to be initiated by anyone, according to a recent literature survey purchased from BIBRA in January[4].

Member companies in IISRP will not know if we really have a potential problem, until we look further and harder by both long term animal tests on butadiene and other chemicals, and by an audit of our worker health experience. Studies are already planned or are underway in both Europe and the U.S.A. on chloroprene, styrene, and acrylonitrile. Styrene has recently been questioned with respect to carcinogenic reactions from long term feeding of mice with water extract from molded polystyrene.

We are recommending to you today that IISRP, with the support of independent butadiene producers, finance long term toxicity and metabolic studies on the effect of butadiene inhalation on animals, as well as a feasibility study on retrospective mortality of our synthetic rubber workers of the past thirty years.

Meanwhile, as responsible producers and prudent businessmen, we should instruct each of our plant managers to reduce all emissions and worker exposure to the chemicals used and produced in our plants - including dusts. If you can see it, smell it, or detect it with an organic vapor analyzer, it's already too much now.

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[4] According to the BIBRA survey, the Russians have long been concerned with the effect of many chemicals, including butadiene, on nerve response times as indicative of medically significant allowable exposure levels. As a result, U.S.S.R. and several other Eastern Bloc countries have imposed a "Maximum Allowable Concentration" on butadiene of 45 ppm. A recent publication of conditioned response tests at that concentration resulted in a recommendation that the MAC be reduced to 4.5 ppm. This compares with the current 1,000 ppm TLV in the U.S.A. and twice that in the U.S. The Russians had a MAC level on vinyl chloride of 12 ppm for years, as a result of similar animal experiments.

This doesn't make any sense

SELECTED GLOSSARY OF TOXICOLOGY TERMS

ACROOSTEOLYSIS
Regression of bone by decalcification, especially in the extremities, such as the finger tips.

ANAESTHETIC
A chemical that induces insensibility to pain, such as chloroform or diethyl ether. Vinyl chloride is also an anaesthetic.

ANGIOSARCOMA (HEMANGIOSARCOMA)
Malignant growth on the inner linings of the blood vessels, often found in areas of high blood vessel concentrations, such as the liver or kidneys.

ADENOMA
Non-malignant enlargement of glandular types, often called benign tumors.

CANCER
A malignant tumor anywhere in the body of a person or animal; its origin is usually in the several types of epithelial tissue and it invades any of the surrounding structures. The characteristic of metastasis or seeding to other organs of the body is positive to this diagnosis.

CARCINOGEN
A highly controversial term, applied generally to any substance that produces cancer, as well as to highly specific chemicals suspected of being the cause of cancer development in any one of many target organs or the body in test animals or human beings. The words "cancer suspect agent" have been used by U.S.A. authorities to cover this possibility. However, NIOSH has broadened this terminology to include any agent reported in the literature to cause or be suspected of causing a tumor development, malignant or benign (see ONCOGENIC).

COHORT
A group of individuals selected for scientific study of toxicology or epidemiology.

CONTROLS
The most important factor in any statistically meaningful study of animals, humans or bacteriological experiments. The nature, number and reproducibility of the controls determine the accuracy and significance of the conclusions from the experimental cohort results (see PROBABILITY).

EPIDEMIOLOGY
The science of determining statistically significant relationships of specific diseases of specific organs of the human body in selected study groups (cohorts) in comparison with appropriately selected controls. When the study relates to the health of living persons, it is called morbidity.

In the U.S.A., the National Center for Vital Statistics updates tables annually with respect to year, age, sex and now county geographic location as to death certificate cause of death. This type of study is called retrospective mortality.

In epidemiological studies, the larger the study group, the greater the probability of an accurate conclusion, providing the control group is appropriate. The latter presents serious problems in morbidity studies.

INDUSTRIAL HYGIENE

The practice of limiting human exposures to vapors, skin, eyes or dusts that are known to have adverse effects on health. This includes washing, removal of skin contacted materials, cleansing and laundering of clothes. It also includes the complex area of inhalation protection by a wide variety of respirators and breathing devices, as well as protective clothing.

METABOLISM

All natural and synthetic chemicals ingested or inhaled by the living body, either animal or vegetable, are subject to chemical transformation in the organism into other products by the continuous myriad of chemical reactions, such as synthesis and oxidative transformation in the organs of the body. Many of these primary and intermediate products find their way to body excretions through lung exhalation, urine, fecus or other expirations. The tracing of these routes are important for specific chemicals and possible relation to disease. Isotope tagged materials are used for these research studies. These studies are often called pharmacokinetic and metabolism research.

METASTASIS

In medicine the shifting of pathogenic cells of a disease, such as a malignant tumor, from one part or organ of the body to another unrelated to it.

MUTATION

A sudden variation in some inheritable characteristic of an individual animal or plant, as distinguished from a variation resulting from generations of gradual change. It is an affect attributed to an action prior to conception of the embryo. It has been correlated with increased incidence of chromosome breaks in the reproductive cells, male or female. Possibility of such an action by VCM has recently been noted in an epidemiology study on PVC production workers, compared with PVC fabricators and rubber workers at the same plant site.

Research in this field in recent years has focused on the development of tests for the effect of chemicals on rapidly reproducing species, such as bacteria and fruitflies. The Ames test, in particular, has been used to identify chemicals that accelerate reversion of specially developed mutant strains of a bacteria salmonella. Certain types will rapidly revert with chemicals which are known to be carcinogenic in animals and humans. This research is interesting, but does not mean that a chemical that is a mutagen will be proven to be a carcinogen.

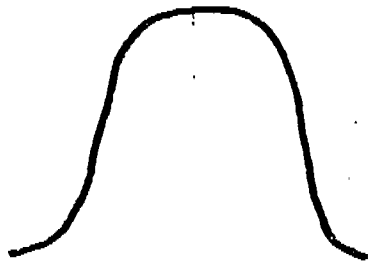
Mutation studies in animals involve two or three generation exposures - e.g. through at least one pregnancy and preferably two, to look for mutations in genetic material of the chromosomes.

ONCOGENIC

A term preferred by some cancer research experts, such as Prof. Maltoni, to identify abnormal cell development in animals or humans.

PROBABILITY (IN LIFE)

Groups of biological forms live a bell-shaped existence in response to anything in their environment:



In the case of human age, vital statistics tables show a skew or even a double hump due to death in infancy and early years. This is far greater in developing countries than in technically advanced countries, due to better medical attention, diet, etc. One thing is certain of all living forms at the time of birth - sooner or later each individual will expire. Today's mice seldom live beyond two years, rats 3, dogs 15, men 90 and women 100 - but California redwoods > 3,500 years.

Perpetuation of each individual's peculiar heredity requires reproduction during his active life. Sexual reproduction creates a new individual with its own peculiar characteristics and ability to respond to a continually changing environment. Scientific toxicity and epidemiology require the search for unusual blips on the "normal" probability curve. The arguments are, whether the blips are statistically significant. The more the number in the study and control groups, the greater the probability of the answer "with certainty of 90, 95, 98%".

PROTOCOL

This term is used in toxicity testing and epidemiology or health studies. It is a detailed definition, in writing, of the experiment to be performed and the subsequent evaluations of the results. It is essential for a meaningful contractor bid, just as are the engineering specifications for a piece of equipment.

TERATOGENICITY

The observation of stillbirths, birth defects or malformations which could be caused by toxic chemicals affecting the growing fetus (transplacental). These studies are of growing importance as the percentage of female workers in our chemical plants increases. Animal studies on this type of effect are becoming essential not only for food and drug chemicals, but also industrial chemicals.

TOXICITY

This is the state, quality or degree of a substance or mixture of being toxic, or poisonous. Toxicology is the science of determining toxic effects of chemicals and identifying potential antidotes. There are several ways in which workers may become exposed to chemicals, and therefore several types of procedures or protocols have been designed for animal exposure toxicity tests:

TOXICITY - cont'd

a. INGESTION

The most commonly used technique since toxicity of various plants and additives to food, medical drugs and beverages have been of primary concern during the past several centuries. Animal testing techniques were elaborated in the past hundred years as the use of synthetic drugs and that of insecticides on food crops became important to increase food supplies. Choice of the daily test animal dosages is a matter of expert opinion and depends on the chemical and physical nature of the substance. Its intended end use determines tests for its degree of acute toxicity, maximum tolerated dose (sub-acute), chronic and long term for species to be tested.

Normally the test material is incorporated in the food or water and dose is calculated from average daily intake of the animal. In certain cases, such as volatile gases or for low concentrations, the animals are given daily or other alternating stomach implantations (gavage) of a suitable solution in a vegetable oil. Controls must also receive the oil gavage without the test materials.

In industrial environments ingestion toxicity is not a primary concern, although the habit of drinking or eating in work areas should be discouraged. However, it is important to polymer and polymer product producers if residual monomers, chemical additives and extractable compounding agents can come in contact with food, drugs or beverages.

b. INHALATION

Worker contact by inhalation is of concern for volatile chemicals and fine dusts. The largest cause of death by any type of cancer in many industrial countries is by lung cancer, especially in people who are smokers. Inhalation animal testing of chemicals and dusts for cancer hazard is long term and difficult. Quality test facilities are limited for long term animal inhalation studies. Appropriate protocols for long term inhalation testing are still a matter for expert opinion. Therefore it is prudent to minimize emissions of all chemicals and dusts, and workers should be protected from excess exposure.

c. INJECTION

In the past, hypodermic injection toxicity (beneath the skin, into the abdomen, into the blood) has been commonly used for preliminary acute and sub-acute chemical screening. It, like implantations of solids, is not particularly pertinent for industrial hygiene studies.

d. IMPLANTATION

During the post-WWII years remarkable progress has been made in prosthetic devices for surgical replacement or repair of defective parts of the human body. This has led to considerable animal testing by this technique of implanting particulate or molded pieces of many metals, plastics and rubbers and watching for long-term effects. As a result, the June 1975 NIOSH list of cancer suspect agents contains many polymers, including cellulose, where tumors and cancers developed near the large pieces of foreign materials.

TOXICITY - cont'd

e. SKIN AND EYE - irritation and toxicity testing have long been used to detect materials which could cause dermatitis, sensitization, or more serious diseases on chronic exposure (including cancer). Eye testing is used primarily to detect the acute irritation or damage potential of a substance, although absorption into the body may occasionally occur through the eye. These tests are useful for industrial hygiene control in physical daily contact with chemicals.

Some chemicals can cause significant health problems, often with a minor proportion of the workers who are unusually allergic to a variety of foreign substances.

Inhalation of certain chemicals is also known to sensitize some individuals and give rise to pulmonary health problems. This can also be considered a mucous membrane surface response. Transfer of the sensitive individuals to other assignments is the best immediate industrial hygiene solution.

Eye damage is also an important factor in acute chemical exposure.

SUMMARY

In all of the above comments on toxicity nomenclature, emphasis has been on animal response testing and only casually on prevention or antidote. This glossary is meant to be informative, rather than instructive, so that we can communicate with our professionals who are responsible for the health of our workers.

The one message to be repeated is that in groups of biological systems - humans, animals, plants or bacteria - there is no absolute. Everything is relative to selected "controls" or "norms", and the results must be expressed in probabilities. There is always the possibility of something else happening.

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