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VINYL CHLORIDE TOXICITY & THE USE OF PVC FOR PACKAGING FOODSTUFFS

A Presentation by the

CEFIC Committee for the Toxicity of Vinyl Chloride

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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.

This CEFIC memorandum is primarily concerned only with item (v) - the possibility of ingestion of vinyl chloride through foodstuffs. The memorandum is divided into five chapters with the following aims:

(1) To outline present knowledge on the carcinogenicity of vinyl chloride

(2) To explore how this knowledge might give guidance on the level of risk involved in the use of PVC in foodstuffs packaging.

(3) To discuss some of the principles relevant to the regulation of foodstuffs, at present under debate in many industry-government circles

(4) To indicate industry's achievements in reducing exposure in the foodstuffs area; and, in the light of (1) to (3) above

(5) To suggest practicable forms of regulation which would ensure the continuing safe use of PVC for foodstuffs.

As already stated, the memorandum is primarily concerned with foodstuffs. However most of the data on vinyl chloride derives from studies of industrial workers or from animal experiments on the effects of vinyl chloride in high concentration ranges chosen to simulate past worker exposure. The major analysis and interpretation of this data - by government authorities, medical institutes, toxicologists etc - has been aimed primarily at the establishment of safe working levels on production plants. This represents a major intellectual input which cannot be ignored. Chapters 1 and 2 must therefore include considerable reference to the conclusions about safety, on production units, since these are a necessary starting point for a consideration of any risk in foodstuffs.

To avoid unnecessary repetition however this information will be presented in summary form only.

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 grew rapidly in the 1950's.

(ii) All of these authenticated cases are among workers engaged on closed-in plants handling very large quantities of liquefied vinyl chloride under pressure. All, except two, were workers 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 Thorotrast and arsenical sprays used in vineyards) has been identified, and they also occur naturally. Nevertheless a connection with vinyl chloride is now convincingly established.

Footnote 2. Of the two exceptions one was a worker engaged on monomer production, but in a closed building in which polymerisation was also carried out; the second worked in an aerosol-filling plant where atmospheric concentrations of vinyl chloride were also likely to be high.

(iii) Of the 48 cases, 18 (9 each) were on two individual polymerisation plants in North America. There are also plants with equally long histories on which no case has been observed.

(iv) All of the PVC production workers were engaged directly on the polymerisation process: and, for long periods, they cleaned reactors where vinyl chloride exposure would have been at its highest. (Appendix 1 lists the 48 cases). No cases have been observed among workers on separate vinyl chloride production plants and no authenticated cases have been found in the PVC fabrication industry where exposure levels, though markedly lower, would have been significant, by current standards, in the past. (See Footnote 3)

There is a strong indication from these facts of a marked dose-response relationship, in particular from the concentration of cases among polymerisation workers and from the highly significant peaks of incidence on certain individual plants. The acceptance of a strong dose-response relationship has been a major factor in permitting the formulation of new exposure limits which will protect the health of workers. Regulations around the world impose limits to atmospheric concentrations in the 1-10 ppm range. These actual numbers have been broadly arrived at by a "best practicable means" approach; but they must also be accepted as providing a high degree of safety, since the best practicable level is unacceptable if it remains unsafe.

Footnote 3. The US government agency NIOSH, has been alone in issuing a list entitled "Reported cases of angiosarcoma of the liver among non-polymerisation workers exposed to vinyl chloride". An inference has been drawn from the last four words of the title that these are indeed all vinyl chloride related cases and that their existence suggests an effect among fabrication workers. In fact, two of the six cases are those reported on in Footnote 2 and included in the total 48 cases in the text above. Of the remaining four, two have been reported - by the US Department of Health, Education and Welfare as establishing "no causal connection between exposure to PVC and angiosarcoma of the liver". In the third case it has not been possible to obtain any evidence for exposure to vinyl chloride while the fourth case, in Italy, has been reported by Professor Maltoni to be not typical.

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)

Years	VCM Polymerisation plant operators	PVC Fabrication operators	VCM Production plant operators
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

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

Bologna. From a comprehensive study of the effect of vinyl chloride inhalation on rats, the following conclusions can be drawn.

(i) inhaled vinyl chloride is carcinogenic to rats, producing tumours at a number of sites (and at atmospheric concentrations ranging from 10,000 ppm down to 50 ppm): of the various tumour types, angiosarcoma of the liver - as observed in humans - is a predominant variety. (See Footnote 4)

(ii) A definite concentration-response effect can be observed, with more tumours identified at high inhaled concentrations. Although a no-effect level for rats has not been positively identified so far, there is a strong suggestion that this is being approached at 50 ppm.

(iii) An even clearer total-dose response relationship has been established by exposing rats for shorter periods of time, but at the same concentrations as in the first experiments.

(iv) In ingestion studies (now past the 84 week stage but as yet incomplete) liver angiosarcomas have been observed in rats dosed with 50 mg/kg body weight and with 16.5 mgm/kg daily for 52 weeks. No angiosarcomas (or other tumours) have as yet been observed in a group dosed with 3.3 mgm/kgm. These ingestion results are not unexpected since the total vinyl chloride intakes by ingestion fall into the same dose range as that encompassed by the earlier inhalation studies.

Footnote 4. For completeness of the record, it should be reiterated that Maltoni's experiments produced tumours at many other sites - notably in the Zymbal gland, kidney and brain - but that angiosarcoma of the liver had by far the highest incidence for a single site.

In man also, angiosarcomas of the liver have occurred among workers exposed to vinyl chloride with an incidence, throughout the world, which is very significantly higher than any control population. Some epidemiological surveys have suggested small increases in the incidence of other tumours among high exposure workers, though in all of these the increase has not been statistically significant.

In view of the rarity of liver angiosarcomas and its very significant incidence among vinyl chloride workers, it is generally accepted that data on this tumour can properly and conservatively be used as a guide to the general carcinogenic potential of vinyl chloride.

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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.

TABLE 2

Man		Rat	
	Annual intake g/kg body wt		Annual intake g/kg body wt
Angiosarcoma confirmed in polymerisation operators	45-90	Very high angiosarcoma incidence	75-180
No cases among other PVC production operators	9	High angiosarcoma incidence	4-15
No cases in PVC fabrication workers	1.8-4.5	Low angiosarcoma incidence	1.5
Current regulated levels for industrial workers	0.2-0.9	No effect level for rats	<1.5
Current performance in European industry	0.5	Possible metabolic threshold for rats	>0.3
Typical ingestion through food in Europe (See Footnote 5)	0.00001 to 0.0000015		

It can be seen that ingestion through food is many orders of magnitude lower (50,000-300,000 x) than the current safe levels required in production plants. It is precisely because the absorption levels in food are so infinitesimally small and so far below the levels at which any effect has been observed - on rat or man - that the task of putting an exact value to a residual risk in this area is impossible. Chapter 2 nevertheless deals with the assessment of risk.

Footnote 5. Variations within this range and between member states are caused by variations in pattern of use and not by variations in technical achievement. Appendix 10 indicates methods of calculating ingestion figures.

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".

It is in this area of sound judgement rather than rigid proof that toxicologists have been prepared to comment. (See Footnote 6)

Their general opinion is that the presence of traces of vinyl chloride in foodstuffs do not constitute a hazard. Nevertheless, clearly there is a need for some form of control to ensure that this position is maintained. If this control is to be by means of regulations setting limits for vinyl chloride in food, then these figures can not be set on a toxicological basis. The only remaining basis for setting limits is technological and is what the industry can achieve ie the regulation should require the production of packaged foods to be consistent with the best manufacturing practice being generally achieved in the industry.

Industry is in complete accord with this view, ie that since the level of risk, though negligible, cannot be precisely quantified, all practicable steps should be taken to reduce exposures to a minimum. As evidence for this, the concentrations of vinyl chloride in foodstuffs have been reduced by at least a factor of ten since early 1974 when the assessments of hazard quoted in Footnote 6 were made.

Footnote 6

(a) "Where vinyl chloride is concerned, expert opinion is united in agreeing that whilst highly exposed workers were greatly at risk, there has never been any real risk to consumers" - Professor Schlatter, Director of Zurich University Toxicological Institute 29/10/75.

(b) "Vinyl chloride is used to make PVC, a plastic which is used for many purposes, including food wrappings, water piping and bottles for beverages. Minute amounts of vinyl chloride are found as a contaminant of the finished product and pass from it into food and drink ..... (The) amounts are tiny in comparison with those encountered in industry .... The cancers that have been produced .... (in industry) .... are an unusual type which normally affects only one or two people a year in the whole of Britain. It would therefore have been possible to detect a hazard to the health of the general public without great difficulty if one had been produced and we can be confident that no serious damage has been done" - Annual Report of the Royal Commission on Environmental Pollution, Her Majesty's Stationery Office, December 1974.

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.

With this number as a danger signal, governments throughout the world have broadly called for an average level of 5 ppm (annual dose 0.45 g/kgm) to safeguard worker health. Although this level does represent the best practicable means of reducing exposure, exposure would be lowered still further if regulations required the continuous wearing of respirators. It is clear therefore that medical and technical opinion has weighed the notional gain in protection from cancer through a reduction below 5 ppm, against the unquantifiable loss in safety from other hazards which respirators might bring; and has decided that the gain, if it exists, is so small as not to counterbalance the inconvenience, discomfort and small increased risk through use of respirators.

It is significant, too, that the US regulations, which set a personal exposure standard of 1 ppm, specifically state that "Exposures below the action level (0.5 ppm) do not present a sufficient hazard to warrant application of the entire standard to the many employers who are .... below that level". In this situation neither monitoring of plant atmospheres nor medical surveillance are required and no other obligations are placed on employer or employee ie at <0.5 ppm concentrations in the atmosphere, vinyl chloride is treated as an innocuous chemical.

Conservatively, therefore, 22.5 g/kgm annually (250 ppm) might conceivably have caused cancer. Against this, the general opinion is that 0.09-0.45 g/kgm annually (1-5 ppm) is safe and 0.045 g/kgm annually (0.5 ppm) provides a sufficient further margin of safety for the monomer to be treated as innocuous. The further question, which then arises, concerns the additional safety factor necessary to provide absolute assurance ("which removes all reasonable doubt") that the consumption of food is safe. Chapter 1 has provided data for the average vinyl chloride intake through food in the Community States. These show the range of current additional safety factors, compared with the levels quoted above, for a typical European consumer to be as follows.

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

that "it may be envisaged that a threshold for carcinogenic activity exists" and points out that "any system of extrapolation from observations made at high exposure levels will give conservative estimates of the effects of low level exposures if it ignores the existence of a threshold". (He then discusses the merits of the Mantel-Bryan extrapolation procedure for calculating risks at low concentrations).

There is therefore good support for presuming the existence of a no-effect level; and then considering whether the present levels of vinyl chloride in foodstuffs might lie below it.

Regrettably the mass of animal data available has not yet been analysed in detail along the lines suggested by the WHO report. However two toxicologists have separately attempted an extrapolation from Maltoni's published results.

(c) Dr M Schneiderman of the US National Cancer Institute (Ref 4) used the Mantel Bryan technique to extrapolate some of Maltoni's results (basically those given in Table 1 of Appendix 3 of this report) to very low levels. Before recording his conclusions it must be noted that, according to the WHO report "extrapolations derived by this (Mantel-Bryan) system are obviously highly conservative". This is because (a) it ignores the existence of a threshold, (b) it takes no account of the effect of competing risks, and (c) it does not take into account the age of occurrence of cancer which must be considered when evaluating a hazard to health. It must be noted too that the calculated risk is for a rat and, as we have seen, there is evidence to suggest that rat is more susceptible than man to vinyl chloride. (See Appendix 5 for fuller quotations from the WHO report).

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.

(d) Dr R F Crampton, Director of the British Industrial Biological Research Association (BIBRA) has published a tentative calculation, aimed simply at establishing an order of magnitude for a safe level, based on the Jones and Grendon hypothesis (Ref 5). This proposes a relationship between dose and latency period, and points out that, at a given low level of exposure, the time taken for a tumour to appear would be in excess of the normal life span of the individual. Crampton suggests that this low level of exposure might correspond to an atmospheric concentration of the order of 5 ppm. Independent calculations based on very limited human data have produced a figure of between 5 and 10 ppm for a 40 year exposure. It is of interest that these "no effect" levels are ca. 1000 times higher than the 11 ppb calculated by Schneiderman - or approximately three of Friedman's "three or four orders of magnitude".

(e) Summary

In summary, a <u>precise</u> mathematical calculation of any miniscule risk to man through foodstuffs packaging will never be possible, since it requires extrapolation of experimental and human data over a minimum of 6 orders of magnitude from the dose levels at which human carcinogenesis has been observed, and five orders of magnitude from the lowest dose levels damaging to rats.

Nevertheless, the minute levels at which vinyl chloride can be ingested through food provide a massive safety factor compared with levels which have been judged safe by government departments, worldwide, concerned with industrial hygiene, and compared also with calculations of exceptionally low risk levels ($\ll 1 \times 10^{-8}$) which have been put forward by some toxicologists. The doses which can be absorbed through food are so infinitely small as to raise the question whether they must not be already well inside the no-effect or threshold level. (See Footnote 7)

Footnote 7. If the minimal nature of the risk cannot be readily appreciated from the numbers themselves, it is of some interest to note that application of the Mantel/Bryan theory to the known data on benzpyrene shows that the eating of 70 g of "charcoal broiled" steak daily involves the consumer in a cancer risk of 8×10^{-6} (Ref. 5). This is 800 times higher than the risk calculated by Schneiderman for a vinyl chloride dose which itself is of the order of (100-500) times greater than the present average intake through foodstuffs.

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.

CHAPTER 3

CONCEPTS AND PRINCIPLES

This chapter deals with a number of concepts connected with control which have been under discussion throughout the world. A review of these can help to establish the principles upon which control procedures should be based. The section examines a number of disconnected items but every effort has been made to present these in a coherent form.

1. The Non-Detectable Concept

The discussion in Chapter 2 has shown that the satisfactory control of vinyl chloride in foodstuffs can only be obtained by the application of the best technological means to achieve the lowest practicable level of exposure. In the absence of precise toxicological definition of minute risks, but in the knowledge that the safety factors are very high, this is the proper course to adopt.

In an attempt to define the desired result, from such a course of action, it has been suggested that the achieved concentration of vinyl chloride in food ought to be below the lowest level which is detectable by a specified method of analysis, preferably the most sensitive method: ie the end result should be a 'non-detectable' level. This definition of the end result is not, however, consistent with the means being used to get there. The possibility of achievement is being confused, and then incorrectly equated, with the ability to measure: the first is connected with the efficiency of a number of sequential industrial physico-chemical processes while the second is dependent solely on the state of advancement of analytical science. The two bear no relation to each other and a non-detectable level can only through sheer chance be the same as the lowest achievable level. The concept that an adulterant is acceptable if it is non-detectable is in reality little more than a statement that it is acceptable until analytical techniques improve!

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.

for control depends on the ability to measure, and to correct changes in quality, before this quality goes outside the accepted standard. Without this ability, the process is a go - no go process. It either happens to make acceptable product - or it doesn't!

2. Alternative Control Concepts

If the non-detectable concept is unacceptable, some other form of control must be sought. Three possible systems can be envisaged

(a) Legislation could simply require that industry uses its best endeavours in order continually to bring exposure levels closer to zero. This has the advantage that it requires government and industry to remain in close contact so that surveillance and reviews of progress are continual: this in turn develops expertise within government, and a relationship between the two groups and, as a result, ensures that pressure is maintained by both to achieve continual improvement. This approach is permissible, in the particular case of PVC, because the levels currently being achieved can be shown (see Chapter 2) to be extremely safe. Dramatic and urgent further reductions in concentrations are not called for.

(b) Control might be achieved by fixing a maximum level of vinyl chloride (in foodstuffs or containers - vide infra) which shall not be exceeded. This has the seeming advantage of simplicity: but it decreases the opportunities for on-going co-operative effort between government and industry, in an area of endeavour which is incompletely defined both scientifically and socially and, being precedent-forming, demands combined intellectual effort.

(c) A modification of (b) would require the fixing of a maximum level combined with the obligation to review this level after a defined period. In this case, the level called for could correspond to a freezing of the situation at the presently achievable levels: a final conclusion could then await the results of work in hand. Action such as this would be based on the philosophy that the correct level is not known (and may well already have been passed) and that there is good reason to believe that current hazards are negligible.

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.

Further the measurements made so far have been carried out in research type laboratories with good facilities. When testing is done in process control laboratories it can be expected that, using similar analytical techniques, the limit of detection will have a higher value and the measurements will become less precise and probably less accurate all in all by a factor of 2 or 3.

Under these conditions it is not possible to argue, on a strictly statistical basis, a level at which compliance can be achieved with any degree of certainty, nor at what level statistical control should be imposed on manufacture to achieve compliance. More data of higher quality are required to do so and efforts are being made to obtain such data. Until that is available decisions must be a matter for judgement and it is suggested that, to take account of the difficulties mentioned, a value of 5 times the current "probable" average would be a reasonable but stringent level for a limit to be complied with at a certainty of 95% ie if a "probable" <u>average</u> level of 1 ppm in the container is being achieved, then a compliance level of 5 ppm - to be met by any container - would set a very tight limit.

In the case of measurement in foodstuffs themselves, similar principles apply, but here the problem is complicated further because the presence of vinyl chloride is governed by a slow diffusion process, and a time element has to be taken into account. Because of this, the difference between the "typical" or <u>average</u> result and the 95% confidence level for every package may be even wider. This aspect is discussed more fully in Chapter 5.

Some of the problems of measurement are considered more fully in Appendix 6, which presents arguments to justify the statements and values quoted in this chapter.

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

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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.

the question whether it is not more practical to regulate the package (since it is at the package-making stage that true manufacturing control is achieved) rather than to attempt to regulate the foodstuff itself which can only be monitored, after the event and on a random basis. Measurement of VCM in the foodstuff must always be retrospective: control of the package can be prospective.

Though there are sound logical and practical reasons for regulating the package, it is recognised that some national regulations may demand control of the foodstuff itself: and this is possible so long as the limits are fixed with proper regard for the process and analytical variations recorded above. In practice, of course, measurements will be made at both locations for control purposes during manufacture. It would be wrong, however, to assume that legislative control should be established at both locations. This is partly because such a decision would diffuse the ultimate responsibility for achievement of safe production between container manufacturer and foodstuffs packer; and partly because inspection of foodstuffs in packaging can only be done on a non-statistical basis. With legal control established on the package there is clearly a need for continual "type testing" of foodstuffs to establish that the relationship between package and foodstuff remains unchanged: with legal control established on the food there is a need for continuous manufacturing control of the package to ensure the legal standard is met.

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

while the concentration of vinyl chloride in food is maintained below 0.050 mg/kgm.

5. Italy

A ministerial decree of November 19, 1974 requires that the migration of vinyl chloride from a container into 50% aqueous ethanol at 5°C 24 hours contact shall be non-detectable by a method sensitive to 0.050 mgm/kgm.

6. Sweden

The Swedish regulation requires that concentrations in the foodstuff shall not exceed 0.050 mgm/kgm but recognises in a document of February 4, 1975 that lower levels can be detected.

7. The USA

In the USA the Food & Drugs Administration published, in September 1975, a proposed regulation for the use of PVC in contact with foodstuffs. This is not yet law and is still the subject of intense debate between government, the PVC industry and other interested parties.

In considering the FDA proposals it is important to note that all US legislation on food chemicals is governed by the so-called Delaney Clause in the 1958 amendment to the basic US Food, Drug and Cosmetic Act. This states that "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 ....".

A further discussion of the "Delaney Clause" is given in Appendix 7. It seems clear that, as accepted, this was not intended to alter the amendment's basic concept of reasoned appraisal of risk, bearing in mind "the anticipated ingestion . .. under likely patterns of use". Since 1958, however, precedent has established the clause as one which places an absolute prohibition on any additive suspected of causing cancer under any conditions. Because of this, American legislators are not free to make any scientific assessment of a possible carcinogenic hazard: their possible courses of action are severely limited and as a result any regulation which falls short of a total ban is much more a political than a scientifically influenced document.

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".

8. Summary

It can be seen that almost all of the proposals listed above fall into one of the three possible categories of regulation proposed earlier (Chapter 3 Section 2). All except Italy and the UK propose a maximum level in the food. Italy uses what is in effect a test on the package, using food simulants, and does introduce the concept of non-detectable, but not explicitly by the most sensitive method. The UK does not propose a numerical limit but requires all practical steps to be taken for the reduction of monomer concentrations. European governments who have suggested maximum limits have all proposed 0.050 mgm/kgm. The US proposals give little useful guidance because of the limiting effect of the Delaney clause on objective analysis.

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 ± 20% but at 1.5 ppm, the 95% confidence limits exceeded ± 100% of the measurement. Vinyl chloride measurements in water taken from a PVC bottle showed a variation of ± 70% at 0.010 mg/kg: but at 0.002 mg/kg, the 95% confidence limit far exceeded ± 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 ≡ x mg/kg

2. Current Achievement

In the past eighteen months, major reductions have been made in the concentrations of vinyl chloride in packaging materials and in foodstuffs. Rather than detailing the position in mid-1974 it is simpler to state that the concentrations reported below are now at least 20 to 50 times lower than they were. This progress is the result of intensive effort applied at every stage in the conversion of vinyl chloride monomer into a fabricated PVC container.

This effort will continue but it is well to caution that the major and obvious improvements have been made. Progress from now on will be slower and evolutionary: further dramatic cuts cannot be expected.

Current achievements are best dealt with in two sections: one dealing with the package, the second with foodstuffs themselves.

(a) Packages

Typical average figures for different types of package are given in Table 4. For flexible plasticised films and coatings, typical figures are significantly below 1 ppm and for rigid unplasticised bottles, hollow containers and for unplasticised PVC foil for shallow thermoforming, vinyl chloride contents are typically below 1 ppm. For all these applications, bearing in mind the variation about the mean and the closeness of the results to the limit of detection of the test, a compliance level of 5 ppm, can be achieved within a 95% confidence limit.

For vinyl chloride copolymer foils for deep thermoforming, typical mean results are below 5 ppm so a higher compliance level would be required. However most of the applications for this product lead to low transfer of vinyl chloride so that the monomer level in the foodstuff falls in the same range as for all other PVC packages.

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.

In considering maximum levels (which must be achieved with a high degree of certainty) all of these factors must be taken into account. Their effect can best be illustrated by considering the main applications separately.

(i) Plasticised film

The process for making plasticised film is such that monomer contents in the film are extremely low and close to or below the detection level. In addition, most of the food which is overwrapped (vegetables, fruit, meat, cheese, etc.) has a short shelf life and vinyl chloride contents, if they exist at all, are below the limit of detection within this shelf life. This is not therefore a problem area.

(ii) Unplasticised foil for thermoforming

In this application also, most homopolymer foil has a very low vinyl chloride content (<1 ppm); further, the contents (butter, margarine etc.) are of the type which require refrigerated storage and even so have very short shelf life. Maximum monomer contents of the food are therefore very low.

Certain applications demand the use of extruded copolymer foil and here the monomer content of the package is higher (typically <5 ppm) but the applications are such (yoghurt, tomato packs, nestings for chocolates, cakes etc.) that shelf life and temperature are very low or that the area of contact between package and food is very small. Maximum vinyl chloride contents are therefore below the limits of detection of the analytical method and notionally of the order of 5-10 ppb or 0.005-0.010 mg/kg.*

* x ppb = 0.00x mg/kg

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 the content
" 6 " " " <30% " " " " " "
" 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

It must be noted that these are maximum real values of vinyl chloride content and that for the vast majority of bottles with monomer contents below 1 ppm and storage lives of less than 3 months (20% migration) the vinyl chloride concentration in the liquid should be only a few parts per billion. This is, in fact, the state of current achievement by industry: with typical monomer contents of the container below 1 ppm, the great majority of beverages sampled from supermarket shelves have monomer levels close to or below the limit of detection: but occasional higher results, as in the table, are observed because of the variation above the mean, of concentrations in the PVC bottle itself, or of shelf life.

Despite the low levels typically achieved, any proposal for a maximum limit, if it is truly to be a maximum, must take note of the distribution of results above the mean and must make allowance for analytical inaccuracies. The situation would be intolerable if, having achieved concentrations generally of a few parts per billion, industry could be penalised for the occasional high result arising from factors largely or wholly outside its control. Taking these factors into account an examination of Table 5 shows that the setting of a limit of 0.050 mg/kg which shall not be exceeded sets industry a tough but acceptable target. Sufficient data has not yet been collected for a full statistical analysis of results in practice at these newly achieved low levels but, with the larger, high production bottles, the margin between ~0.030 mg/kg and 0.050 mg/kg is probably sufficient, at this concentration, to allow for analytical inadequacies. Problems may arise with smaller bottles and with other small containers or wrappings: Table 5 shows that as the ratio of content weight to PVC weight decreases, the ultimate theoretical concentration of monomer in the contents tends to increase. However, the smaller packages are not produced in large quantities and the probability of prolonged storage coinciding with a high monomer content container must be low. Vinyl chloride contents greater than 0.050 mg/kg are likely therefore to be rare, though they may occur. (The Dutch regulation, limiting migration across a defined area of surface, makes some allowance for these examples).

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 0.030 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

0.002-0.003 mg/kg: and this finding is confirmed by direct measurement. It is these measurements of real exposure which have been used in the earlier calculations (Chapter 1) of the average intake by the consuming public.

This characteristic of the control system has to be clearly understood. The imposition of a 0.050 mg/kg maximum requires industry to operate at real average levels of a few parts per thousand million. At these levels the public exposure is some 100-500 times lower than an exceptionally conservative estimate of a safe level (Schneiderman) and 50,000-300,000 times lower than levels of exposure currently achieved and believed safe in production plants. The need for any further reduction in maximum levels has still to be demonstrated; and, if achievable, would be of dubious significance. Nevertheless industry will continue to take all sensible and practicable steps, which are open to it, in order to limit exposure.

AWB/MH
2 February 1976

APPENDICES

APPENDIX 1

Reported cases of vinyl chloride-related angiosarcoma of the liver

Country	Plant	Age at death	Years from first exposure to death	Total years of exposure	Year of death
France	1	43	21	19	1967
	2	63	15	12	1975
	3	55	29	29	1975
Germany	4	40	14	12	1971
	4	38	12	12	1969
	5	44	17	17	1974
	5	49	21	14	1975
	6	43	13	12	1975
	7	38	13	5	1974
	?	(50)	18	18	alive
	Aerosol Plant	43	21	21	1973
Italy	8	43	15	6	1972
	9	55	22	19	1975
UK	10	71	26	20	1972
	11	37	9	4	1974
Belgium		No cases reported			
Holland		No cases reported			
Switzerland		No cases reported			
Spain		No cases reported			
Norway	12	56	22	21	1975
Sweden	13	43	19	18	1970
	VCM Plant	61	27	27	1972
Czechoslovakia	14	46	16	16	1974
	14?	40	15	15	1966
Yugoslavia	15	59	20	20	1973
	15?	42	23	18	1973
Canada	16	not available	15 to 27 yrs	15 to 27 yrs	1968 to 1974
	16	not available			
	16	not available			
	16	not available			
	16	not available			
	16	not available			
	16	not available			
	16	not available			
	16	not available	16	0	
USA	17	49	22	16	1973
	17	38	15	13	1971
	17	58	28	28	1973
	17	43	15	15	1968
	17	52	20	18	1964
	17	46	13	12	1975
	17	41	17	4	1969
	17	43	17	17	1975
	17	(43)	19	19	alive
	18	(46)	21	13	alive
	19	41	15	15	1961
	19	55	17	17	1968
	19	61	23	23	1970
	20	45	24	18	1968
	20	52	30	30	1974
	20	(60)	32	32	alive
	21	50	20	15	1969

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.

APPENDIX 2

NIOSH list of angiosarcoma cases in non-polymerisation workers

This list comprises six cases. Of these, two are the monomer-production worker and the aerosol can-filling worker, both of whom handled liquid vinyl chloride under pressure and were probably exposed to high atmospheric concentrations similar to those of polymerisation workers. In the present report therefore these two cases are included in the comprehensive list given in Appendix 1 and are not regarded as being different in kind from the other cases in this list.

Of the remaining four, two derive from south western Connecticut in the USA. The "Morbidity and Mortality Weekly Report" - a publication of the Centre for Disease Control in the US Department of Health, Education and Welfare - for June 22, 1974 gives a first report on these two cases; an Editorial Note while calling for "further studies throughout the nation .... to define the possible risk factors in persons who have worked with PVC" states that "these findings establish no causal connection between exposure to PVC and angiosarcoma of the liver". Since then no further cases have been reported from the USA.

Of the two cases, one was a worker in a cable factory: a later report from the US National Cancer Institute (July 31, 1974) states "in brief we are not completely certain that this is an angiosarcoma of the liver or even a primary sarcoma of the liver. It is not like any of the other tumours we've seen in the livers of VC-PVC workers". The second case was of an accountant who worked for ten years with a PVC film and sheet fabricating company. His office was not located in the production area but he made occasional visits to the area because the vending machines were located there.

Of the last two cases, one was in the UK (year of death 1970) and the only link with vinyl chloride is a note made by his doctor that the patient had worked with "PVC-oil mixture". It has not been possible to give more precision to this statement since the company, for whom the man worked, closed down some years ago.

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).

APPENDIX 3

Experimental data on the carcinogenicity of vinyl chloride

Results from Professor Maltoni's rat experiments are summarised in the tables below. Table 1 collates the results from two series of inhalation experiments aimed at determining the effect of vinyl chloride concentration in the inhaled air on tumour incidence.

TABLE 1

52 weeks exposure

60 rats/group, total experiment time 135 weeks; except for asterisked groups where 120 rats/group were used and total time was 118 weeks. Results for asterisked groups are normalised (halved) to 60 rats/group for comparability.

Atmospheric concentration ppm	Annual intake g/kg body weight	Liver angiosarcomas	Total tumours
6000	180	13	31
2500	75	13	32
500	15	7	22
250	7.5	4	16
*200	6	3.5	12.5
*150	4.5	2.5	10.5
*100	3	1	8.5
50	1.5	1	10
zero	zero	zero	6

A concentration (dose) - response relationship is suggested by these numbers, both for liver angiosarcomas and for total tumours: for both sets of numbers there is an indication that at 50 ppm (1.5 g/kg annual intake) the effect of vinyl chloride is becoming small.

The effect of increasing total dose - at constant atmospheric concentration - is shown even more markedly by comparison of some of the results of Table 1 with the results from a further experiment in which rats were exposed at the same levels for 17 weeks instead of 52 weeks (Table 2).

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) 52 wks	17 wks	Liver angiosarcoma 52 wks	17 wks	Total tumours 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

It is possible to bring the inhalation and ingestion results into a single table by using the common parameter - annual intake in g/kg body weight - as a linking factor. Use of this device involves assumptions about the relative retention factors for ingestion and inhalation (see Footnote 10): but it is of interest to see whether the two sets of results can be brought into one general pattern. (Note that the use made ultimately of this comparison, in the main text, is not sensitive to the nature of the assumption).

TABLE 4

Annual intake g/kg body weight	Method	Liver angiosarcomas (in a 60 rat group)	Total tumours (in a 60 rat group)
180	inhalation	13	31
75	inhalation	13	32
15	inhalation	7	22
12.5	ingestion	6	8
7.5	inhalation	4	16
4.5	inhalation	2.5	10.5
4.2	ingestion	4	4.5
1.5	inhalation	1	10
0.8	ingestion	zero so far	zero so far

Table 4 demonstrates that the dose levels in the ingestion experiments are in the same range as for the inhalation experiments: the incidence of tumours is also of the same order for ingestion and inhalation routes though, because the ingestion experiment is not yet complete, ingestion, at least by the particular experimental technique used (gavage), may ultimately show a somewhat higher incidence than inhalation at the same dose level.

Footnote 10: Maltoni's rats were exposed for 4 hours daily, 5 days/week. A ventilation rate of 6 litres of air/hour or 24 litres/day has been assumed for the rat at rest; and the average weight of a rat has been taken as 500 g.

Men at work have been assigned a ventilation rate of 10 M^3 per 8 hour shift, and an average weight of 70 kg.

In comparing inhalation with ingestion results, the same retention factor has been assumed for both methods of absorption, since vinyl chloride given into the stomach in oil would be slowly absorbed into blood over a period of several hours and the situation would not be too different from that applying to prolonged inhalation. With this simplifying assumption it is possible to compare total doses by different routes.

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
Rats	75-180	very high incidence 20% of grp
	4-15	high incidence 4-10% of grp
	1.5	low incidence 2% of grp
Humans		
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 comparision 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.

APPENDIX 4

Metabolic Studies

During 1975 studies of the metabolic fate of vinyl chloride in rats has been published by the Dow Chemical Company (Ref. R E Hefner, P G Watanabe & P J Gehring, Annal NY Acad Sci 246, 1975, 135-148) and by ICI (Ref. T Green, D E Hathway, Chem-Biol Interactions 11, 1975, 545-562). Both studies show that the rate of metabolic breakdown is dose-related in a way that indicates a saturable process. Unchanged vinyl chloride is rapidly eliminated by the lungs. Formation of the major urinary metabolites involves glutathiones and prolonged high exposure to vinyl chloride would deplete the body glutathione pool. Present thinking is that depletion of this kind would reduce the body's protection against abnormal alkylating reactions by normal physiological metabolites and could allow changes in RNA or DNA or other controlling cell constituents to occur that might eventually result in the appearance of tumours. In the Dow study progressive depletion of liver non-protein sulfhydryl content was found with increasing exposure to vinyl chloride; rapid depletion at atmospheric concentrations of 100-250 ppm, slow depletion at 50 ppm and no depletion at 10 ppm over the period of observation. Rumanian investigations of vinyl chloride operatives have also shown significant blocking of non-protein sulfhydryl groups in the blood, least pronounced in workers with discontinuous contact (Ref Gina (Bucharest 13, 1964, 409-418). It would however be premature to argue a case for safe exposure levels on little evidence and more work to identify a significant interaction with cell constituents at low levels of exposure will be required to produce a reliable indication of a safe level.

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 & Bryan 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." ....

Annex. A Proposed Procedure for the Assessment of Health Hazards of Carcinogens at very Low Levels of Exposure - by L Friedman, Ph D

"It may be envisaged that a threshold for carcinogenic activity exists. However, the threshold level cannot be accurately estimated at the present time, owing to the lack of relevant biological data. It should be remembered that any system of extrapolation from observations made at high exposure levels will give conservative estimates of the effects of low-level exposures if it ignores the existence of a threshold.

The first method of assessing the health hazards for carcinogens at very low levels of exposure was that proposed by Mantel & Bryan in 1961. They took the position that the problem of determining what dose levels of an agent are safe, eg, non-carcinogenic, cannot be resolved unless one first defines some level of permissible risk, no matter how small, rather than insisting on absolute safety. Furthermore, because of practical consideration and statistical variation, the determination of low-risk dose levels - for example, 1/100 million - cannot be made directly but only by extrapolation from observations at much higher levels. They describe a conservative approach for accomplishing this. In addition to an arbitrary definition of "virtual safety", it is necessary to define an arbitrarily high statistical assurance level and a rule for extrapolation by use of an arbitrarily shallow slope. They defined "virtual safety" as a probability of carcinogenicity of less than 1/100 million at a statistical assurance level of 99% and a conservative probit slope of 1 probit per 10-fold dose increase.

The choice of 1/100 million is arbitrary. The choice of a 99% statistical assurance level is, of course, also arbitrary, but it is obviously desirable for this level to be as high as possible. However, it may be that 90% would be adequate. The slope of a probit per 10-fold dose increase has been justified on the basis that the slope of the dose-response curve near zero is bound to be less than the slope in the range of actual observation. The choice of 1 probit rather than 1 logit per 10-fold dose increase cannot be justified on the basis of available knowledge, but is an attempt to avoid being too conservative. Additional factors that are known to play a role in the determination of actual

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 fromexposure to low levels of carcinogens be "calibrated" by calculation of the "Mantel-Bryan risks" for those

carcinogens present as low-level contaminants in many foods that are generally regarded as safe and wholesome and have been widely used for many decades. Such calculations for the levels of polycyclic hydrocarbons, carcinogenic mycotoxins, nitrosamines, goitrogens, naturally occurring estrogens, and ergot, which are usually found in low concentrations in traditional, safe foodstuffs, would provide "calibrations" for the "Mantel-Bryan risks", that would render them useful for practical risk-benefit deliberations and practical decision making situations."

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 $\mu g/kg$).

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:

Amount of Water (% of bottle capacity)	% of VCM in Water
25	35
50	65
75	80

2. Errors in Separation and Measurement

A series of measurements has shown that VCM present at a concentration exceeding 50 ppb in an oil can be determined with a precision of ± 15% (95% confidence interval). When the concentration of VCM was less than 50 ppb this technique had a precision of ± 45%. A different technique used at the lower levels (down to 30 ppb) had a precision of ± 15%.

No tests have been carried out at levels of concentration below 30 ppb in oil but lower concentrations have been analysed in aqueous solution. Three laboratories analysed an aqueous solution containing 10 ppb VCM and found the precision of their method to be ± 25%, ± 19%, ± 70%. An attempt to repeat this experiment at 2 ppb showed that the 95% confidence limit far exceeded ± 100% in all cases. This is not surprising because the concentration is about the level of detection of the method of measurement.

The mean values obtained by the different laboratories in these experiments also varied widely, from 6 to 10.5 in the first experiment and from 1.5 to 3.5 in the second. It is not yet known whether this is due to systematic error in the analytical procedures or bias arising from difficulty in calibration at these low levels.

Measurement of the precision of the method of determining VCM in PVC is complicated by the difficulty of providing strictly comparable samples for test. However, in a determination of approximately 20 ppm of VCM in PVC a precision of measurement (95% confidence) of ± 20% was achieved.

An attempt to make a similar comparison at a VCM level of approximately 1.5 ppm showed that the 95% confidence limits exceeded ± 100% of the measurement. This again is not surprising because the level concerned approaches the level of detection.

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.

APPENDIX 7

The Delaney Clause

The Delaney Clause was introduced by Senator Delaney as part of an amendment to the Food, Drug & Cosmetic Act in 1958 which itself was the culmination of eight years of hearings and deliberations. As originally drafted this amendment contained no specific reference to carcinogens but was concerned generally with the use of chemicals in foods. The concept of safety underlying the whole amendment was that safety requires proof of a reasonable certainty that no harm will result; not with the provision of an absolute certainty in any conceivable circumstance (see Footnote 11).

Into this general intention, Senator Delaney injected an additional amendment which required that the "Secretary shall not approve for use in food any chemical additive found to induce cancer in man or, after test, found to induce cancer in animals". Opposition to the clause was initially based by the Department of Health, Education & Welfare on the argument that it was unnecessary and added nothing to the existing draft. "This Department is in complete accord with the intent of these suggestions - that no substance should be sanctioned for uses in food that might produce cancer in man .... but the draft amendment (with no specific reference to cancer) ...." will accomplish this intent".

Footnote 11: "The concept of safety used in this legislation involves the question of whether a substance is hazardous to the health of man or animal. Safety requires proof of a reasonable certainty that no harm will result from the proposed use of an additive. It does not - and cannot - require proof beyond any possible doubt that no harm will result under any conceivable circumstance.

The safety of a given additive involves informed judgements based on educated estimates by scientists and experts of the anticipated ingestion of an additive by man and animals under likely patterns of use".
H Rep No. 2284, in legislative record at 12-13 (emphasis added).

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.

Because of these changed circumstances, the Delaney Clause can now be more of a hindrance than a help since it denies FDA the right to attempt an assessment of risk. Through precedent, it now insists that foods shown to contain a carcinogen must be banned, however insignificant the concentration and regardless of the consumption pattern or the intensity of the carcinogenic effect. Increasingly it comes under attack (Ref. 9) from responsible scientists but politically it must be almost impossible to annul or amend.

APPENDIX 8

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.

(5) PREPARATION OF SAMPLES

Place 10 ml or 10 g of the product to be examined in a 50 ml antibiotic flask, add 10 ml dimethylacetamide, stopper rapidly, cap and homogenize.

(6) PREPARATION OF STANDARDS

In the case of foodstuffs, it is necessary to have available a sample of the product to be examined which has not been in contact with vinyl chloride.

Prepare five stoppered, capped 50 ml antibiotic flasks containing 10 ml or 10 g of the product to be examined (this product not having been in contact with vinyl chloride) and 10 ml dimethylacetamide and inject respectively into four of these, 2, 4, 6 and 10 ul of the standard solution prepared as in section 4. Mix well.

(7) DETERMINATION

(7-1) Equilibration of the solutions

Place the flasks in a 45° C ± 1° C thermostatic bath for two hours. Then remove the flasks from the bath and allow their temperatures to return to room temperature (about 20° C) for 1 hour.

(7-2) Measurement by gas-liquid chromatography

In order to diminish the risks of interference, two determinations are carried out under different conditions.

(7-2-1) Examination of a polar phase

- chromatograph provided with a flame ionization detector
- 1 mV full scale potentiometric recorder
- stainless steel column

length : 2 m

internal diameter : 2 mm

stationary phase :

Hallcomid M 18 : 5 g

Carbowax 400 : 5 g

on Chromosorb T (40-60 mesh) : 100 g

- carrier gas : nitrogen 3 l/h
- flame : hydrogen 1.8 l/h

air about 10 l/h

- 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.

(10) COMMENTS

In general, the values found with the two chromatographic systems correspond with one another, but in certain cases (wines, natural oils) it is possible to find a noticeable difference. It is therefore essential to check that the test foodstuff really corresponds with the sample placed in contact with polyvinyl chloride packaging. In the latter case, only the lowest result ought to be considered valid.

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 µl 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.

Inject the 25 ml vinyl chloride slowly into the 50 ml dimethylacetamide present in the flask and then reweigh the flask. Using the increase in flask weight, calculate the vinyl chloride content of the solution thus obtained.

(4) SAMPLE PREPARATION

Place 1.00 g of the test sample in a 50 ml antibiotic flask. Add 10 ml of the solution 2.4, stopper rapidly and cap. Place the flask in a 45° C ± 1° C thermostatically controlled bath for 16 h (overnight) (1).

(5) CHROMATOGRAPHIC CONDITIONS

(5-1) Chromatograph provided with a flame ionization detector

(5-2) 1 mV. full-scale potentiometric recorder

(5-3) Stainless steel column with the following characteristics

- length : 3 m (2)
- internal diameter : 3 mm
- support : Chromosorb W-AW treated DMCS (80-100 mesh)
- stationary phase : Tris-(2-cyancethoxy)-1,2,3-propane (20 g for 100 g support).

(5-4) Vector gas : nitrogen 2.4 l/h

(5-5) Flame : hydrogen : 1.8 l/h
air : 8.0 l/h

Footnote.

(1) The equilibration time may be reduced by working under the following conditions:
Heat the flask at 70° C while stirring by means of a magnetic stirrer until the sample has completely disappeared. Then equilibrate the flask for at least 30 minutes at 45° C ± 1° C.

(2) The length of the column was fixed at 3 m in order to reduce the time required for determinations. To ensure that there is no interference in the VCM peak, it is possible to double the length of the column, but, in this case, it is also necessary to double the concentration of the internal standard (1-2 mg/l) and to measure the area under the peaks obtained (instead of their height) to establish the standard curve and carry out the calculations.

(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.

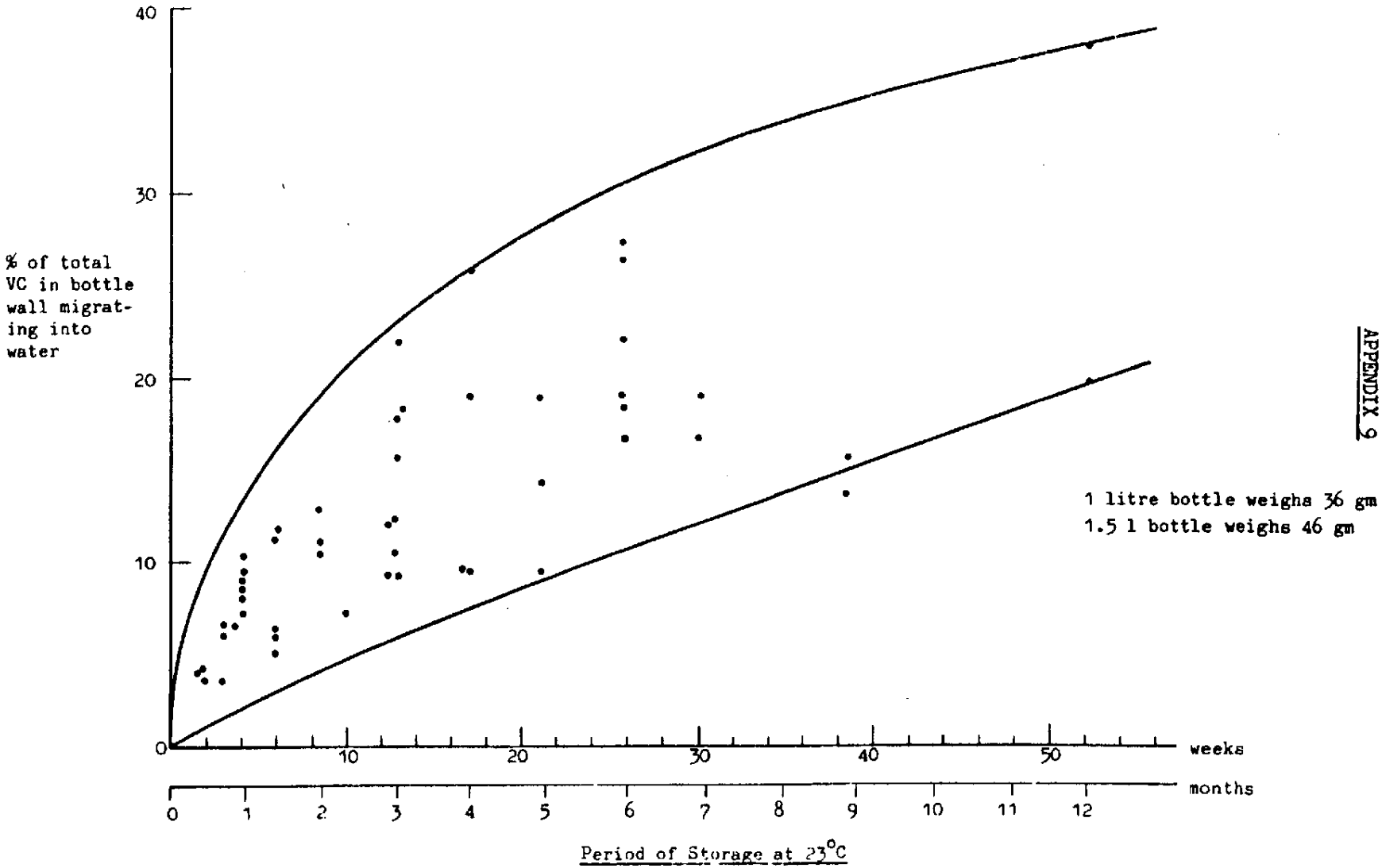
Footnote.

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

The procedure described enables VCM levels in the range 0.5 - 5.0 mg/kg to be determined to the nearest 0.5 mg/kg and levels in the range 5.0 - 15.0 to within the nearest 10%.

In order to determine levels higher than 15 mg/kg, use the same method but reduce the sample.

MIGRATION IN MINERAL WATER



1 litre bottle weighs 36 gm
1.5 l bottle weighs 46 gm

APPENDIX 9

SPI-26141

APPENDIX 10

Calculation of VCM Ingestion Figures

1. UK

As will be recalled from the main text page 20, PVC bottles contain typically <1 ppm of VCM and copolymer foil <5 ppm. A calculation of the amount of VCM which could migrate into foodstuffs has been done on the basis of some higher than typical VCM contents in the package and also on the assumption that complete equilibrium is reached in the exchange between package and contents. The high figures assumed are within the range proposed by CEFIC for control of the different types of package.

Package	Bottles		Plasticised Film	Foil	
Contents	Orange Squash	Cooking Oil	Meat/Vegetables	Margarine	Biscuits
PVC pa (tonnes)	4,300	1,200	5,300	1,800	5,300
Partition Coefficient	250	150	1000	300	1000
Av ratio of weights (package : contents)	$\frac{1}{25}$	$\frac{1}{25}$	$\frac{1}{250}$	$\frac{1}{20}$	$\frac{1}{35}$
VCM Content of Package	3 ppm	3 ppm	0.2 ppm	7.5 ppm	10 ppm
VCM Content of Food at equilibrium	1290 gm	600 gm	170 gm	900 gm	1900 gm

∴ For a population of 50m, max total VCM ingested = 4860 gm

∴ Average max ingestion/person/kg body weight = $\frac{4860}{50\times10^{6}\times60}$ gm/kg/pa

(assuming 60 kg av body wt)

= 0.0000015 gm/kg/pa

2. France

(a) Range of consumption ..... 0.1 ⟶ 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

$\longrightarrow$ $5 \times 365 \times 1 \times 10^{-9}$ Kg

(d) Typical yearly consumption/kgm body weight = $\frac{5 \times 365 \times 0.1 \times 10^{-6}}{60}$ gm/Kgm

$\longrightarrow$ $\frac{5 \times 365 \times 1 \times 10^{-6}}{60}$ gm/Kgm

= 0.000003 — 0.000030 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%

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

= 0.0045 gm

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

= 0.00007 gm/kg/pa

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