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16th March 1976
Bruxelles, le

Mr. Ralph L. Harding, Jr.
SOCIETY OF THE PLASTICS INDUSTRY INC.
Park Avenue 250
New York, New York 10017
U. S. A.

Dear Mr. Harding,

I have pleasure in enclosing copies of a book that we have prepared entitled "Vinyl Chloride Toxicity and the Use of PVC for Packaging Foodstuffs". The book is almost entirely the work of Barry Barnes. It is intended to bring together all the facts concerning the use of poly vinyl chloride food packages and to make an assessment of the risk factors and thus provoke, what we hope will be useful, discussions leading to a better understanding of all the factors involved.

The book has been distributed quite widely in Europe to government authorities, research centres and within industry. It has not been released to the press.

In view of the fact that national governments and the European Commission have copies we would have no objections if you wish to discuss the document with the FDA or any other branch of the US government. As a matter of interest we would like to know if this document is shown to a government department what protection from further publication copyright affords us.

Yours sincerely,

A.S. Garnett

A.S. Garnett

cc: Mr. Heckman

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Conseil Europeen des Federations
de L'Industrie Chimique

European Council of Chemical
Manufacturers' Federations

VINYL CHLORIDE TOXICITY & THE USE OF PVC FOR PACKAGING FOODSTUFFS

A Presentation by the
CEFIC Committee for the Toxicity of Vinyl Chloride

VINYL CHLORIDE TOXICITY

AND

THE USE OF PVC FOR PACKAGING FOODSTUFFS

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VINYL CHLORIDE TOXICITY AND THE USE OF PVC FOR PACKAGING FOODSTUFFS

A CEFIC Presentation

Evidence showing that vinyl chloride could be carcinogenic to man was discovered, for the first time, in January 1974. Since then industry world-wide has worked to reduce exposure wherever man might come into contact with vinyl chloride. This effort has been deployed at every interface, regardless of whether the exposure levels were high or already very low, since the dual aims have been both to ensure safety and also to reduce concern. Simultaneously, government authorities throughout the world have been engaged in regulatory action with the same objectives.

Exposures ranging from high to very low, can occur in several situations. These are listed below in decreasing order of intensity.

- (i) On vinyl chloride polymerisation plants
- (ii) On vinyl chloride production plants
- (iii) In PVC fabricating and compounding plants
- (iv) In the very close neighbourhood of the first two above. Very low vinyl chloride concentrations in the atmosphere can occur here
- (v) Through ingestion of foodstuffs or beverages wrapped or bottled in PVC. This last exposure level is many orders of magnitude lower than any of the preceding four.

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CHAPTER 1

PRINCIPAL FACTS ABOUT VINYL CHLORIDE AS A CARCINOGEN

(a) Human data

The ultimate identification of vinyl chloride as a carcinogen has come from the discovery of a significant excess of cases of a rare cancer - angiosarcoma of the liver - compared with the general population, among workers inhaling vinyl chloride gas while handling liquid vinyl chloride under pressure. (See Footnote 1) Throughout Western Europe and North America and including some Eastern Bloc countries, a total of 45 deaths and three living cases have now been identified, with an average latency period from the date of first exposure of about 20 years.

A number of characteristics of these bare statistics need highlighting.

- (i) The 48 cases in Europe and America have occurred over a total period of 14 years. The number of cases per year shows an increase with the years, but some of this increase may be due to the enlarged total workforce exposed, as PVC production increased rapidly in the 1950's.
- (ii) All of these authenticated cases are among workers employed in closed-in plants handling very large quantities of liquid vinyl chloride under pressure. All, except two, were employed in the polymerisation sections of plants. (See Footnote 2)

Footnote 1. Liver angiosarcomas are not uniquely associated with vinyl chloride: a connection with other materials (notably phosphorus arsenical sprays used in vineyards) has been identified, but does not occur naturally. Nevertheless a connection with vinyl chloride has been convincingly established.

Footnote 2. Of the two exceptions one was a worker employed in PVC production, but in a closed building in which polymerisation was carried out; the second worked in an aerosol-filling plant. In both cases, high concentrations of vinyl chloride were also likely.

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The concentration range to which men have been exposed during the 40 year life of the PVC industry cannot be stated with precision. Nevertheless estimates have been made of the atmospheric concentrations which existed in the workplace at different periods and for a range of jobs. The figures given in Table 1 below provide a background against which the known incidence of angiosarcomas may be qualitatively assessed; and the two together provide a basis upon which an assessment of risk in specific situations may be judged (see Chapter 2).

TABLE 1
History of Exposure of Workers in the PVC Industry
(Typical ranges)

<u>Years</u>	<u>VCM Polymerisation plant operators</u>	<u>PVC Fabrication operators</u>	<u>VCM Production plant operators</u>
1945-1960	Up to and beyond 1000 ppm	? ?	Up to and beyond 500 ppm
1960-1970	~300-400 ppm	possibly 10-20 ppm	>5 ppm
1973	~150 ppm	~5 ppm	~5 ppm
Now	~5 ppm	<2 ppm	<2 ppm

Plant to plant variations around these figures will have occurred: particular workers in specific jobs will have had higher exposures. For polymerisation operators, for instance, figures as high as 3000 ppm have been reported as existing for significant periods in some operations in the early years: in fabrication operations, too, theoretical calculations show that, where ventilation was poor and the process carried out in a confined space, atmospheric concentrations could have reached high levels in the past, even though typical levels were low. In monomer production, a sharp decrease occurred in the mid 1960's when the production process was changed. Prior to this, high levels could have occurred in some plants although worker exposure would still have been lower than on polymerisation plants.

(b) Animal feeding data

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Of the large number of studies of the effect of vinyl chloride on animals the first and most complete is that carried out by Professor Maltoni in

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Details of the Maltoni results are given in Appendix 3 and an attempt is made to correlate these with human experience. Though imprecise, the correlation does provide some support for the belief, which has been expressed, that the rat is more susceptible to damage from vinyl chloride than is man.

(c) Metabolic studies

During 1975 two studies of the metabolic fate of vinyl chloride in rats were published by the Dow Chemical Company and by ICI (Refs 1, 2). Both studies show that the rate of metabolic breakdown is also dose-related in a way that indicates a saturable process, the Dow results suggesting tentatively that saturation might occur between 10 ppm and 50 ppm for a rat. Suggestions have been made that further work might provide a relationship between the saturation level and a no-effect level: but it would be premature to argue a case for safe exposure levels on the present limited evidence alone (Note: Appendix 4 gives a more scientific synopsis of these results). Further metabolic studies are being carried out by Professor Henschler at the University of Wurzburg, at the Mario Negri Institute in Italy and in other academic centres in Europe.

(d) Summary

The facts of the preceding sections and of Appendix 3 can be summarised on the common basis of annual intake in gms/kgm of body weight. This unifying technique makes possible the comparison of past exposures with current regulated levels in production plants; it also makes it possible for vinyl chloride ingestion through food to be put into some perspective with those exposures known to have produced liver angiosarcomas in the past and with levels of exposure now permitted elsewhere. (Note that assumptions made in calculating annual intakes are given in Appendix 3 Footnote 10. In particular, a constant retention factor has been taken for ingestion and inhalation. However the conclusions reached are not sensitive to this assumption).

Footnote 4 contd. Other non-carcinogenic effects of vinyl chloride in high concentrations have been reported over the past ten years: acro-osteolysis, Raynaud's syndrome, scleroderma, minor liver function disturbances and thrombocytopenia. The prevalence and significance of these, if any, among production workers is still under review but their occurrence is not relevant to a discussion on the use of PVC with foodstuffs.

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CHAPTER 2

ASSESSMENT OF RISK

A precise calculation of the angiosarcoma risk associated with any particular level of exposure to vinyl chloride is not possible in the present state of knowledge. Human data is limited even on a world scale: rat data is more complete but overall there remains the problem of defining the relationship between human and rat response. Precise calculation of a risk from foodstuffs is immeasurably more difficult because exposure levels here are many orders of magnitude lower than those to which any existing data (human or animal) relates. The problem is therefore one of extrapolating from incomplete data over many orders of magnitude, to a risk level which by inspection is infinitesimally small.

Because of this, toxicologists, when asked to define the level of risk in foodstuffs, can only reply that the scientific evidence necessary to advise with precision on this question does not exist.

If is self evident, of course, that absolute safety could be assured by absolutely zero exposure. But this is a totally theoretical concept which is of no assistance in the solving of a practical problem. If absolute assurance of the absolute is demanded then no scientific evidence will ever be adequate since in risk analysis as in chemical analysis there is no technique for proving or demonstrating absolute zero. In these circumstances, what has to be sought is "an assurance of safety which removes all reasonable doubts. There remains a gap between reasonable doubt and absolute certainty which science cannot cross".

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Nevertheless, despite the impossibility of calculating a precise risk factor, it is clear that toxicologists have made a qualitative assessment of risk and have concluded that this is at a very low level indeed. Without such a conclusion, the statements in Footnote 6 that "there has never been any real risk to consumers", that "we can be confident that no serious damage has been done" and that "there is no need to restrict the use of PVC" could not have been made.

Some of the reasons for these reassuring, albeit qualitative, conclusions have been touched on in Chapter 1. They and others can be summarised as follows

- (a) Vinyl chloride-related liver angiosarcomas have occurred in workers probably exposed to at least 500 ppm: No cases have occurred in other workers who have been exposed to at least 50 ppm and possibly to considerably higher figures. The gap between 50 and 500 ppm is inadequately characterised since groups of workers who were clearly exposed, twenty years ago, to 200, 300 or 400 ppm have not been identified. In these circumstances, a conservative approach would be to assume that the known angiosarcoma cases might have occurred after prolonged exposures as low as 250 ppm or an annual dose of 22.5 g/kgm body weight.

Footnote 6 contd.

- (c) "The results (of a study of monomers in food and drink from PVC) have been submitted to the Food Additives & Contaminants Committee which considers that at the tiny levels at which these monomers are present, and in view of the lack of evidence of a hazard to health through ingestion, there is no need to restrict the use of PVC". R Moyle, Minister of State, Hansard, 4/4/74.

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TABLE 3

Additional Safety Factors Compared With		
Risk level of 250 ppm or 22.5 g/kg	Safe level of 5 ppm 0.45 g/kg	Safe level of 0.5 ppm 0.045 g/kg
2 million to 15 million	50,000 to 300,000	5,000 to 30,000

The size of these additional factors shows why toxicologists accept a best technological means approach and why they do not demand a ban on the use of PVC for foodstuffs. Moreover, with numbers of these dimensions it does not make sense to demand further increases, by a factor of two or three, unless these improvements are genuinely practicable and reasonable to achieve. A halving of existing vinyl chloride levels, while exceedingly difficult to achieve, would only increase an additional safety factor of 50,000 into one of 100,000 which in the context is not meaningful: wherever some improvement can be practically achieved, at not excessive cost to the community, however, industry has already accepted that it should be done.

- (b) The annual intake levels through food are so infinitesimally small as to raise the question whether they could in any circumstances have significance. Some years ago protagonists of the "one-molecule" theory argued that even a single molecule of a carcinogen can cause cancer, and that there is no such thing as a threshold limit. This proposition has increasingly been challenged: in particular a recent WHO report (Ref 3) concludes that "the possible existence of a threshold to the effects of both chemical carcinogens and mutagens should be envisaged". In an Annex, the late Dr Leo Friedman, formerly Director, Division of Toxicology in the US Food & Drugs Administration, states

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Because of these major conservative factors, Friedman points out that "the calculated permissible levels obtained - (by the Mantel-Bryan approach) are between three and four orders of magnitude lower than those obtained by the more conventional approaches used to determine acceptable daily intakes".

Because of this we cannot endorse the general use of Schneiderman's conclusions and their application to other situations. It is nevertheless of interest to present his conclusions and to consider whether, despite their conservatism, they can still give guidance about the safety of PVC for foodstuffs.

Schneiderman calculated from Maltoni's results the atmospheric concentrations at which no more than one rat in varying sized populations would develop liver angiosarcoma.

TABLE 4

Risk of one angiosarcoma in	100,000 rats	1 million rats	10 million rats	100 million rats
Atmospheric concentration	= 251 ppb	82 ppb	29 ppb	11 ppb

(ppb = parts per billion -
or one thousand million)

Schneiderman concludes therefore that a risk of one in 100 million will occur at atmospheric concentrations of 11 ppb. Using the same techniques as before (see Footnote 10 Appendix 3) this concentration corresponds to an annual intake of 0.0003 g/kg body weight for a rat or 0.0009 g/kg for an active man. Annual average intakes through foodstuffs in all member states are below this figure by factors of 100-500. There would seem little reasonable doubt that an assurance of safety is provided by this analysis.

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It is the extremely low concentrations which make it impossible for toxicologists to define a risk; but it is also the high factors of safety derived from these low levels which make it acceptable for control to be based on the best practicable means concept. It is important to accept though that the emphasis in best practicable means must be just as strongly placed on the word 'practicable' as on the word 'best'. To achieve a definition of what is best and practicable requires close liaison between governments and industry.

The assessment of practicability, as the word itself implies, requires a common sense approach: and good sense will recognise that when a risk has approached so close to zero as effectively to be zero, further minor risk reductions (from 1.0 to 0.5 in 1000 million for instance) are not, in reality, meaningful; they should only be sought as part of a longer term, evolutionary and practical co-operative programme.

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The idea, therefore, that migration should be limited to a "non-detectable" level when measured by the most sensitive analytical method must be rejected because

- (a) the setting of this level involves no consideration of whether it can or cannot be achieved
- (b) the setting of the level by this means involves no detailed examination of the known facts about vinyl chloride and no assessment of the risk or lack of risk associated with foodstuffs packed in PVC. The "least detectable" level is related simply to the state of analytical science - which is irrelevant both to the question of hazard and to that of feasibility of achievement.
- (c) it leaves industry in a state of total uncertainty of what it must achieve in the future and whether it can in fact achieve this - and government in a state of uncertainty about what it has decreed.
- (d) While the sensitivity of a test method when used on a clean sample can be defined, the ability to detect, in practice, will depend on the nature of the material to be measured and on the ease of getting representative samples consistently; and on the quality of the control laboratory carrying out the tests: eg although a very low level of VCM may be measured in solution in pure water, the same analytical technique will give nothing like the same sensitivity in wine and even less in margarine where interfering substances are present. The least detectable level is therefore by no means as clearly defined a concentration as it would appear.
- (e) The concept of least detectable ignores the fact that in any manufacturing process there is an inevitable spread of achieved results about a mean. For a non-detectable limit always to be met, all of these results must be below the least detectable level so that, if the most sensitive analytical method is indeed being used, the manufacturer can have no knowledge of variations or trends in his daily production. All of his results will be zero - until they aren't! Control of a manufacturing process is impossible if no information can be obtained on what the process is achieving,

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The extent to which different governments have already used these concepts will be reviewed in Chapter 4; and industry's current views on the optimum method will be outlined in Chapter 5.

This chapter of the memorandum is concerned only with principles and concepts: and both (b) and (c) above, through incorporating a maximum level, raise the question of how and where achievement against this maximum should be assessed.

3. The Accuracy and Precision of Measurement

The values quoted later in this document (Chapter 5) are the average of measurements, made by the best analytical technique currently available, on a range of materials from production. This average can be taken as a measure of current achievement but must be interpreted with care.

The average quoted is the arithmetic mean of measurements. In any system where the end result is obtained after many separate and sequential processes, however, the individual results will vary widely about the mean. Measurements of the vinyl chloride content of PVC containers so far, show that actual values extend over a range exceeding 10 times the average but 95% of the values do not exceed 5 times the average. The average itself is open to some doubt because a number of the values are below the level of detection of the method of measurement and the calculated mean depends on the statistical treatment of these values.

Again, the precision of measurement of these values is not yet known because variations in sampling are known to occur and interpretable replication, for determination of precision of measurement, is difficult. However measurements become much less precise as the limit of detection is approached and this is the case with current measurements.

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4. Where should control be established?

The preceding paragraphs have discussed the problems and the significance of measurement. There remains the question of where control should be exercised - on the foodstuff or on the container?

Control of vinyl chloride in the foodstuff puts the obligation on the foodstuff packer to meet the regulation; but he is not always himself in control of the contaminant, since this derives from a container which may be purchased from another supplier; nor, because of the slow rate of diffusion from container to food, can he even measure his achievement until possibly weeks after his product is made. If the maximum permitted concentration in the foodstuff is set at a level which is close to the limits of achievement and of measurement, neither the food manufacturer, nor the container supplier can be sure, as a result of plant control tests, that the limit will invariably be met; logically but ad absurdum the margarine packer for instance would have to retain his product until it was unsaleable before he could satisfy himself that migration was within statutory limits.

If, on the other hand, the limiting concentration in the foodstuff is set high enough to take account of the analytical, process and time variations, mentioned in section 3 above, then controlled manufacture can proceed. It is scarcely necessary, here, to emphasise that legislation on food contaminants (other than a complete ban) must establish a proper relationship between feasibility and statutory requirement, since one of the main purposes of legislation must be to enable the manufacturer to establish primary control.

This primary control can be established by the manufacturer (if the limits in foodstuffs are properly set) through process control of the vinyl chloride content of the package, since a good correlation between this parameter and the ultimate level of vinyl chloride in the packaged foodstuff has been established. (See Footnote 8) This observation raises

Footnote 8. It should be noted that PVC does not depolymerise, as do some other polymeric materials. Vinyl chloride concentrations in the foodstuff can therefore only derive from the traces of residual, unpolymerised monomer which are left in the package after fabrication.

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CHAPTER 4

CURRENT LEGISLATIVE POSITIONS

Chapter 3 of this memorandum has established a list of principles upon which legislative action might be based. With these principles as background, it is useful to review progress made so far by national governments to regulate the use of PVC for foodstuff packaging, and to consider how far these conform to the principles set out in the preceding chapter.

1. UK

In the UK it is not normal practice to specify concentration limits for food contaminants which may have damaging effects. The Ministry of Agriculture, Fisheries and Food insists, however, that maximum effort should be used to reduce concentrations to the lowest practicable and reasonable level. This requirement has applied to PVC since early 1974. In the intervening two years major and continuous testing of foodstuffs has been carried out by government and industry scientists in a co-ordinated programme. Joint surveillance of this kind enables pressure to be maintained for the continuing reduction of vinyl chloride levels.

2. France

No definitive restriction has been placed on PVC packaging for foodstuffs. A directive from the Ministry of Agriculture (Ref. 6) says that firm decisions should await the results of toxicological studies now being undertaken. In the meanwhile a recommendation is made that the vinyl chloride content of liquid food should not exceed 0.050 mgm/kgm

3. Holland

No formal regulation is in force but a letter from the Ministry of Public Health & the Environment (Ref. 7) requests action if the migration of vinyl chloride into food exceeds 0.05 mgms per 6 square decimetres of surface. This corresponds roughly to 0.050 mgm/kgm of liquid.

4. Germany

No formal regulation exists but a statement from the Kunststoffskommission (Ref. 8) says that no health risk is to be expected by consumers of food

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Because of this restriction, none of the proposals in Chapter 3 are available for control of vinyl chloride. The setting of a maximum limit is impossible, because any concentration of a carcinogen is prohibited by Delaney. Similarly the use of the "non-detectable" concept poses problems since the term itself - (non-detectable) - implies that vinyl chloride might still be present, and might indeed be detected through the use of more advanced analytical research techniques.

In this situation, FDA has produced a new form of words. PVC may be used in contact with foodstuffs "where the potential for migration of vinyl chloride is diminished to the extent that it may not reasonably be expected to become a component of food". Against this definition FDA have decided that certain PVC articles may continue to be used without any regulatory control. For other types of PVC package, "prior sanction" for their use with food will be withdrawn. Strictly speaking this is not a ban since it is open to any producer to demonstrate that the quality of his product is within the FDA criterion: and if he were successful in convincing FDA then sanction for use of the product could be given.

FDA's distinction, between two different groups of PVC packaging, was based on very limited and out of date analytical information. The levels they quote for the products no longer to be sanctioned are more than two years old and have been very significantly reduced since then. A major dialogue is now proceeding between US industry and FDA, the aim of the former being to demonstrate that all PVC food containers now come within the FDA's approved quality and that "prior sanction" should not be withdrawn.

The outcome of this debate is impossible to predict. Although a mass of analytical data will undoubtedly be presented, the FDA criterion quoted above is so qualitative and subjective in nature that the final decision will inevitably owe as much to semantics as it does to science (See Footnote 9).

Footnote 9. Already the Health Research Group, which seeks a total ban on PVC for foodstuffs, has stated in a submission to the Hearing Clerk that "the oversights and charades connected with the diethylstilboestrol case, wherein FDA officials for seventeen years pretended that residues did not exist, are sure to be repeated with FDA's vinyl chloride proposal" (emphasis added). At the same time, the Council on Wage & Price Stability, which seeks deferment of the proposed regulations states that "the risks do not specifically define a minimum amount of vinyl chloride presence" because "no level of reasonableness is defined".

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CHAPTER 5

THE ACHIEVEMENTS OF INDUSTRY

Chapter 4 has set out the current attitudes of governments to the problem. In general, the current consensus view sets a limit of 0.050 mg/kg for permitted vinyl chloride concentrations. Chapter 5 presents the current achievements of European industry and considers the extent to which these are consistent with governmental recommendations.

1. Method of Measurement

The results discussed in the following paragraphs have been obtained by gas-liquid chromatography based on the so-called "head space" method. Minor variations of the technique exist but the basic methods, as practised in France, are outlined in Appendix 8. The limit of detection of the method, in the hands of a research analyst, is between 0.005 mg/kg and 0.025 mg/kg in foodstuffs, depending on the nature of the foodstuff; and is of the order of 0.5 mg/kg in PVC packaging materials themselves. The precision of the method has been discussed in Chapter 3 and Appendix 6. As might be expected, reproducibility decreases markedly - even in the hands of expert analysts - as concentrations approach the limit of detection. At 20 ppm* in a PVC container, the precision of measurement was $\pm 20\%$ but at 1.5 ppm, the 95% confidence limits exceeded $\pm 100\%$ of the measurement. Vinyl chloride measurements in water taken from a PVC bottle showed a variation of $\pm 70\%$ at 0.010 mg/kg: but at 0.002 mg/kg, the 95% confidence limit far exceeded $\pm 100\%$.

As will be seen, the average achievements of European industry now approach the limit of detection quite closely, so a factor must be applied to most results before they can be declared different from one another or from any applied standard. A factor of five has been suggested in Chapter 3.

* x ppm $\equiv$ x mg/kg

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TABLE 4

Type of Package	Typical Mean ppm	Compliance Level ppm
Flexible plasticised films	< 1	< 5
Bottles, most containers	1	5
Copolymer foils for deep drawn containers	5	~10

(b) Foodstuffs

Uncertainty about the eventual vinyl chloride content of a single PVC package arises only from the normal variations about the mean of any industrial production process. Once the package is made, the real vinyl chloride content is fixed and the remaining uncertainty is concerned solely with analytical precision.

In the case of vinyl chloride in foodstuffs, the situation is much more complex and the actual vinyl chloride content of a foodstuff taken at random from a retailer's shelf can, in the limit, vary much more widely. Clearly, at the time of filling a PVC container, all of the monomer is absorbed in the PVC and the level in the foodstuff is zero. Monomer reaches the food by a slow diffusion process, in competition with diffusion to outside air and to air within the containers, and the amount of vinyl chloride migrating into the food will increase from zero over the whole period of distribution and storage. The process will go at different speeds - and possibly to different limits - with change of temperature, and the concentration in the food at a given percentage migration across the interface will depend on the relative weights of containers and food (container size) and also on the concentration of vinyl chloride originally in the container.

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Applications (i) and (ii) are of the type where the very low monomer contents of the package or the short shelf lives, often at low temperatures, of the packed product assist in the production of food with negligible vinyl chloride contents in the 0 to 0.010 mg/kg range. Higher contents exist however (though these are still, in absolute terms, very low) in the case of beverages and foods packaged in bottles or other hollow containers. The situation can be exemplified by a study of the bottle situation.

(iii) Rigid PVC bottles

Extensive studies have been made of the migration of vinyl chloride from PVC bottles into a range of contained liquids over a period of a year, using bottles with initial vinyl chloride contents of 2 ppm upwards. Not unexpectedly, in view of the variables mentioned earlier, there is a considerable scatter of results but, in all cases, a similar envelope encompasses all the results. (A typical graph for mineral water is given in Appendix 9). The characteristics of this common envelope show, in terms of migration, that in the most extreme situation after 3 months of storage <20% of the total VC has migrated to

"	6	"	"	"	<30%	"	"	"	"	"	"	the content
"	12	"	"	"	<40%	"	"	"	"	"	"	"

Simple arithmetic calculation, from this finding, shows that, for bottles of different vinyl chloride contents and of different sizes, the maximum content in the liquid after 12 months storage might be expected to be as in Table 5.

TABLE 5 - Theoretical Maximum Possible Migration

Monomer content of bottle	Monomer content of liquid (ppb) in		
	0.336 32g Bottle	2 litre 90g Bottle	1 litre 36g Bottle
0.75 ppm	29	13	10
1.0 ppm	38	18	14
1.5 ppm	57	27	21
2.0 ppm	76	36	28

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3. Summary

Industry is now able to operate to a maximum limit, strictly observed, for vinyl chloride in food, of 0.050 mg/kg in nearly all applications. Exceptions to this may occur with small containers and, recognising this, industry is continuing its work to get all results below 0.050 mg/kg. The achievements of industry are therefore now in line with the targets set by several European governments during 1975.

There are four major features of this achievement which need to be thoroughly understood

- (i) The difficulty of meeting any imposed maximum level for every individual container, lies in the extreme tail of the distribution of results above the mean.
- (ii) Because this tail is partly a natural result of a sequence of operations and in part a consequence of events which occur after the package has left the manufacturer's control, the problem of reducing the tail further is a difficult one. Further significant reductions of the maximum level are not likely to be achieved quickly, nor without major and costly efforts which may be totally disproportionate to the advantage gained.
- (iii) The use of a maximum limit concept concentrates thought and effort on the few "rogue" results at the tail of the distribution rather than on the much larger number of typical results which are at a very much lower level. Since, in the protection of the public, we are concerned with the continuing average exposure and not with the very infrequent high result, the merits of a joint government-industry procedure for continual review of progress are obvious. This method of control (proposed as one alternative in Chapter 3 and practised by the UK) concentrates attention on the average result and the real exposure of the public, and not on the largely irrelevant extreme result.
- (iv) Because of these characteristics, the 0.050 mg/kg limit gives a false impression of the true achievement. Reference to the graph in Appendix 9 and to Table 5 shows that though a litre bottle of water may, rarely, contain 0.050 mg/kg of vinyl chloride, the water in almost all bottles, based on a typical storage time of 4 weeks, will be consumed with a vinyl chloride content of only

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APPENDICES

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Notes

- 1 The German case reported as still living is open to some doubt. Further enquiries are being made about this case.
- 2 As reported in the main text, all of these cases, except two, were among polymerisation workers who spent a significant proportion of their time in the manual cleaning of polymerisation reactors. The two exceptions (in Germany and Sweden) were a worker in a monomer plant and a worker in an aerosol-filling plant.
- 3 In the absence of detailed epidemiological studies, a very crude indication of the variability of incidence can be obtained by noting the number of cases on individual plants and also the number of plants which have operated for more than 20 years and which have no recorded angiosarcomas.

Analysis along these lines shows

2 plants (in USA and Canada)	have nine cases each
2 plants (both in USA)	have three cases each
4 plants (two in Germany, two in E Europe)	have two cases each
13 plants	have one case each

Approximately 20 plants in Western Europe and USA, which are more than 20 years old, have no reported cases.

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The final case was of a worker in Italy who had been involved in the production of PVC packs. This case has been reviewed by Professor Maltoni who has recorded that the case is not homogeneous with the other liver angiosarcomas because the primary site, although difficult to define, seems to be pericardium: and also because of the much shorter latency time and period of possible, though unquantified, exposure (six and three years respectively).

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TABLE 2

60 rats/group: exposure time 52 weeks: experiment time 135 weeks
exposure time 17 weeks: experiment time 143 weeks

Exposure for → at ↓	Annual intake (g/kg)		Liver angiosarcoma		Total tumours	
	52 wks	17 wks	52 wks	17 wks	52 wks	17 wks
6000 ppm	180	60	13	1	31	16
2500 ppm	75	25	13	1	32	13
500 ppm	15	5	7	1	22	6
250 ppm	7.5	2.5	4	0	16	7
50 ppm	1.5	0.5	1	0	10	6
zero	0	0	0	0	6	10

Maltoni's ingestion experiments are, as yet, incomplete but the results so far are summarised in Table 3.

TABLE 3

80 rats/group: exposure time 52 weeks: experiment time so far 84 weeks
(The data in the table is normalised to a 60 rat-group to allow comparability with Tables 1 and 2)

Daily dose mgm/kg body wt	Annual intake g/kg body weight	Liver angiosarcoma	Total tumours
50	12.5	6	8
16.65	4.2	4	4.5
3.33	0.8	zero	zero
zero	zero	zero	zero

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Data on human reaction to vinyl chloride is much more rudimentary, but for comparison purposes with Table 4, the following table has been constructed (see Footnote 10 for method of calculation of human dose).

TABLE 5

	Annual intake g/kg body weight	Liver angiosarcomas
<u>Rats</u>	75-180 4-15 1.5	very high incidence 20% of grp high incidence 4-10% of grp low incidence 2% of grp
<u>Humans</u>		
Operators exposed to 500-1000 ppm	45-90	angiosarcomas occur
Operators exposed to 100 ppm	9	no cases
Fabrication plant operators in early years, exposed to 20-50 ppm	1.8-4.5	no cases

In attempting a comparison between rats and humans on an annual intake basis, it should not be overlooked that a year, for a rat, is half a lifetime. On a total cumulative dose basis, therefore, the intake by men has been very much higher, relative to the rat, than the figures in Table 5 suggest. This factor may well strengthen further the inference which has been drawn from the figures in Table 5, that rats are more susceptible to damage by vinyl chloride than is man.

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APPENDIX 5

Extracts from WHO Technical Report No 546

"Assessment of the Carcinogenicity and Mutagenicity of Chemicals"

Section 6. Assessment of Hazards

"The term "carcinogen" has caused confusion because it applies to agents that are so varied in their quantitative and qualitative characteristics that their control requires many different approaches. However, common usage would seem to necessitate retention of the term. Chemical carcinogens can vary in potency in comparable test systems by a factor as high as 10^7 .

Since all chemical carcinogens pose a hazard, human exposure must be reduced to the feasible minimum."

...."It would seem logical that tumour induction be considered as a manifestation of toxicity to be studied as an individual problem in each instance. In some cases, the data available may permit the logical determination of a tolerance level whereas in others, currently the great majority, no such approach is possible."

Section 8. Recommendations

.... "(3) In those situations where carcinogens are unavoidable, or where the banning of a substance would impose a hardship or an unrealistic economic burden, the toxicologist must assess the risks associated with different levels of exposure. Proposed approaches for such evaluation include those made by Mantel & Eryan and by Albert & Altshuler. All the proposals suffer from lack of sufficient data to establish their validity and/or from arbitrary assumptions that lead to unrealistic estimates. Friedman (see Annex) has proposed the incorporation of the equivalent of a reference standard to make relative assessments possible. This whole area is of great practical importance and it is suggested that WHO should convene a separate meeting to evaluate this subject."

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hazard are: (1) the probabilities that an individual will experience a given exposure; (2) the likelihood that the risk being studied will be overshadowed by some other competing risk and therefore will not have become fully operative; and, related to this, (3) the fact that the age of occurrence of cancer must also be considered when evaluating the hazard to health, especially as there is a long latent period for carcinogenesis, which usually gets longer as the exposure gets smaller."

.... "Since the Mantel-Bryan approach does not take into account many of these other factors that determine actual hazard, the extrapolations derived by this system are obviously highly conservative. The calculated permissible levels obtained are between three and four orders of magnitude lower than those obtained by the more conventional approaches used to determine acceptable daily intakes. Since it seems evident that despite the theoretical and practical deficiencies of current safety evaluation procedures, they work very well for practical purposes, it must be concluded that something is lacking in the Mantel-Bryan approach that makes the extrapolation by this method unrealistic. Nevertheless, such estimates could be very useful if it is recognized that the choice of each of the three factors in their system is arbitrary and that, for practical purposes, other choices could be equally justified. For example, a probit slope of 1.5 rather than 1 would make a considerable difference in the extrapolation and still be consistent with the experience of those engaged in evaluating the safety of food components. A 90% confidence interval is not an unacceptable level of statistical assurance, and the meaning in real life of the probability of 1/100 million is hard to imagine in comparison with other everyday risks. Nevertheless, regardless of these specific details, the numbers obtained must be calibrated in some way to practical real life experience so that they can be set in the proper perspective for purposes of making benefit/risk comparisons that will lead to policy decisions."

.... "As an initial step, I recommend that the Mantel-Bryan approach to assessment of risks from exposure to low levels of carcinogens be "calibrated" by calculation of the "Mantel-Bryan risks" for those

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APPENDIX 6

Accuracy and Precision of Measurements

VCM in foodstuffs and plastics can be measured by a number of methods. None of these methods can measure low levels of concentration directly within the solid or liquid matrix and all depend on some technique of separation. All the methods in general use are comparative and require calibration with standards of known concentration. Thus the accuracy and precision of the measurement is a function of the errors associated with the various stages of sampling, separation, measurement and calibration.

So far most of the analytical work of this type has been carried out in research type laboratories during investigations of contamination and migration. The analytical techniques have been chosen to provide the maximum information possible on the sample under investigation and only limited work has been done on determining the precision and accuracy of the methods. Such information as is available is summarised below. In view of the limited data available the values of precision and accuracy are calculated only approximately. For simplicity in presentation concentrations, unless otherwise stated, are expressed in ppb (1 ppb = 1 $\mu\text{g/kg}$).

1. Sampling Variation

Duplicate samples taken from a PVC food container with a low content of VCM regularly show a ratio of 2:1 in the VCM content of the samples.

The VCM content of samples of solids taken from PVC containers shows a wide variation according to the part of the solid selected.

Samples of liquids taken from PVC containers can show differences according to the amount of airspace in the container. For example, if VCM is extracted by water from a PVC bottle at 25°C the VCM within the bottle will be divided between the water and the airspace. The amount of VCM in the water will depend on the quantity of water present in the bottle as follows:

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In the above paragraphs the 95% confidence limits have been calculated in the normal manner. When the levels of measurement approach the limit of detection of the analytical method, the variations about the mean of a number of results becomes of the same order as the level of measurement and some of the usual statistical parameters cease to have meaningful values. The statistical treatment of the limit of detection of a method of analysis is complicated and cannot be dealt with here in detail. It may be seen from the above, however, that as the value measured approaches the limit of detection the error in analysis can often lead to a value of measurement of two or more times the true value.

The results quoted above were obtained in laboratories working on research or development activities. If the same types of analyses were carried out under process control conditions, greater variation in results would be expected. No tests have been made to check this variation on the particular analyses concerned, but on another analysis of similar type and complexity it was found that the research laboratory showed a relative standard deviation of 7% and a works laboratory showed 20%. It is to be expected that a similar ratio would be found in the analyses in question, particularly at low levels of concentration. One works laboratory has reported a limit of detection about five times that accepted in research type laboratories but this may be due to special circumstances not yet resolved.

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Ultimately however the Department accepted and themselves redrafted Senator Delaney's clause "to allay any lingering apprehension" but the Senate Committee on Labor and Public Welfare recorded that "we believe the bill reads and means the same with or without the inclusion of the clause". The revised wording of the clause was ".... no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal".

Clearly, at the time, this was intended to be read in the total context of the amendment with its emphasis on testing, on the probable consumption level, on safety factors and on reasonable certainty under the conditions of use.

However since 1958, precedent has established the clause as an enactment with a separate and different message of its own which uniquely places an absolute prohibition on any additive suspected of causing cancer under any conditions.

Parenthetically and retrospectively, it is interesting to observe that there was probably a reasonable case for this narrow interpretation in 1958. Seventeen years ago, analytical techniques were much inferior and in the case of vinyl chloride for instance the non-detectable level in foodstuffs would probably have been several orders of magnitude greater than is possible with present-day techniques. In 1958, therefore, the non-detectable approach to a carcinogen could have been unacceptable because of the insensitivity of the test method. Paradoxically as we have seen, the non-detectable approach is equally unacceptable in 1975 because advances in analytical technique have now outstripped both the ability of process controls to achieve the levels which can be measured, and the ability of toxicologists to comment with precision on the significance of these levels.

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1. DETERMINATION OF VCM IN FOODSTUFFS AND THEIR SIMULANTS(1) PRINCIPLE OF THE METHOD

The vinyl chloride monomer present in foodstuffs or their simulants is determined by gas-liquid chromatography with flame ionization detection using the "head space" method after dilution or suspension in dimethylacetamide.

(2) REAGENTS

(2-1) N, N-dimethylacetamide free of volatile impurities likely to interfere, with vinyl chloride monomer under the measurement conditions.

(2-2) Vinyl chloride monomer (VCM)

Use a product of purity greater than 99.5%.

(3) PREPARATION OF A STANDARD SOLUTION CONTAINING APPROXIMATELY 1.3 g/l VINYL CHLORIDE MONOMER

Vinyl chloride must be handled in a ventilated fume cupboard.

Weigh to the nearest 0.1 mg a stoppered, capped 50 ml antibiotic flask containing 50 ml dimethylacetamide.

Fill a 50 ml syringe with gaseous vinyl chloride monomer. Leave this in contact with the syringe for about 3 minutes, empty the syringe and then refill it with 50 ml gaseous vinyl chloride.

Fit a hypodermic needle on to the syringe and reduce the volume of the gas contents of the syringe from 50 to 25 ml.

Inject the 25 ml vinyl chloride slowly into 50 ml dimethylacetamide present in the flask and then reweigh the flask.

Using the weight increase of the flask, calculate the vinyl chloride content of the solution thus obtained.

(4) STANDARD SOLUTION OF ABOUT 0.13 g/l OF VINYL CHLORIDE MONOMER

In a dilution flask, dilute the solution prepared as in section 3 tenfold with dimethylacetamide, at the same time reducing the volume of air (head space) as much as possible. If necessary, carry out a check on the solution obtained by gas-liquid chromatography using direct injection with an internal standard.

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- temperatures :

injector 130° C

detector 130° C

oven 54° C

Inject 1 ml of the gas contained in the "head space" by means of a calibrated gas syringe.

(7-2-2) Examination on a non-polar phase

- chromatograph equipped with a flame ionization detector 1 mV,
full scale potentiometric recorder

- stainless steel column

length : 6 m

internal diameter : 2 mm

stationary phase : SE-30 15% on AW, DMCS Chromosorb (60-80 mesh)

vector gas : nitrogen, about 1.5 l/h

flame : hydrogen 1.8 l : h

air about 10 l/h

temperatures :

injector 200° C

detector 230° C

oven 65° C

Inject 1 ml of the gas contained in the "head space" using a calibrated gas syringe.

(8) STANDARD CURVE

For the two chromatographic systems, prepare a standard curve by plotting the quantities of vinyl chloride monomer present in the standard samples along the abscissae and the surface area beneath the corresponding peaks along the ordinates.

(9) CALCULATIONS

For each test, plot the surface area beneath the peak obtained and note the quantity of vinyl chloride monomer present in the flask (let this be V ug).

The vinyl chloride monomer present in the product being examined, expressed in mg/kg, is equal to 0.1 V.

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2. DETERMINATION OF VCM IN MATERIALS BASED UPON POLYVINYL CHLORIDE(1) PRINCIPLE OF THE METHOD

The material is dispersed in dimethylacetamide in a stoppered flask.

The vinyl chloride present in the gas phase in equilibrium with the liquid phase is determined by gas-liquid chromatography.

(2) REAGENTS

(2-1) N. N-dimethylacetamide free of volatile impurities likely to interfere under the conditions of measurement employed (5), with the vinyl chloride monomer.

(2-2) Diethyl ether (internal standard)

(2-3) Solution containing about 1 mg/ml diethyl ether in dimethylacetamide

Into a 20 ml graduated flask containing 20 ml dimethylacetamide, inject 25 μ l diethyl ether using a calibrated syringe and plunging the needle of the syringe into the solvent.

Stopper the flask and mix well.

(2-4) Solution containing about 1 mg/l diethyl ether in dimethylacetamide

To be prepared freshly by diluting the above solution a thousandfold.

(2-5) Vinyl chloride monomer (VCM)

Use a product of purity greater than 99.5%

(3) PREPARATION OF THE STANDARD SOLUTION CONTAINING ABOUT 1.3 g/l VINYL CHLORIDE MONOMER

Vinyl chloride monomer must be handled in a ventilated fume cupboard.

Weigh to the nearest 0.1 mg, a stoppered, antibiotic flask containing 50 ml dimethylacetamide.

Fill a 50 ml syringe with gaseous vinyl chloride monomer and leave this in contact with the syringe for 3 minutes. Empty the syringe and then refill it with 50 ml gaseous vinyl chloride. Fit a hypodermic needle to the syringe and reduce the volume of the gas in the syringe from 50 to 25 ml.

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(5-6) Temperatures

- oven : 25° C
- injector : 150° C
- detector : 150° C

(5-7) Injection

Introduce the needle of the syringe via the stopper into the gaseous phase of the flask equilibrated at 45° C, draw out about 2 ml gas into the syringe, expel the gas back into the flask and then draw out 1 ml gas and allow the internal pressures of the flask and the syringe to equilibrate for 15 seconds, and then rapidly inject the millilitre of gas thus sampled into the injection chamber of the chromatograph.

After five injections, it is necessary to clean out the column by heating for 2 h at 130° C after having taken the precaution of disconnecting the detector in order to avoid its becoming soiled.

Standard Curve

Prepare five stoppered, crimped antibiotic flasks, containing 10 ml of the solution 2.4 and inject respectively 1, 2, 5 and 10 µl of solution 3.

Place the five flasks into a 45°C ± 1°C thermostatically controlled bath for 16 h and continue as described under section 5.7.

Prepare the standard curve by plotting the quantities of VCM present in the flasks along the abscissae and the heights of the corresponding peaks along the ordinates, after having applied correction according to the height of the diethyl ether internal standard peaks.

Calculations

Plot the height of the peak obtained in the test (after correction according to the height of the internal standard peak) on the standard curve and read off the quantity of VCM present in the flask (3). For a 2 g sample, the VCM quantity expressed in y g corresponds to the VCM content in mg/kg or ppm present in the material.

Footnote.

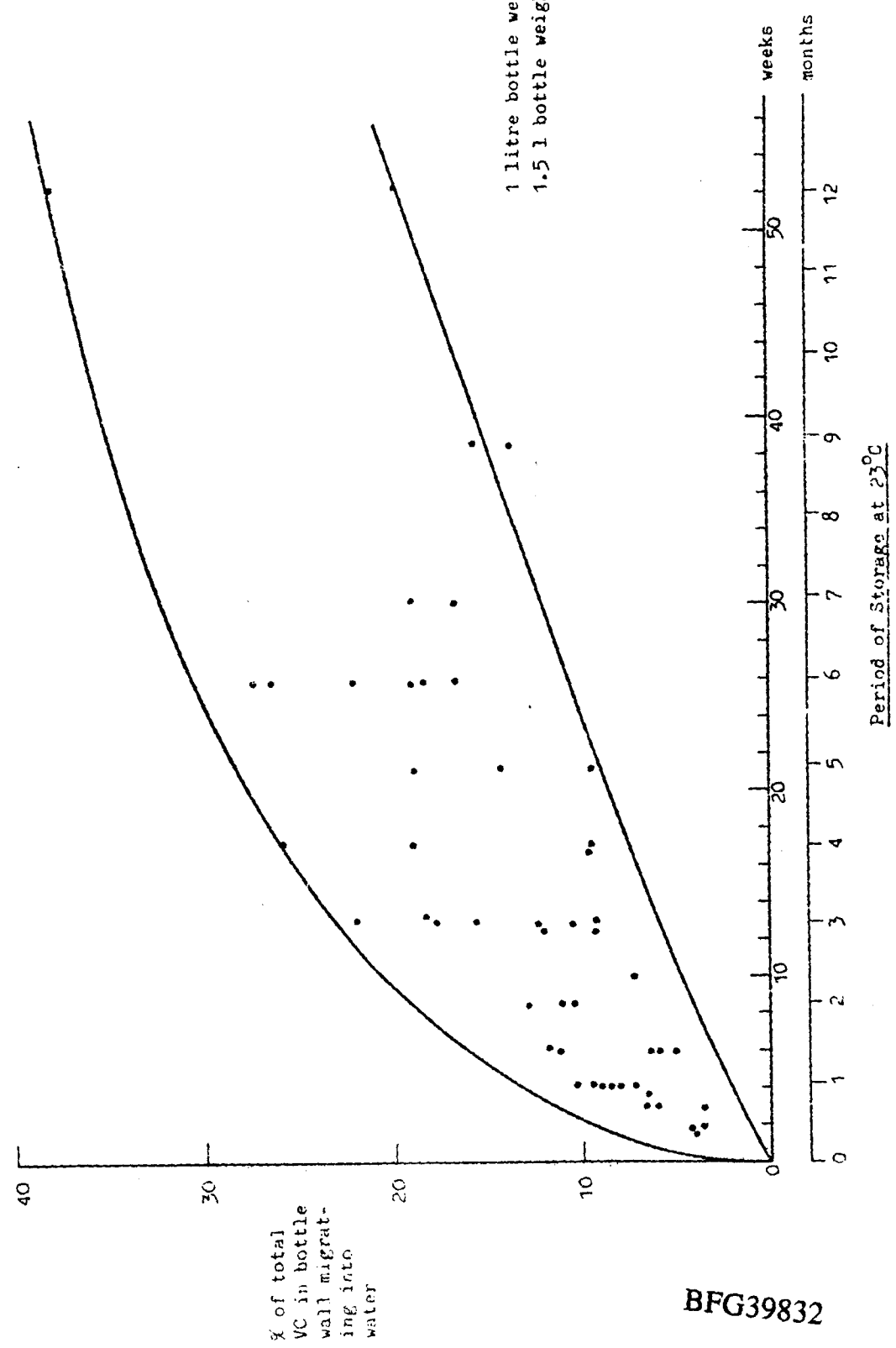
(3) Related, where appropriate, to the AFNOR T 01-005 standard.

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APPENDIX 9

MIGRATION IN MINERAL WATER



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2. France

- (a) Range of consumption 0.1 $\rightarrow$ 1.0 kg of food & liquid from PVC/day
- (b) Typical concentration of VCM in foodstuff/liquid 5 ppb
- (c) Typical yearly consumption per person = $5 \times 365 \times 0.1 \times 10^{-9}$ Kg
 $\rightarrow 5 \times 365 \times 1 \times 10^{-9}$ Kg
- (d) Typical yearly consumption/kgm body weight = $\frac{5 \times 365 \times 0.1 \times 10^{-6}}{60}$ gm/Kgm
 $\rightarrow \frac{5 \times 365 \times 1 \times 10^{-6}}{60}$ gm/Kgm
 $= \underline{\underline{0.000003 - 0.000030 \text{ gm/Kgm}}}$

3. Alternative Method of Calculation for France

French usage of rigid PVC for packaging = 120,000 tpa

Take 5 ppm as VC content of packaging

Pop. of France = 52m

Max migration of VCM = 40%

$$\therefore \text{Max intake of VCM per person pa} = \frac{40}{10^2} \times \frac{5}{10^6} \times \frac{1.2 \times 10^5 \times 10^6}{52 \times 10^5} \text{ gm}$$

$$= 0.0045 \text{ gm}$$

$$\therefore \text{Max intake of VCM/kg body wt/pa} = \frac{0.0045}{60} \text{ gm}$$

$$= \underline{\underline{0.00007 \text{ gm/kg/pa}}}$$

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