

MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL
NATIONAL INSTITUTE FOR OCCUPATIONAL SAFETY AND HEALTH

TO : Office/Division Directors

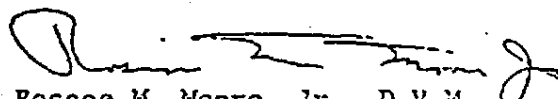
DATE: October 29, 1976

FROM : Chief, Technical Evaluation and Review Branch
Office of Extramural Coordination and Special Projects

SUBJECT: Vinyl Chloride - Induction by Inhalation of Mammary Tumors in Laboratory Rats

In a letter dated October 11, 1976, the National Institute for Occupational Safety and Health (NIOSH) was informed by B. F. Goodrich Company of a recent unpublished report on the carcinogenicity of vinyl chloride. In this report, Dr. Cesare Maltoni presented the results of 52-week inhalation studies in rats using concentrations of 50, 25, 10, 5, and 1 ppm vinyl chloride. The results of the 50 ppm trial involving 300 rats confirmed a previous trial (using fewer rats) in which vinyl chloride was seen to have an oncogenic effect. Specifically, after 100 weeks, an increased incidence of mammary neoplasms (43 of 300 rats) was observed. At the lower concentrations, a carcinogenic effect (i.e., mammary tumors) was also seen.

This office is evaluating these findings with regard to occupational exposure and with particularly emphasis on possible effects among women in the workplace.


Roscoe M. Moore, Jr., D.V.M.

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TEXT PROPOSED BY THE COMMISSION OF
THE EUROPEAN COMMUNITIES

- measuring and monitoring techniques necessary for this purpose, as well as other preventive measures,
- guidelines for medical surveillance.

Article 2 unchanged

Article 3

3.1. The fundamental aim of technical monitoring shall be to reduce to below measurable levels the atmospheric concentrations of VCM to which workers are exposed. All working areas in works referred to in Article 1.1 shall therefore be monitored for the presence of VCM.

3.2. For new VCM/PVC works, a maximum atmospheric concentration of 5 ppm, which may not be exceeded, shall be laid down as the technical long-term limit value for VCM.

3.3. For existing VCM/PVC works, a maximum atmospheric concentration of 10 ppm, which may not be exceeded, shall be laid down as the technical long-term limit value for VCM.

3.4. The necessary technical measures with respect to the limiting technical values given under 3.2 and 3.3 shall not in any case result in VCM pollution of the environment outside the works.

TEXT AMENDED BY THE EUROPEAN PARLIAMENT

Article 3

3.1. unchanged

3.2. For new VCM/PVC works, a maximum atmospheric concentration of 1 ppm, which may not be exceeded, shall be laid down as the technical long-term limit value for VCM.

3.3. Existing VCM/PVC works shall be allowed an adjustment period of up to one year.

3.4. The necessary technical measures with respect to the limiting technical values given under 3.2 shall not in any case result in VCM pollution of the environment outside the works. The emission and immission problems arising in connection with the implementation of this Directive are to be dealt with in a separate Directive.

Articles 4 and 5 unchanged

Article 6

A monitoring system which gives continuous mean values for at least one hour shall be provided to detect abnormal increases in concentration levels caused by technical failures in working areas in works producing VCM/PVC.

6.1. The threshold concentration at which the alarm is triggered shall depend on the measuring system and on operating conditions.

6.2. An increase in VCM concentration shall be regarded as abnormal when it exceeds approximately five times the mean weekly value. In such an event, technical measures to discover the causes shall be taken without delay.

Article 6

A monitoring system which gives continuous mean values for at least one hour shall be provided to detect abnormal increases in concentration levels caused by technical failures in working areas in works producing VCM/PVC.

6.1. unchanged

6.2. unchanged

4. Urges the Commission to work out a Community reference method in order to check the VCM measuring systems so that the workers concerned are not exposed to VCM concentrations reaching the scientifically acknowledged danger thresholds;
5. Takes the view that, for the purpose of determining the maximum concentration to be laid down as the 'technical long-term limit value', no distinction should be made, except for the adjustment period provided for, between existing and new VCM/PVC production units;
6. Believes that the area of application of this Directive should be extended to workers in the PVC processing sector;
7. Shares the Commission's view that the maintenance of the established limit value should on no account result in VCM pollution of the environment outside the works; requests the Commission, however, to deal in a separate Directive with the emission and immission problems which arise in this connection;
8. Believes it essential that the present Directive be continually revised in the light of developments in technology and occupational medicine and that Parliament always be consulted on such revisions;
9. Asks the Commission therefore to make the following amendments to its proposal pursuant to the second paragraph of Article 149 of the EEC Treaty.

TEXT PROPOSED BY THE COMMISSION OF
THE EUROPEAN COMMUNITIES (1)

TEXT AMENDED BY THE EUROPEAN PARLIAMENT

Council Directive on the approximation of Member States' laws, regulations and administrative provisions on the protection of the health of workers occupationally exposed to vinyl chloride monomer

Preamble and recitals unchanged

Article 1

1. The object of this Directive is the protection of workers employed in works in which:

- vinyl chloride monomer, hereinafter referred to as VCM, is produced, reclaimed, stored, discharged into containers, transported or used in some other way,
- vinyl chloride monomer is converted into unformed vinyl chloride polymers, hereinafter referred to as PVC,

who are exposed to the effects of VCM in their working area.

2. This protection shall be ensured by the establishment of:

- limit values for the atmospheric concentration of VCM in the working area,

Article 1

1. The object of this Directive is the protection of workers employed in works in which:

- vinyl chloride monomer, hereinafter referred to as VCM, is produced, reclaimed, stored, discharged into containers, transported or used in some other way,
- vinyl chloride monomer is converted into unformed vinyl chloride polymers, hereinafter referred to as PVC and into finished products,

who are exposed to the effects of VCM in their working area.

2. unchanged

(1) For complete text, see OJ No C 291, 10. 12. 1976, p. 5.

TEXT PROPOSED BY THE COMMISSION OF
THE EUROPEAN COMMUNITIES

13.2. Member States shall communicate to the Commission the texts of the main provisions of national law which they adopt in the field covered by this Directive.

TEXT AMENDED BY THE EUROPEAN PARLIAMENT

13.2 unchanged

Article 14 unchanged

Annex I to be amended in accordance with Article 3.2

Annex II unchanged

Prevention of accidents at work

Mr Masullo moved the oral question with debate which, together with Mrs Goutmann, Mr Pistillo, Mrs Squarcialupi and Mr Veronesi, he had put to the Commission on institutions and norms for the prevention of accidents at work (Doc. 137/77).

Mr Vredeling, *Vice-President of the Commission*, answered the question.

Agenda for next sitting

The President announced the following agenda for the next sitting on Tuesday, 14 June 1977:

10 a.m. and 3 p.m.:

- Lautenschlager report on a European Cooperation Grouping;
- Cousté report on double taxation;
- Jahn report on bird conservation;
- oral question with debate to the Commission and Council on recruitment policy;
- Osborn report on the annual accounts of railway undertakings (without debate);
- oral question with debate to the Commission on safety standards for hotels.

3 p.m.:

- Question Time

The sitting was closed at 8.30 p.m.

H. R. NORD
Secretary-General

Emilio COLOMBO
President

TEXT PROPOSED BY THE COMMISSION
OF THE EUROPEAN COMMUNITIES

6.3. The alarm threshold shall not, however, be greater than 40 ppm. If this value is exceeded, technical and personal protective measures shall be taken without delay.

TEXT AMENDED BY THE EUROPEAN PARLIAMENT

6.3. The alarm threshold shall not, however, be greater than 10 ppm. As soon as this value is exceeded, technical and personal protective measures shall be taken without delay.

Articles 7 and 8 unchanged

Article 9

9.1. A register shall be kept of workers employed on operations described in Article 1.1, with particulars of the type and duration of work, and the resulting exposure. A copy of this register shall be given to the industrial medical officer responsible for surveillance, unless the register is kept by the officer himself.

Article 9

9.1. A register shall be kept of workers employed on operations described in Article 1.1, with particulars of the type and duration of work, and the resulting exposure. A copy of this register shall be given to the industrial medical officer responsible for health protection at work, unless the register is kept by them.

9.2. The register referred to in subparagraph 1 shall be open to inspection by workers and their representatives.

Article 10 unchanged

Article 11

11.1. This Directive shall be reviewed at least every two years in the light of developments in technology and occupational medicine.

11.2. A Committee consisting of representatives of the Member States, with a representative of the Commission as chairman shall be set up for this purpose.

11.3. The Committee shall draw up its own Rules of Procedure.

Article 11

11.1. This Directive shall be reviewed at least every two years in the light of developments in technology and occupational medicine. Parliament shall be consulted on such revisions.

11.2. unchanged

11.3. unchanged

Article 12 unchanged

Article 13

13.1. Member States shall bring into force the laws, regulations and administrative provisions needed in order to comply with this Directive within 18 months of its notification and shall forthwith inform the Commission thereof.

Article 13

13.1. Member States shall bring into force the laws, regulations and administrative provisions needed in order to comply with this Directive within eight months of its notification and shall forthwith inform the Commission thereof.

TEXT PROPOSED BY THE COMMISSION OF
THE EUROPEAN COMMUNITIES

TEXT AMENDED BY THE EUROPEAN PARLIAMENT

13.2. Member States shall communicate to the Commission the texts of the main provisions of national law which they adopt in the field covered by this Directive.

13.2 unchanged

Article 14 unchanged

Annex I to be amended in accordance with Article 3.2

Annex II unchanged

Prevention of accidents at work

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dents; however, another 20% offer no courses, however short, on polymers.

Two objectives should be distinguished; one is to provide chemistry majors with an adequate and comprehensive understanding of polymers, both natural and synthetic; the second is to provide a fully polymer-grounded degree structure. We have favored the latter and our experience is that a satisfying treatment necessitates blending the physics and technology of polymers along with their chemistry. This leads to a teaching program firmly based on chemistry, physics, and mathematics which leads to an integrated view of polymer science in both its "pure" and "applied" aspects. In turn, this approach has caused the formation of separate polymer departments, as at Manchester, or of interdepartmental structures.

Alas, like Dr. Wicks, we find the current problem to lie in the availability of students. The past few years have seen a decline in entrants at the B.Sc. level while the M.Sc. course attracts many more overseas than home students; this is a national trend, not just endemic to Manchester. One is saddened by the reluctance of students to take up an area of education which, despite its apparent specialization, in reality offers a balanced and integrated science education and produces graduates for whom there is a real demand, even by industry in recession.

Dr. G. J. Howard
Reader in Polymer and Fibre Science, University of Manchester

Validity of animal testing

SIR: As a now-retired, but for nearly 40 years a research biochemist, I have serious reservations as to the validity of the animal tests so widely mentioned as indicating or proving the carcinogenicity of saccharin in man. I have discussed these reservations with other qualified biochemists and find them in complete agreement.

It is now well known that the induction of cancer by chemicals, or even by ionizing radiation, is a chemical process—that is to say, is a process involving one or more chemical reactions, the first of which involves the so-called proximal carcinogen. Chemical reactions proceed at rates proportional to the concentration of the reactants: The higher the initial concentration, the faster the reaction, and the higher the concentration or amount of product. Any subsequent reactions will likewise be accelerated, and any final product (the proximal carcinogen) will be more rapidly accumulated or increased in amount, and the "effect" (cancer) more likely to appear. This, of course, is the basis of the so-called Canadian tests as well as others: Large amounts for a short time equals small amounts for a long time.

However, this simple reasoning ignores three basic biochemical facts: 1. detoxification mechanisms, many of which are known, and which can be overwhelmed by large amounts of the toxic substance; 2. "repair" mechanisms:

The body material damaged by the proximal chemical may be regenerated (as has been shown, for example, in the case of DNA damaged by ionizing radiation or similar agents); 3. differences in metabolism—body chemistry—between animal and man (vitamin C, not required by the rat, is an example of such a difference). To these may be added a physiological factor: differences in rate of excretion of either the original chemical or the proximal material formed from it. (I realize that this can be regarded as a special case of point 3 above.) I discuss each of these briefly below.

1. Detoxification mechanisms for many classes of unnatural compounds (hydrocarbons, drugs, etc.) are known. Further, many such compounds cause an increase in the enzyme systems that do the detoxification; "tolerance" to certain drugs is based on this body reaction to the foreign substance. When an organism that has not built up that tolerance is suddenly overwhelmed by large doses, the result may be quite different from that occasioned by repeated small doses: The existing body defense mechanisms are overwhelmed, and the body has no time to develop the inducible defense mechanisms (enzyme systems).

2. Repair, like the induction of detoxification systems, takes time. The concept here is similar to the detoxification induction mentioned above: The greater the damage, or the more extensive the damage, the longer repair will take (skin cuts or abrasions exemplify this). Major short-term damage may overtax the repair mechanism, leading to irreversible changes (death, cancer), whereas the same total insult, spread over a longer time, may be repaired as fast as the damage is incurred (the same as for the detoxification mechanism described above).

3. Differences in metabolism between species are common. The rat can synthesize vitamin C; the guinea pig (and man) cannot. Man has a high-potassium, low-sodium red blood cell; in the dog, we find the reverse. There is no reason to believe that the chemical reactions, from administered substance to its excretory product (or to its "proximal" insult form), will be identical in rat (or any animal) and man. Even within man, we find different rates of reaction for the same enzyme system between one tissue and another.

I have been given to understand that the rat holds urine in the bladder longer, proportionally, than does man. This would be one more prejudicial factor: High concentration, for the first two reasons given above, and long time of exposure would probably yield, even in the same species, a different result from low concentration and short time of exposure. And repair could not keep up. (I might note here that diabetics and those ingesting large amounts of fluid—as in "diet" drinks—excrete a more dilute urine and excrete more urine than others; their exposure is thus lessened.)

For all these reasons, I contend that there are valid scientific grounds for challenging the assertion that the "Canadian" tests, or others involving large amounts of saccharin (or any ex-

traneous agent) over a short time span have significance for man. Neither cause and effect, nor epidemiology (in my view) has approached the degree of definitivity we now have with respect to cigarette smoking.

If this essay appears to challenge the "any amount" and "any animal" phrases in the Delaney amendment, it is so intended.

Waldo E. Cohn
Senior Biochemist (retired), Biology Division,
Oak Ridge National Laboratory.

CHEMICAL SAFETY

In support of Dr. de Jongh

SIR: I wish to support the warning of Dr. H. A. P. de Jongh (C&EN, Aug. 1, page 31) that all reductions with hydrides be carried out in a nitrogen or other inert atmosphere. The same holds for hydroborations, transformations of organoboranes, Grignard reactions, and those of most organometallics, even though many of these can be carried out without an inert atmosphere with only minor losses in yields. In the case of the $3\text{NaBH}_4/\text{AlCl}_3$ reagent in diglyme, tests showed that the reagent was stable to dry air and did not inflame when poured through air (J. Am. Chem. Soc., 78, 2582). However, these tests were performed with the clear, dry solution. Our solutions were prepared by mixing a clear solution of AlCl_3 in diglyme with a clear solution of NaBH_4 in diglyme. I agree with de Jongh that the presence of water, solid AlCl_3 , and possibly sodium borohydride, indicated as present in the reaction mixture that exploded, could produce a hydrogen-air mixture in the explosive range, ignited by spontaneously inflammable materials produced in the interaction of solid AlCl_3 with NaBH_4 (J. Am. Chem. Soc., 75, 209).

Herbert C. Brown
Purdue University, West Lafayette, Ind.

Inhaling alkylating compounds

SIR: The Journal of the American Medical Association for July 25, 1977, page 356 has abstracted the following article from *Deutsche Medizinische Wochenschrift*: "Occupational Lung Cancer after Inhalation of Alkylating Compounds: Dichlorodimethyl Ether, Monochlorodimethyl Ether, and Dimethyl Sulfate, U. Bettendorf. A 42-year-old chemist died from extensive pulmonary carcinoma, having inhaled for over seven years dichlorodimethyl ether and small amounts of dimethyl sulfate. This exposure took place in circumstances that, in animal experiments, have led to the development of cancer. A causal connection between the occupational exposure to these chemicals and carcinogenesis is implicated."

I thought a note on this would be of value to any unwary chemists working with these compounds.

Joseph D. Teller
Worthington Biochemical Corp., Freehold, N.J.