VINYL CHLORIDE

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TRANSLATION OF CERTAIN PARTS OF THE PROCEEDINGS OF THE 20TH MEETING OF THE CHEMICAL CARCINOGENESIS CLUB IN PARIS, 10TH NOVEMBER 1979

SUBJECT: ANIMAL AND HUMAN EPIDEMIOLOGY - THE VINYL CHLORIDE MONOMER CASE

PRESIDENT: PROFESSOR R LATARJET

The definitive text of the Proceedings of the 20th. Meeting of the Chemical Carcinogenesis Club is written in French and will be published early in May 1980. Professor C Maltoni has kindly provided an English version of the original French paper he gave on 10th. November 1979 and this is included in the Proceedings. So that the other papers and the record of the discussion can be understood by a wider audience, the following English translations have been made. Translating technical papers is fraught with peril. The translator has made many qualifications to his English text and these are documented. If time had permitted, these problems and ambiguities would have been discussed with the authors and a solution agreed. In the interests of speed however, it was decided to make the attached translation available simultaneously with the French Proceedings. Will you please note however that the French text is the only definitive one and where there is any doubt or disagreement, the French text should be consulted.

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CLUB DE CANCEROGENESE CHIMIQUE

Meeting of 10.11.79

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1. INTRODUCTION BY PROF.R LATARJET

Today's meeting organised by the Club de Cancérogénèse Chimique is evidence of the interest we all have in genotoxic, mutagenic and p ssibly carcinogenic pollution problems. It is a sequel to the first meeting devoted to vinyl chloride which we organised at the Institut Curie in 1976.

One of the great obstacles to the solution of the problems presented by this pollution is that experiments with low doses administered over very long periods are impossible. And if we wish to use experiments we must extrapolate, with all the risks which this involves. The most effective way of getting round this difficulty is to have recourse to epidemiological surveys, which can cover large groups of people and sometimes tell us whether a given type of exposure, quantitatively defined, is or is not accompani d by a significant difference from the normal incidence of a given genetic or somatic lesion.

Before calling on Dr Berrod to address the meeting I have to express our gratitude to the active members and organisers of the Club de Cancérogénèse Chimique, a particularly lively scientific society even though it has no funds, no subscription and no enrolment, but complete freedom with all the flexibility this gives.

I thank M.Jean-Claude Thomas and Dr Berrod, who have been the particularly efficient king-pins, and Prof.Coussement, who let us have the lecture room, and my friend Prof.Truhaut, membre de l'Institut, for honouring us with his presence; I thank certain foreigners, well known in this field, who have made the journey in spite of the transport difficulties with which we are

currently familiar, in particular Dr and Dr Hopkins, from London, Dr Robert Frois, from Louvain, Dr from Holland, and Prof. Viola from Rome, in whom I salute the father of the whole of this long story.

I call upon Dr Berrod to address the meeting.

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2. HISTORICAL PERSPECTIVE OF THE VCM CASE (Paper 1 - Dr Berrod)

M le Président, Mesdames, Messieurs, I should like, for this 20th. meeting of the Club de Cancérogénèse Chimique, to make a rapid historical survey of the pathology of this vinyl chloride problem.

Vinyl chloride or monochloroethylene was known to chemists for over a century after its discovery by Regnault in 1835. It is a halogenated derivative of aliphatic hydrocarbons which the growth of the plastics industry since the 2nd.World War has developed for numerous uses. PVC is obtained from the monomer, vinyl chloride, which polymerises very readily. PVC has b en the basis of numerous applications; it is probably the most used of current plastics, and used for numerous applications. To give only one figure, the French industry alone produces over 700,000 t.p.a.

This polymerisation of vinyl chloride is effected by polyaddition of monomer molecules. The macromolecular chain grows almost spontaneously in an[1] industrial process which means that in industrial hygiene human intervention is necessary much less often than in the past; but it is still necessary, and therefore necessitates extremely substantial precautions. To vary the properties of the base material, the resin, it is necessary to use several additives[2], in particular plasticisers which give flexibility and stabilisers which prevent degradation.

What did we know of the toxicological properties of VCM ? We knew of its narcotic effects, which are due to its high solubility in lipids and its volatility, which is also high; we knew of several cases of coma from massive inhalation, and above all, we knew that it was a flammable and explosive product when mixed with air in proportions of 4-20% v/v[3]. Consequently the industry was aware of certain characteristics, but that was all until 1963, the year in which very special bone conditions were obs rved for the first time in certain workm n in polymerisation plants, with osteolytic bands on the ungual phalanges of several fingers, whence the

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name of acro-osteolysis which was given to this syndrome; they were or were not accompanied by circulatory phenomena of the peripheral anoxia[4] type, as in Raynaud's disease.

This pathology was the subject of three papers at the International Congress of Industrial Medicine in Tokyo in 1969, and it was there that I had the occasion to meet Prof. Viola, who is here today, the author of one of the first papers on acro-osteolysis.

A year later, we still did not know whether it was VCM or one of the ingredients which was involved. We knew that the conditions affected the people who handled the product most and entered the autoclaves to scrape the walls free of build-up after each run, and in consequence could show these finger conditions. But what we also knew was that some of them had serious bone conditions without any skin lesions and it therefore seemed difficult to admit that there was only one, uniquely local cause. We tended more towards a systemic disease.

I went to see Prof. Viola in Italy on these acro-osteolysis problems and he was kind enough to tell me confidentially of his anxiety. In carrying out animal experiments to examine the bone disorders he had found extremely substantial tumoral lesions at a variety of sites[5]. This led him shortly after, in 1970, to make a communication to the Cancer Research Congress in Houston which had a most resounding effect.

The French and European industries reacted to this problem. The Italian industry then entrusted to Prof. Maltoni of the Bologna Cancer Research Institute, who is with us today, a long-term animal research programme under extremely rigorous conditions. The author himself will be talking about this in a few minutes, and I believe it is at present the largest programme of animal experiments on chemical carcinogenesis which has been undertaken in the world.

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The French company Péchiney-St.Gobain, the Belgian company Solvay and the English company ICI decided to join the Italian company Montedison in participating in this programme of animal experiments by Prof.Maltoni, which began in 1971 and ended, as he will tell you, in 1977.

This confirmed the preliminary findings of Prof.Viola. We were justified in hoping that we should not, perhaps, have the unpleasant surpris of finding that this animal carcinogen was also a human carcinogen. Unfortunately, following Prof.Maltoni's experiments, the United States, knowing what the position was with animals, began, with their well known rigour and above all the relative facility which they had since they possessed cancer registers, an epidemiological study which resulted in the discovery of cases of human tumours of the hepatic angiosarcoma type.

We were therefore faced with an animal and human carcinogen. A difficult problem arose for industry and industrial hygiene in a climate which was emotional and, of course, as always, well politicised.

What has happened ? After the first measures taken in 1973 it was in 1974, on the announcement of this human epidemiology, that analytical, technical and medical committees began to be created. The original methods of analysis using an explosimeter were rapidly replaced by others, much more sophisticated, for atmospheric analysis by gas chromatography. Finally, extremely accurate environmental monitoring devices(7) were set up on the plant which have now resulted in automatic industrial chromatography. There are ten or so points on the plant where probes give results every two minutes; thus, each point is analysed about every twenty minutes, making a total of the order of over 700 analyses per day, requiring a computer for processing the data. This results in a knowledge of the mean ambient level for an 8-hour shift every day, which is extremely important. I may add that there is a pre-set alarm system to warn the personnel when a given dos is exceeded. The personnel is th refore perfectly kept completely up to date with its

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history of exposure(8), corresponding to the ambient level on th plant. I may also add that there are portable analysis units, for use purely in emergency, which are placed in contentious areas and which consequently, at present, enable access(9) if the standard individual precautions in similar cases,eg the wearing of respirators(10), are taken.

Various precautions were taken by the technical sub-committe , which followed the development of analytical methods with a much more thorough checking of the sealing of the vessels, a reduction in the time for which the apparatus was open and, above all, the introduction in 1974 of prolonged hydraulic de-scaling which has enabled us to minimise the exposure of cleaners; prolonged stripping(11) has, moreover, made the levels found today really insignificant. At the same time, the personnel were educated; as we know, the supervisory staff and key-workers(12) in a firm have been given more responsibility.

As to the medical problem, a committee of French doctors for vinyl chloride has tried to take the problem in hand. We all know the limitations and the great difficulties that we have in finding parameters for the early biological monitoring of cancer; we still have practically no valid ones, but we have, even so, followed scientific developments and established a monitoring programme, in particular by hepatic echotomography. Epidemiological surveys have also been undertaken, one a retrospective survey to recover the individual histories, which was very difficult, and the other a prospective one which we are just starting, to know, from now on, what will eventually happen.

We have had numerous(13) meetings with staff, particularly those on the health and safety committees, to explain what was happening, and w have now told the staff that they can, with all the prudence appropriate in such cases, be relatively optimistic for the future and think that the cases(14) which we now face and which, unfortunately, we are still likely to find because they are dependent on the past, are going to decrease(15), and, we hope, disappear in the near future.

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Th re, very rapidly, is the story of vinyl chloride. In conclusion, I should like to say this. It was a model[16] problem, model b cause, faced with an unknown toxicity of a product in very widespread us the whole scientific, medical, industrial and even political world was mobilised. All the biologists, epidemiologists, anatomo-pathologists and fundamental research workers[17] joined in; all the doctors concerned, French and European colleagues, met, and their discussions were very fruitful. The companies have been as one; following the four companies initially associated with Prof. Maltoni's work there were numerous[13] contacts with other European companies and companies throughout the world, in spite of their competing interests.

Professor Truhaut, my dear master, may I recall about the industry that one day in the summer of 1975, when we were editing a note for th INRS records, you said to me "We must be strict and give the industry standards which will perhaps be a constraint on them[18], but we cannot do otherwise in view of what we know". I acquiesced completely in this proposal, of course, although I was a little worried about reporting it to the Head of the Polymers Department[19] of my firm, but faced with facts as serious as this he showed himself to be in complete agreement, already knowing, moreover, the precautions we had begun to take.

Finally, from the political point of view, the vinyl chloride problem has enabled us to set up discussions with the authorities, with the trade unions kept informed, and shown that mere ideas of profit were not the thing compared with[20] the protection and health of the workmen[21].

Finally, I think that the joint efforts of everybody over the vinyl chloride problem have been, are and will remain a model for various studies of chemicals we are now handling in the chemical world we are living in.

I thank you for your attention.

3. ANIMAL EPIDEMIOLOGY **625195**

Prof. Latarjet called upon Prof. Maltoni to address the meeting.

A. Experimental plan, results, commentary and conclusions (Paper 2 - Prof.C Malto

[please see Prof. Maltoni's English text in French Proceedings]

Prof. Latarjet, aft r having expressed his admiration for such a gigantic work, conducted so well and for such a long time, called on Dr Tassignon to address the meeting.

B. Methodology of handling data (Paper 3 - Dr J P Tassignon)

1. Plan of the statistical analysis

Statistics will not give an interpretation differing from that given by Prof. Maltoni, but will enable the uncertainties to be more or less quantified.

The statistical effort was applied largely to the inhalation and ingestion studies in Sprague-Dawley rats. I shall restrict myself to th inhalation studies (Fig.1).

Biological statisticians work on paper, on the mountain of data from the laboratory note-books which give the condition of the rats on autopsy, but also the changes occurring(22) during the experiment, that is, the weight at various stages, the behaviour of the animals and certain palpable tumours.

The present study comprised first (Fig.1) collecting data from the laboratory note-books but also from sections - where necessary - according to the coding(23) of the tumours. This enabled us to establish a standardised form for each rat. The data from this form were then transcribed onto punched cards, the set of thousands of punched cards giving us as a by-product, in plain language, the listing(24) of the figures on the cards. These cards were then checked and it was then possible to start work on three lines of analysis (Fig.3).

a) Weight curves

The simplest is the analysis of the weights of the rats, since this was a factor which might be influenced by vinyl chloride. We have looked at the development of the weight curves for the animals with the standard deviations and analysed the deviation from the weight curve in the different groups exposed to various doses in relation to their own control.

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We did not observe any effect of the long-term administration of vinyl chloride on the weight of the rats.

b) Analysis of the ages at death and of the number of tumours

We then drew up Tables showing the various rats, starting at rat No.1 and going on to rat No. 3,000 or so, one to each line. We noted, in columns, the lesions which these rats could display in Prof. Maltoni's code, which covers over 160 different lesions. The age at death of the animals was noted in this Table. From the initial Tables we drew up sec nd generation Tables having the lesions, eg hepatic angiosarcoma, on s parate lines,and columns for the doses and sexes, for example a column for 30,000 ppm/ males.

From these Tables we were able to compare the number of rats affected by a given lesion appearing at a given dose with the number of rats affected by the same lesion in other groups. When a positive effect appears statistically probable (25) we can then examine possible dose/effect relations.

We developed this line of analysis by carrying out a correspondence (26) analysis.

The analysis of the ages at death enabled us to establish survival curves for the various groups. We observed that the survival of the animals as a function of time decreased progressively from 100% until the point when the last rat died, and we observed that the last rat died increasingly soon as a function of the dose. Such curves can be compared. We compare th curve for a given dose with the survival curve for the controls to assess whether or not there is increased mortality which is due to the dose. We can examine whether the mortality increases in parallel with or in proportion to the dose and then establish actuarial-type analyses which take into account both the frequency of the tumours and the moment at which the rats die of the tumour when it is a lethal cancer or are affected by the first symptoms of the tumours (for example, for mammary cancers we might tell the moment

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2. The target organs by the Fisher test

What are the target organs, or what are the tumours specifically induced by vinyl chloride ? There are over 90 cancers in both the controls and the exposed animals and over 60 benign tumours in both the controls and the exposed animals, some in excess in the exposed animals, others possibly in excess in the controls. It was necessary to distinguish by a simple test between what was probably due to the vinyl chloride and what was probably the effect of spontaneous carcinogenesis in the colony of rats studied. We used Fisher's exact probability test, which only retains what is statistically significant at a single dose and in a single sex. This enabled us to define the limit of what is acceptable to the biologists and significant with a probability of error of less than 5%. From the Fisher test (Fig.4) carcinomas of Zymbal's gland, hepatic angiosarcomas and mammary adenocarcinomas seem extremely significant. At the 5% level, only neuroblastomas and papillomas need to be retained. We may wonder how far we can go in this probability scale. The answer is for the biologists to say. Effectively, Prof.Maltoni, this morning, stressed hepatocarcinoma as significantly linked with vinyl chloride, contrary to what the Fisher test proposed for acceptance. There is, in fact, biological reasoning, side by side with the statistics, which can only be described differently. This reasoning takes precedence, but statistics are helpful in enabling the uncertainty to be quantified. We might also retain hepatic angiosarcomas from the biological point of view, but here the Fisher test indicates such a large probability of error that no statistician could accept it. The Fisher test is used in chronic, long-term, routine experiments at the US National Cancer Institute, but it is already coming up against[27] a first problem, which is that it may very well be that the tumours which reach a statistically significant level, like mammary adenocarcinomas, are of no importance to a biologist. Others, like hepatocarcinomas, which do not reach a significant level, are of importance to the biologist. We cannot, therefore, trust blindly in the simple Fisher test.

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3. Apparent dose/effect relations

By going into the[28] statistical techniques and examining each of the tumours which may be targets for vinyl chloride with greater precision, we have attempted to work out dose/effect relations. When we have an effect which increases continuously as a function of dose it is clear that the substance studied has an effect and that the carcinogenic effect is peculiar to this substance. This type of curve is relatively rare, for it only applies to powerful carcinogenic effects. We shall now examine the profile for various tumours.

Firstly, hepatic angiosarcoma (Fig.5). In the controls, the incidence is zero, and then the effect gradually becomes more and more pronounced, the curve rising continuously with the dose, which strengthens us in our conviction that angiosarcomas are definitely linked with vinyl chloride - there is a dose/effect relation.

Another argument which enables us to attribute an effect to the substance studied is that the mean latency period of the cancer decreases with the dose. Hepatic angiosarcomas are lethal tumours. The latency period is taken to be the time between the beginning of the exposure and the death of the animal. If we plot the logarithm of the dose along the abscissa and the logarithm of the age of the animal along the ordinate we have experimental points which are roughly on a straight line (Fig.6). Linear regression illustrates what happens. We find, as is standard in experimental carcinogenesis,a proportional decrease in survival of the animals which is a function of the dose. This was very simply because of the extraordinarily low spontaneous incidence of angiosarcomas in rats.

For cancer of Zymbal gland (Fig.7) the incidence increases as a function of the dose. The curve is entirely typical, with a proportionality between eff ct and dose which increases up to 30,000 ppm.

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Nephroblastomas (Fig.8) hav a different curve, which is hump-backed; in fact, at 30,000 ppm we return to a zero level of the effect, that is, comparable with what is observed in the controls. Nevertheless, from the fact that nephroblastomas are extremely rare in the controls, we can attribute this tumour to the effect of vinyl chloride. The differenc between males and females can also be studied; it is not very large.

Neuroblastomas (Fig.9) are also very rare tumours in the various control groups; they do not occur at medium doses and then very gently begin to appear only to disappear again at very high doses. What are we to make of this dose/effect curve ? Since the tumour is extremely rare in the controls the effect is nevertheless attributed to the dose.

Mammary carcinomas (Fig.10), which were put in parentheses by Prof. Maltoni, are tumours with a certain frequency in the controls. We know that they are tumours which fluctuate enormously in the same colonies. We observe an increased effect at very low doses of the order of 1 ppm, which is not significant. At 5 ppm it is significant, and at 10 and 25 ppm. At 50 ppm we have a possible control, since two experiments used the 50 ppm dose. In one, there were few mammary adenocarcinomas, and in the other there were many, and this is significant. The dose/effect curve tails off and at very high doses we no longer see the appearance of an excess of mammary adeno-carcinomas. How are we to interpret the third type of curve with a large excess at very, very low doses ?

By having recourse to the second argument for a relation with th carcinogen, that is, the reduction in the mean survival of the rats ? In this particular case (Fig.11) this will not help us because the latency period between the first exposure and the death of an animal with mammary adenocarcinoma does not represent the true latency period of the tumour since it is not a lethal tumour.

Let us take the case of another type of tumour, a benign one, which from time to time appears in the controls and from time to time also in the exposed groups, which only breaks away from the base line at 30,000 ppm, the forestomach papilloma[29] (Fig.12). There, we cannot even show the dose/effect relation or the reduction in the mean survival time of the animals because we have too few results. What, then, are we to think of an isolated dose at which a tumour appears in excess, without any dose/effect relation ?

Hepatocarcinomas (Fig.13) do not reach, in the Fisher test, the probability level currently accepted in biology, but here we see a curve which dies down[30] very quickly and there is then no further effect at very high doses. The fact that we found hepatocarcinomas in massive excess in new-born animals exposed for 5 weeks and then observed for the rest of their life justifies us in thinking that this effect is due to vinyl chloride.

The Fisher test showed that forestomach papillomas[29] were in excess in the exposed animals. This was the only benign tumour in excess. In this experiment we could restrict ourselves in the quantitative analysis to malignant tumours.

Malignant tumours as a group increase with the dose (Fig.14)

Actuarial analysis (Figs. 15 and 16) of the incidence of cancer in rats also shows that the dose induces many more cancers than would be proportional to the increase[31], for both males and females. We may conclude that the tumorigenic power of vinyl chloride increases with the dose.

4. Analysis of the survival of rats

The median survival (Fig.17) of the animals as a function of dose gives a very large scatter in the controls, particularly with the males; on the other hand, we note a reduction in the median survival time in proportion to the increase in dose. This is a very important factor to remember for the overall interpretation of the phenomenon; not only, on the one hand, is there

an increase in the cancers but on the other hand an increasingly large increase in mortality. We may wonder whether this increase in mortality is due to the fact that with increasing dose the animals are affected by more cancers; the more cancers there were the greater would be the mortality and consequently this reduction in median survival as a function of the dose is a reflection of this.

In reality, on examining the mean survival as a function of dose, taking all the malignant and all the benign tumours into account (Fig.18) or one particular tumour, for example, a tumour clearly linked with vinyl chloride, hepatic angiosarcoma (Fig.19), we find a reduction in the mean survival time which is proportional to the dose. This phenomenon of th reduction in the median survival time of the animals is therefore independent of the tumours present in these animals at death, and must be attributed to "systemic toxicity". There are, therefore, two phenomena which are acting: cancers arising in various tissues and an increased mortality of a chronic general toxicological order which we have not yet defined.

We can establish the correlation (Fig.20) between the increased mortality and the increase in cancer from the mean number of tumours p r exposed animal for a well-defined dose.

5. Correspondence analysis[26] between lesions and doses

Only data-processing methods[32] can enable us to integrate so many ideas (over 90 malignant tumours, over 60 benign tumours, and an intercurrent increase in mortality), which is why correspondence analysis [26] has been brought in here. (Figs. 21, 22, 23).

This factorial analysis enables us to identify the underlying factors in the experiment of which two are relatively important and would constitute almost 75% of the information contained in the contingency table. Th first factor is probably linked to the dose and to the initiating power of vinyl chloride. Thus nephroblastomas appear at relatively low doses

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(200, 250, 500 and 2,500 ppm). Angiosarcomas are strongly induced at higher doses. Hepatic angiosarcomas are found at low doses but become more prominent[33] at high doses. Neuroblastomas are most prominent at high doses, as are carcinomas of Zymbal gland. Forestomach papillomas[29], being exclusively linked to the 30,000 ppm dose, also appear in the analysis very close to this 30,000 ppm dose.

We might, perhaps, push this type of analysis further. From the biochemical kinetics side we have discovered that the liver enzymes responsible for the detoxification of vinyl chloride operate with a threshold which is found to be of the order of 200 ppm; the primary metabolic pathways are superseded[34] and other, secondary metabolic pathways are induced at that point. (See the great distance between TM and NpB in Fig.23).

The other factor is the increased mortality. When there is a large increase in mortality we do not see many nephroblastomas, which have a long latency period. In contrast, carcinomas of Zymbal gland become increasingly prominent with increasing dose.

We may conclude that the dose affects organs with increasingly high initiation thresholds, and the initiation threshold of Zymbal gland is higher than that of the kidney. But the increased mortality is also due to the systemic toxicity.

6. Conclusion

A complete analysis must therefore be made by various statistical methods, some of which can be very powerful, to obtain a quantitative result[35].

STUDIES ANALYSED

INHALATION	BT 1	SD rat	10 000 ppm 6 000 2 500 500 250 50 0	4 h/d, 5 d/w, for 52 w
	BT 2	"	200 150 100 0	"
	BT 6	"	30 000	"
	BT 9		50 0	"
	BT 15		25 10 5 1 0	"

Fig.1: Plan of Prof.Maltoni's inhalation studies on Sprague-Dawley rats

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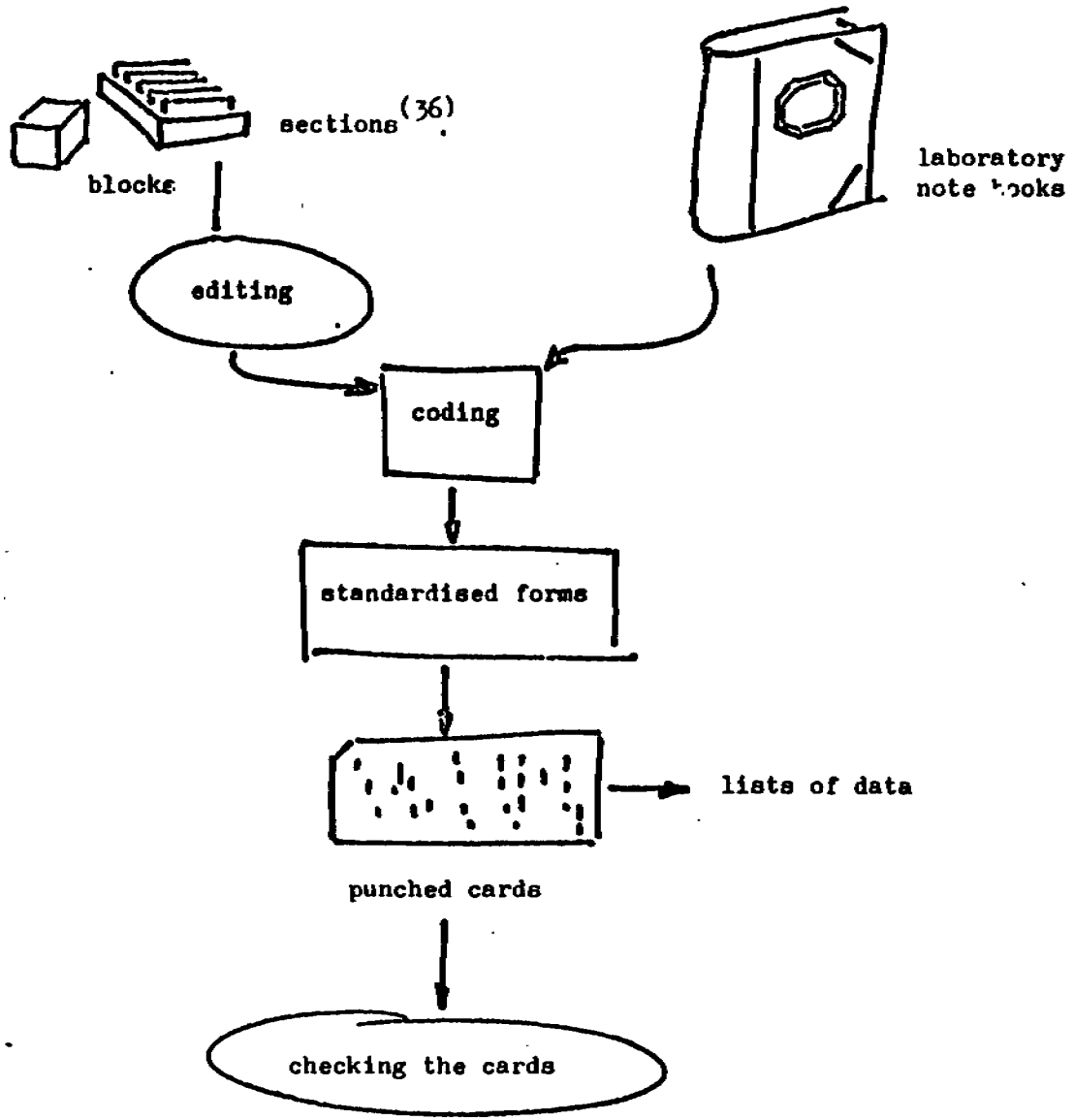


Fig.2: Plan of the statistical analysis (data collection)

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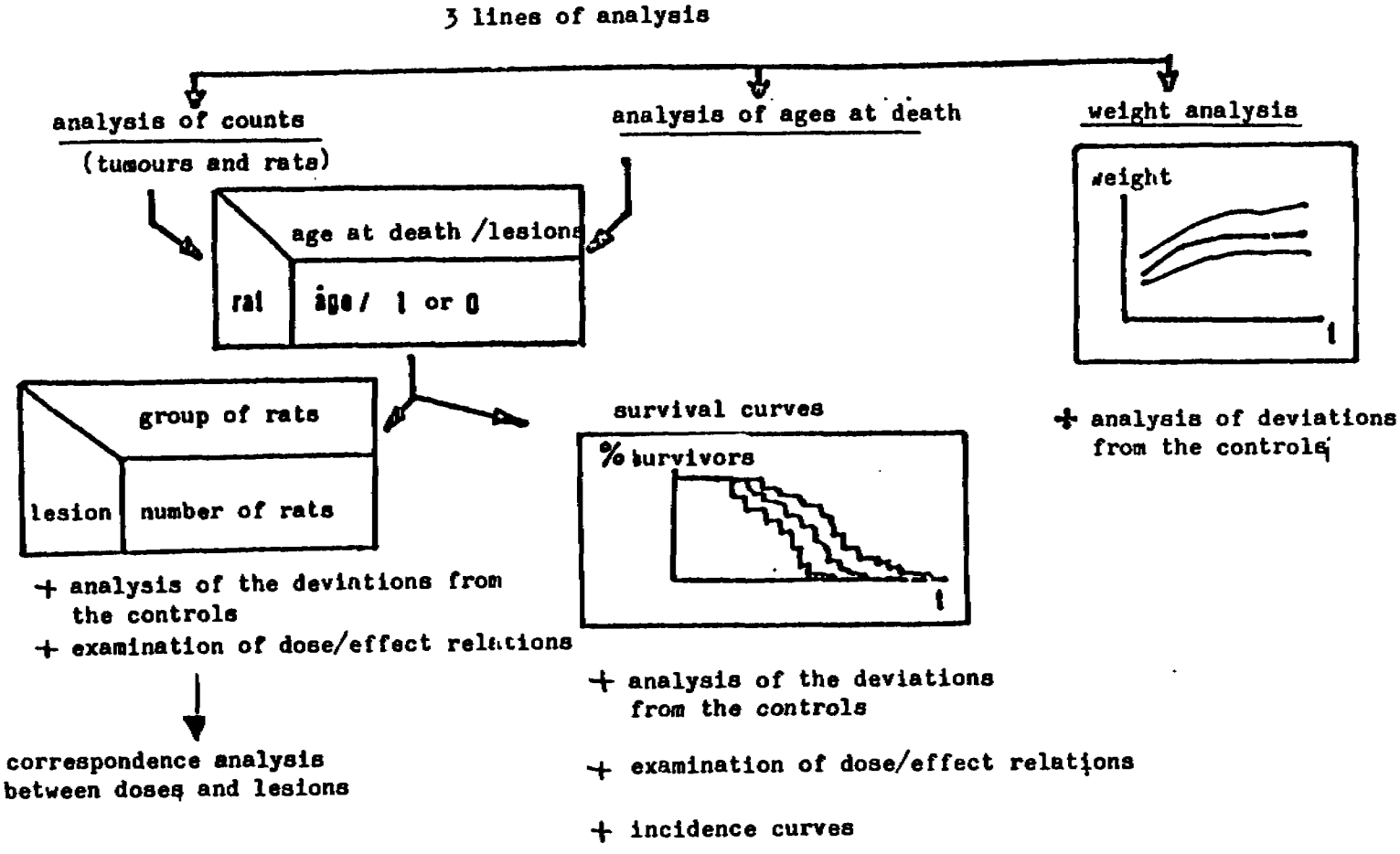


Fig.3: Plan of the statistical analysis (analysis of the data)

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Fig.4: Fisher's exact probability test. From what probability level is vinyl chloride involved ?[37]

P at at least one dose for at least one sex	
P≤0,01	Carcinoma of Zymbal's gland Hepatic angiosarcoma Nephroblastoma Mammary adenocarcinoma
P≤0,05	Neuroblastoma Pre-gastric papilloma[29]
0,1<P≤0,15	Hepatocarcinoma Adenoma of Zymbal's gland
0,15<P≤0,2	Extra-hepatic angiosarcoma

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HEPATIC ANGIOSARCOMA

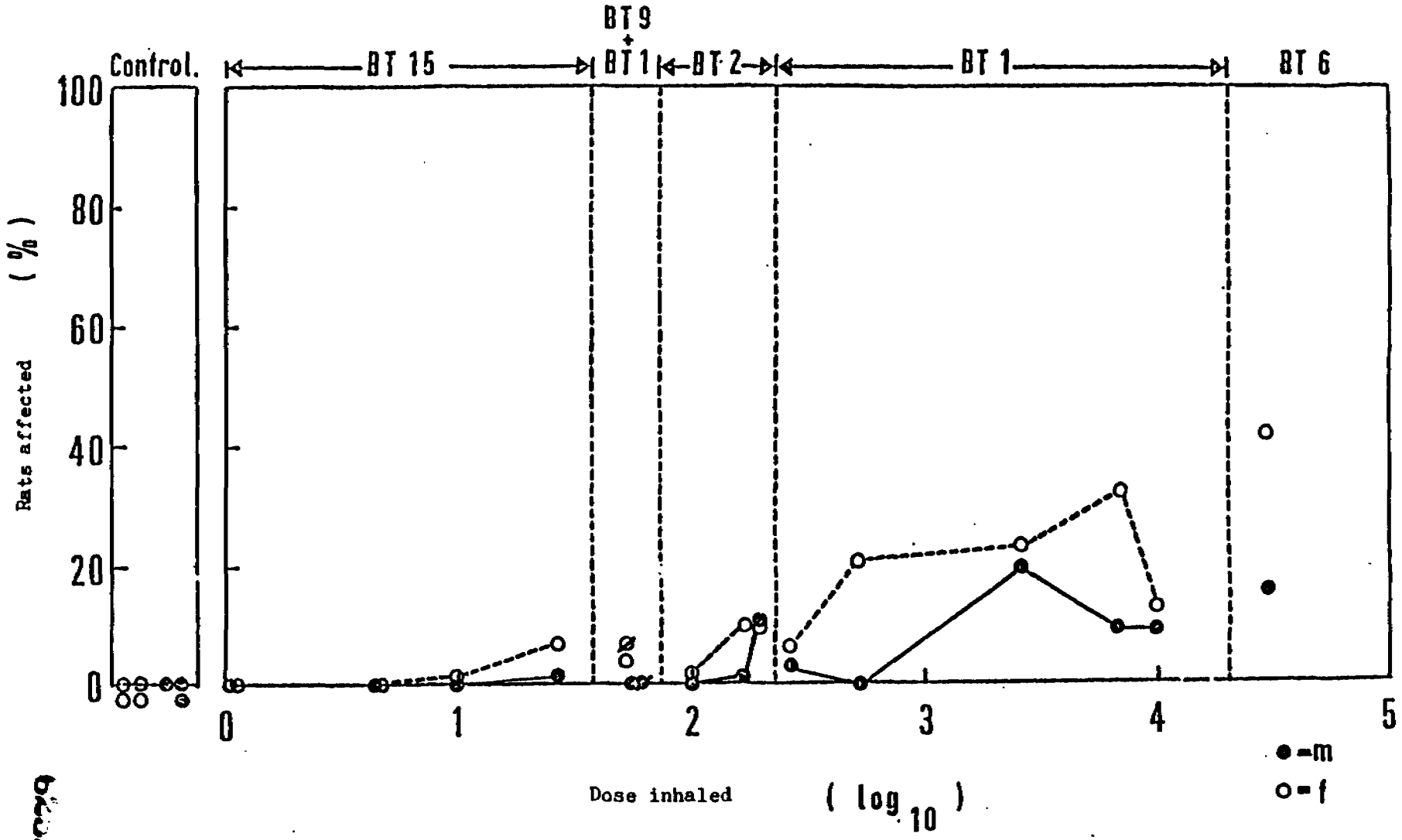


Fig.5: Proportion of rats affected by hepatic angiosarcoma as a function of the dose

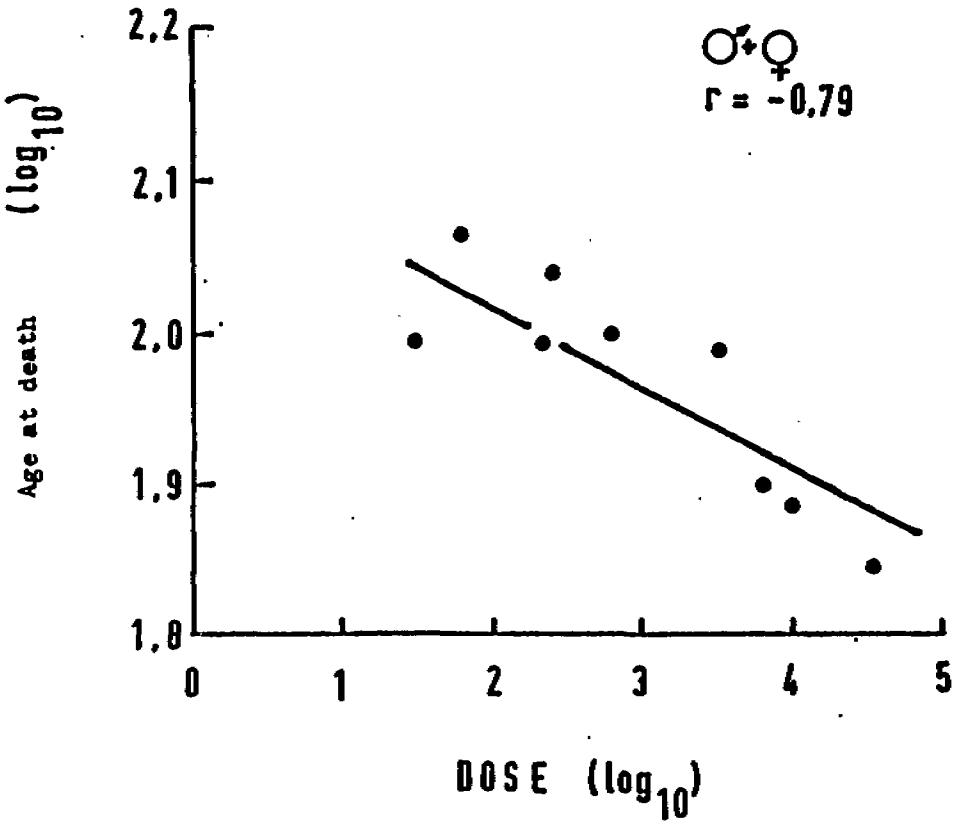
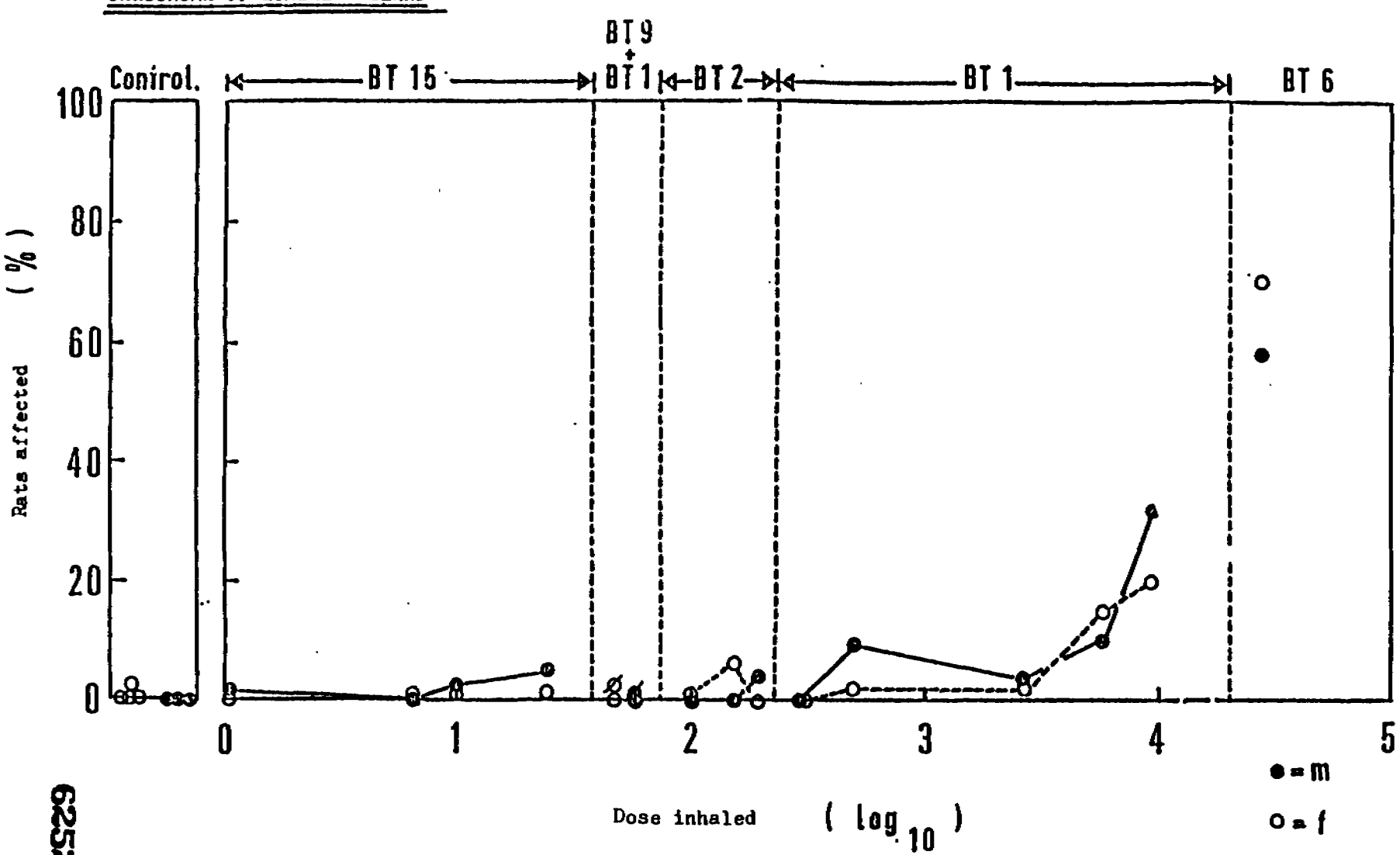


Fig.6: Rats with hepatic angiosarcoma. Reduction in mean survival time

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CARCINOMA OF ZYMBAL GLAND



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Fig.7: Proportion of rats affected by cancer of Zymbal : gland as a function of the dose

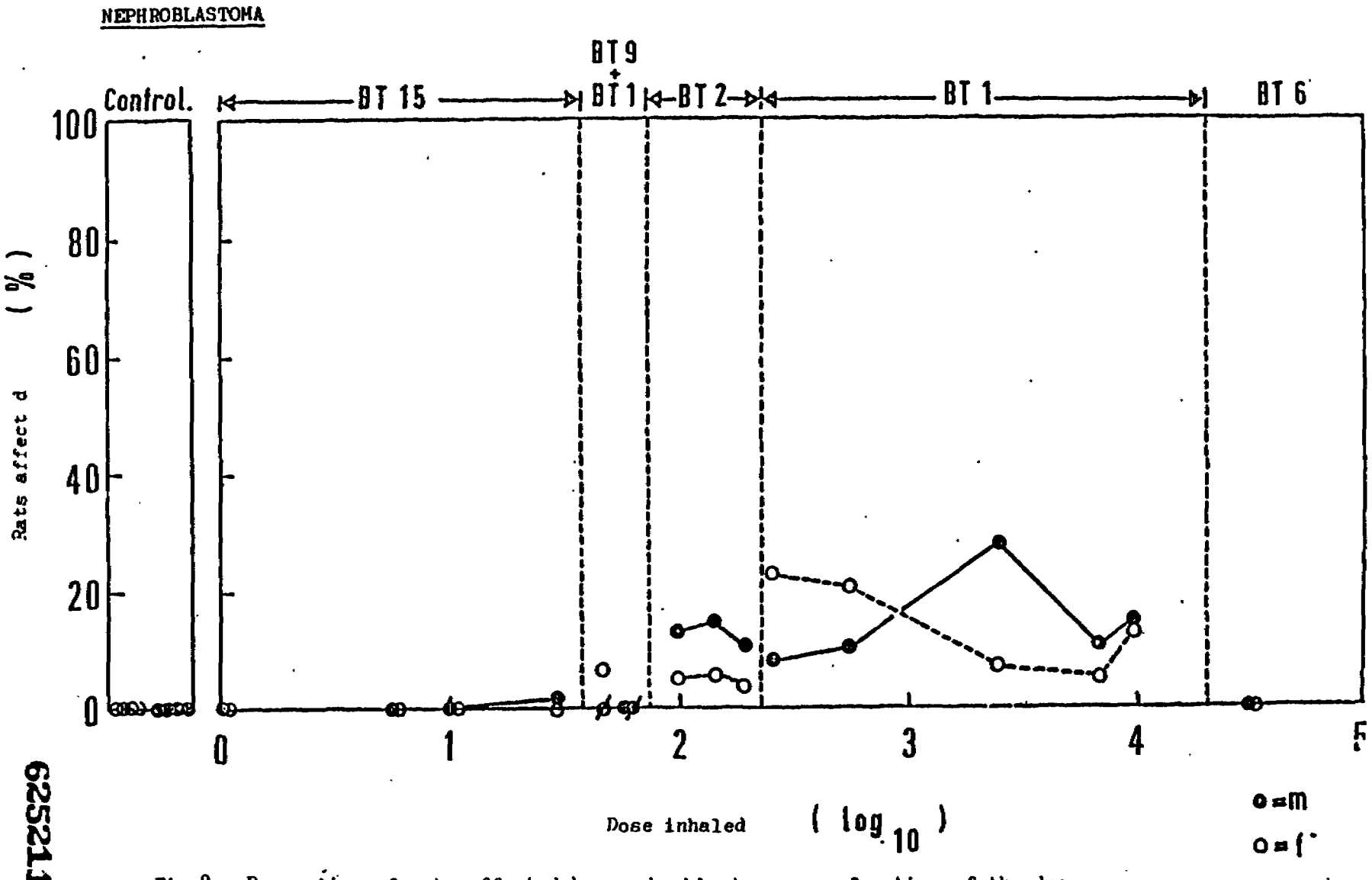


Fig.8: Proportion of rats affected by nephroblastoma as a function of the dose

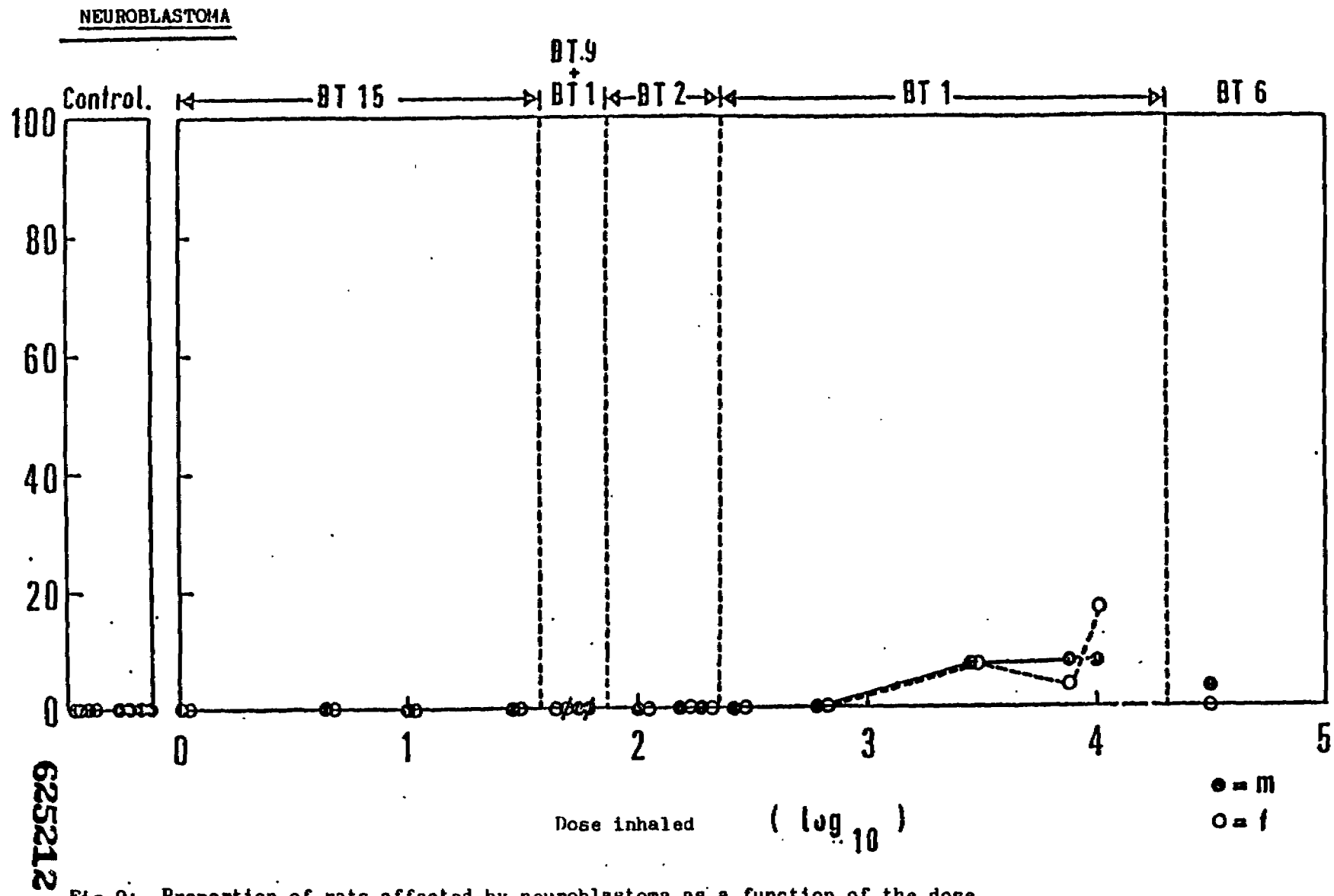


Fig.9: Proportion of rats affected by neuroblastoma as a function of the dose

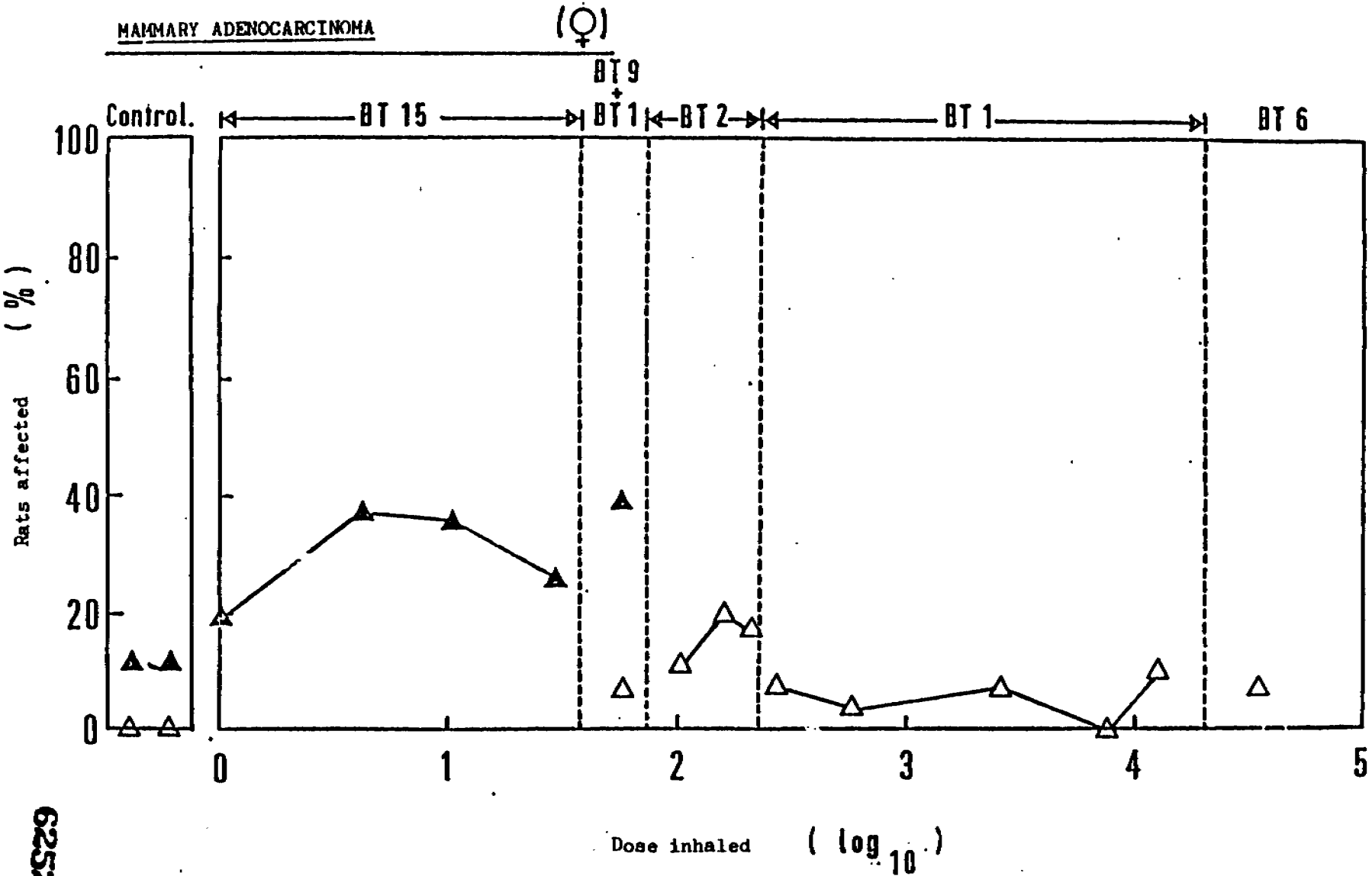


Fig.10: Proportion of rats affected by mammary adenocarcinoma as a function of the dose

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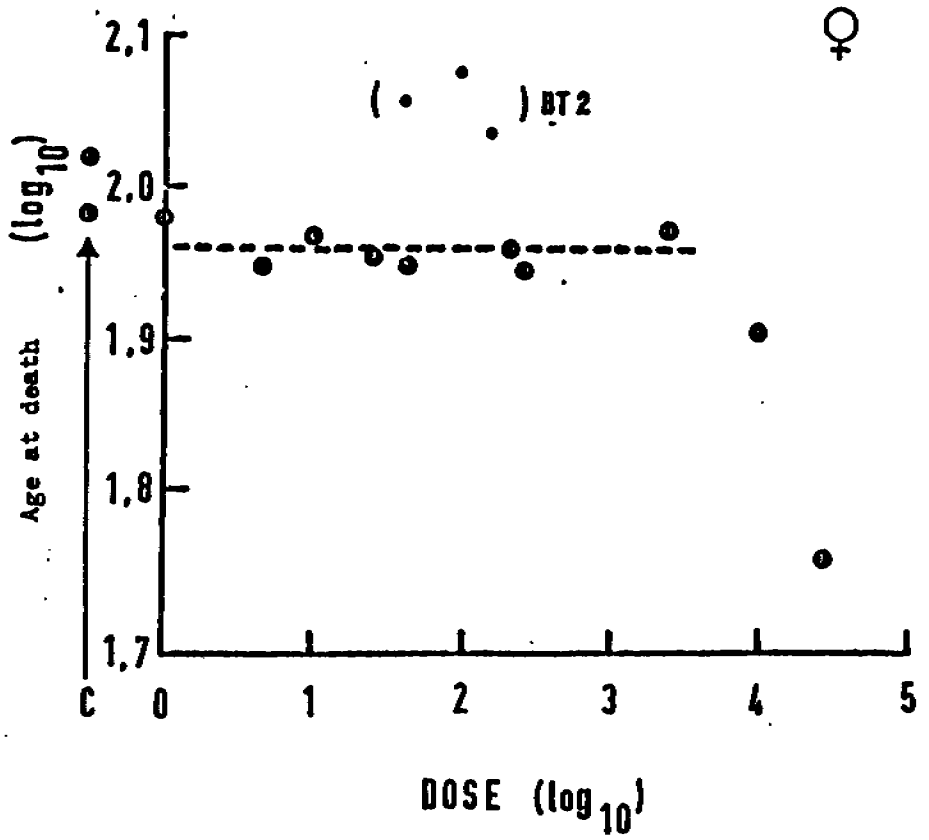


Fig.11: Female rats with mammary adenocarcinoma: no shortening of life

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FORESTOMACH PAPILLOMA (29)

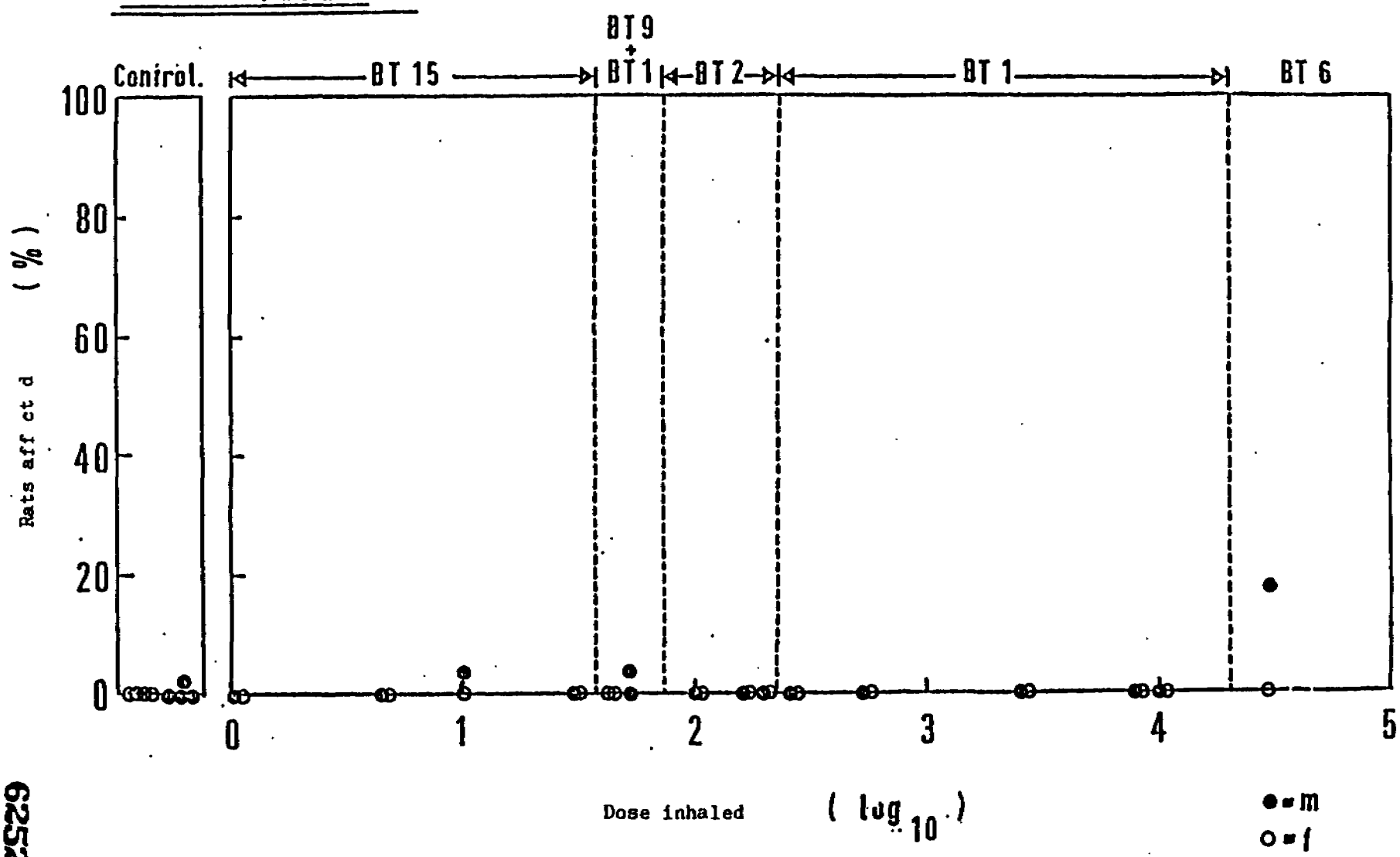


Fig.12: Proportion of rats affected by forestomach papilloma (29) as a function of the dose

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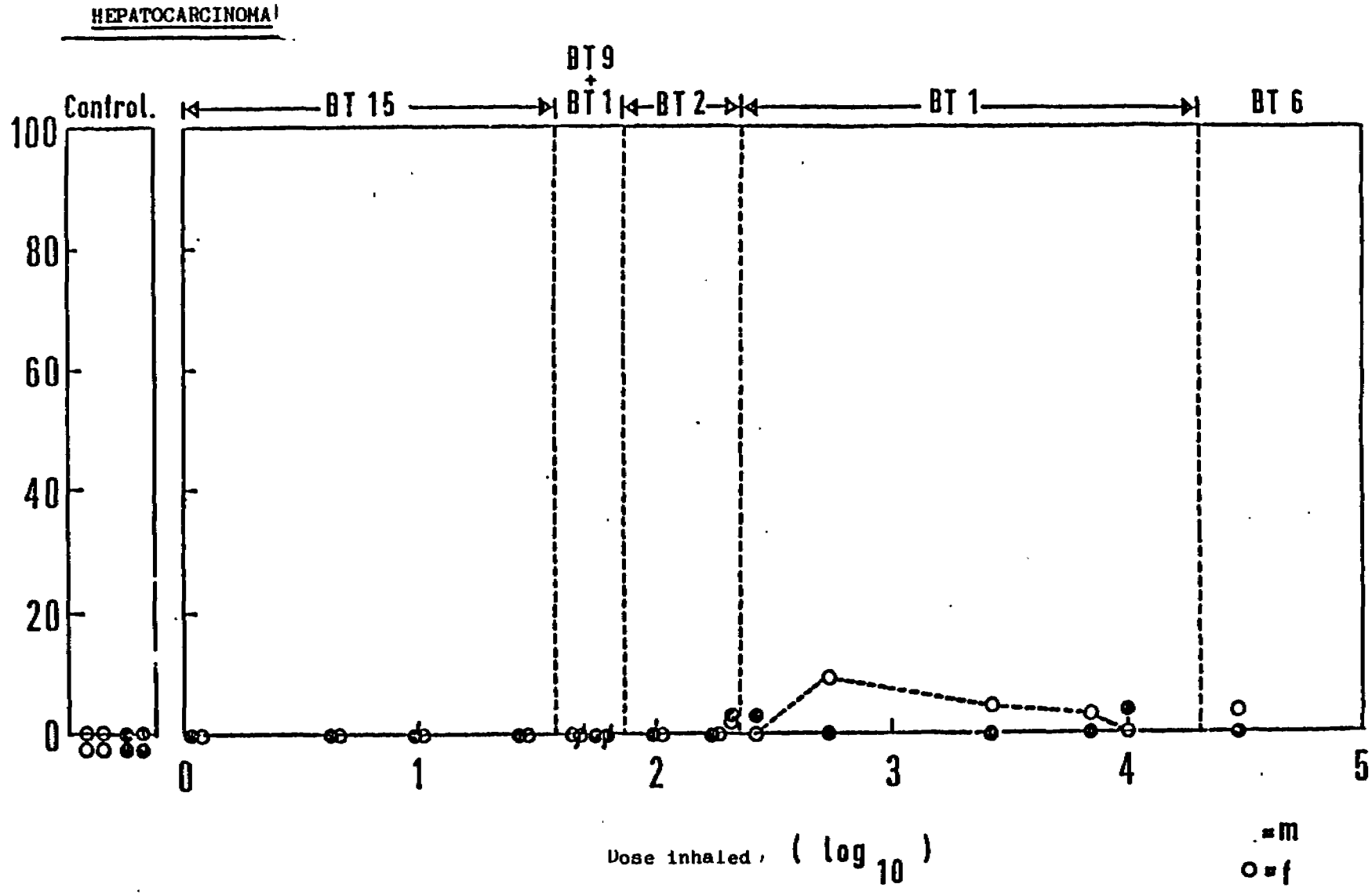


Fig.13: Proportion of rats affected by hepatocarcinoma as a function of the dose

6252216

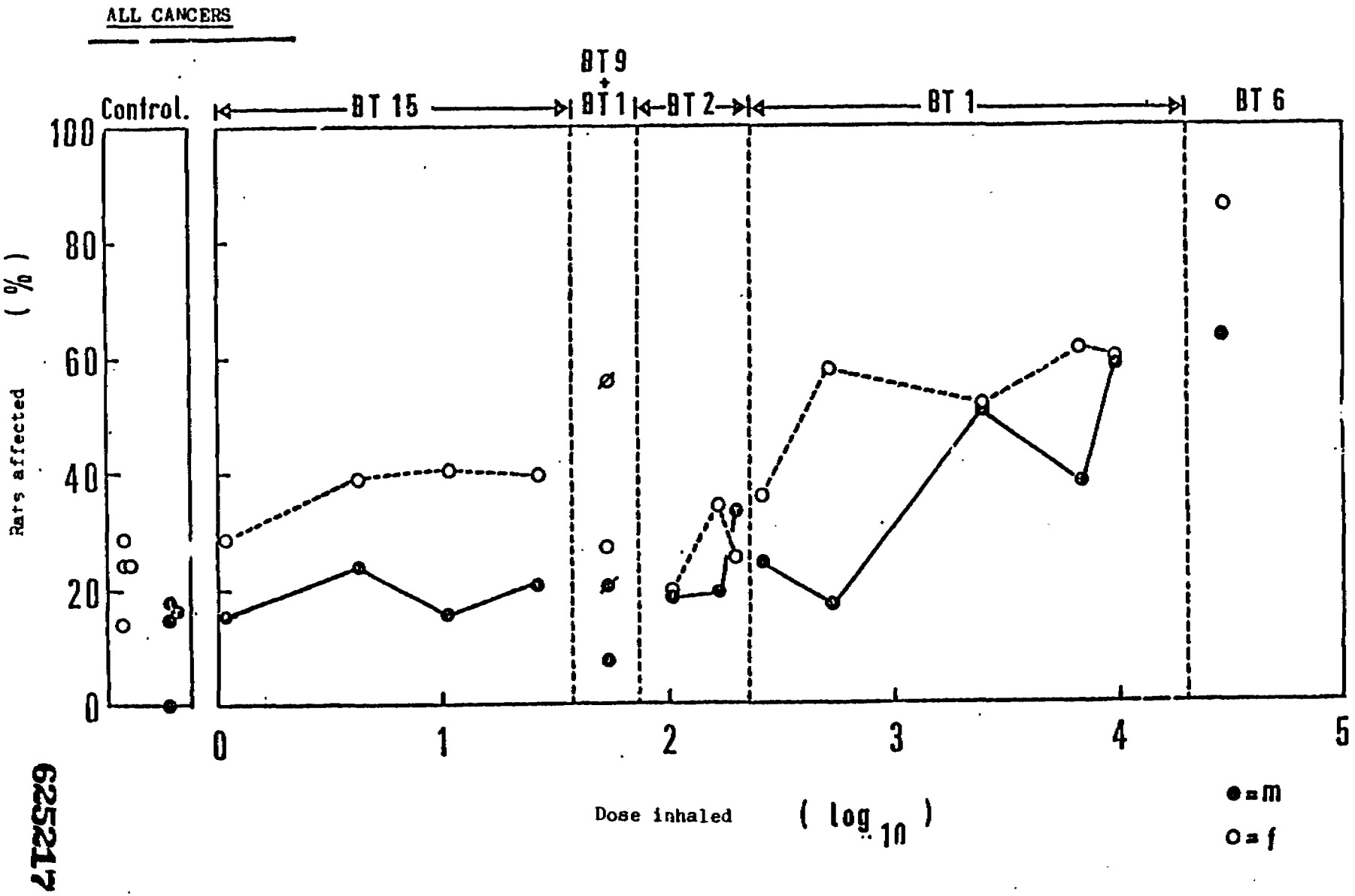


Fig.14: Proportion of rats affected by all cancers as a function of the dose

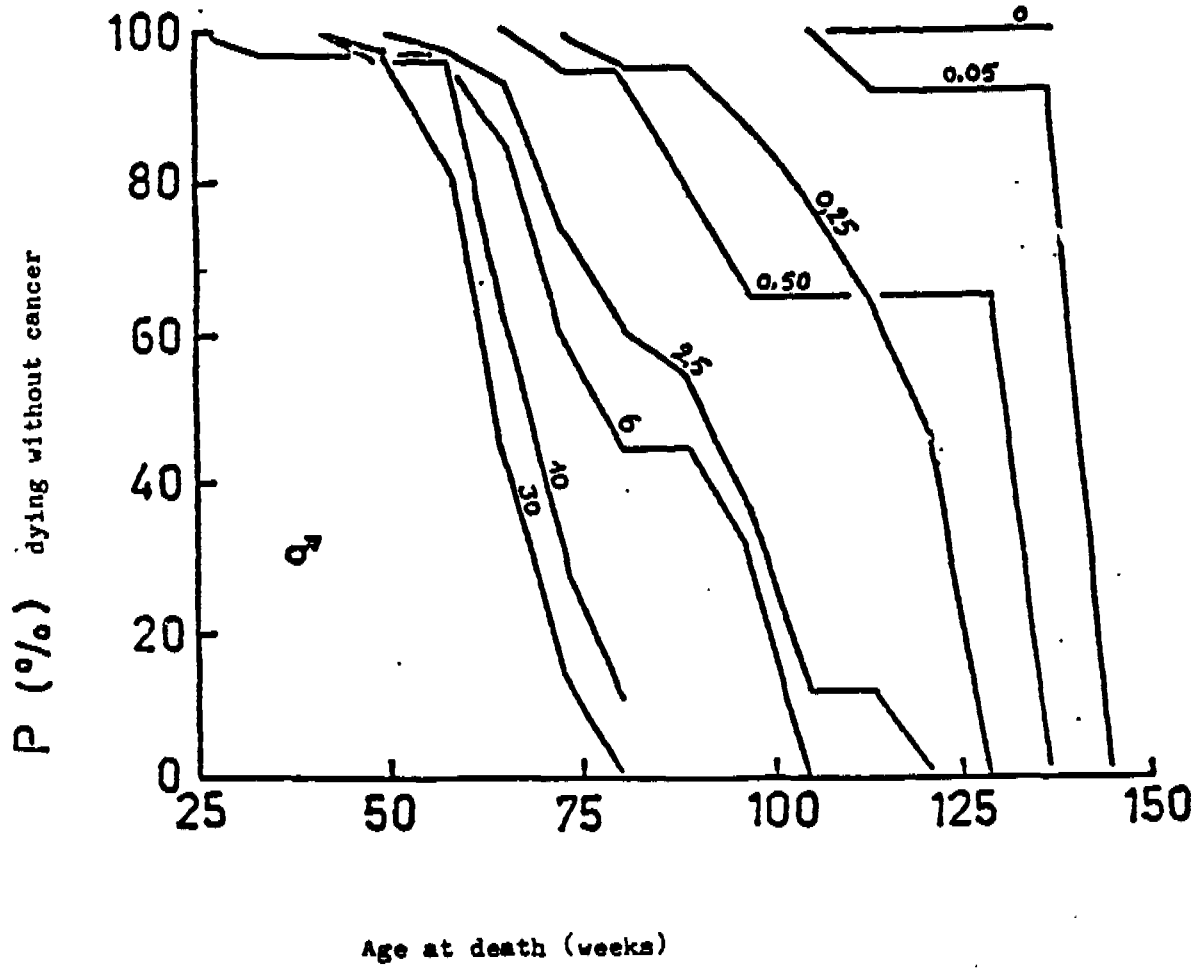


Fig.15: Actuarial method. Survival without cancer in the Sprague-Dawley rat exposed by inhalation to various doses of VC (expressed in 10^3 ppm, 4 h/d, 5 d/w for 1 year). Maltoni's data.

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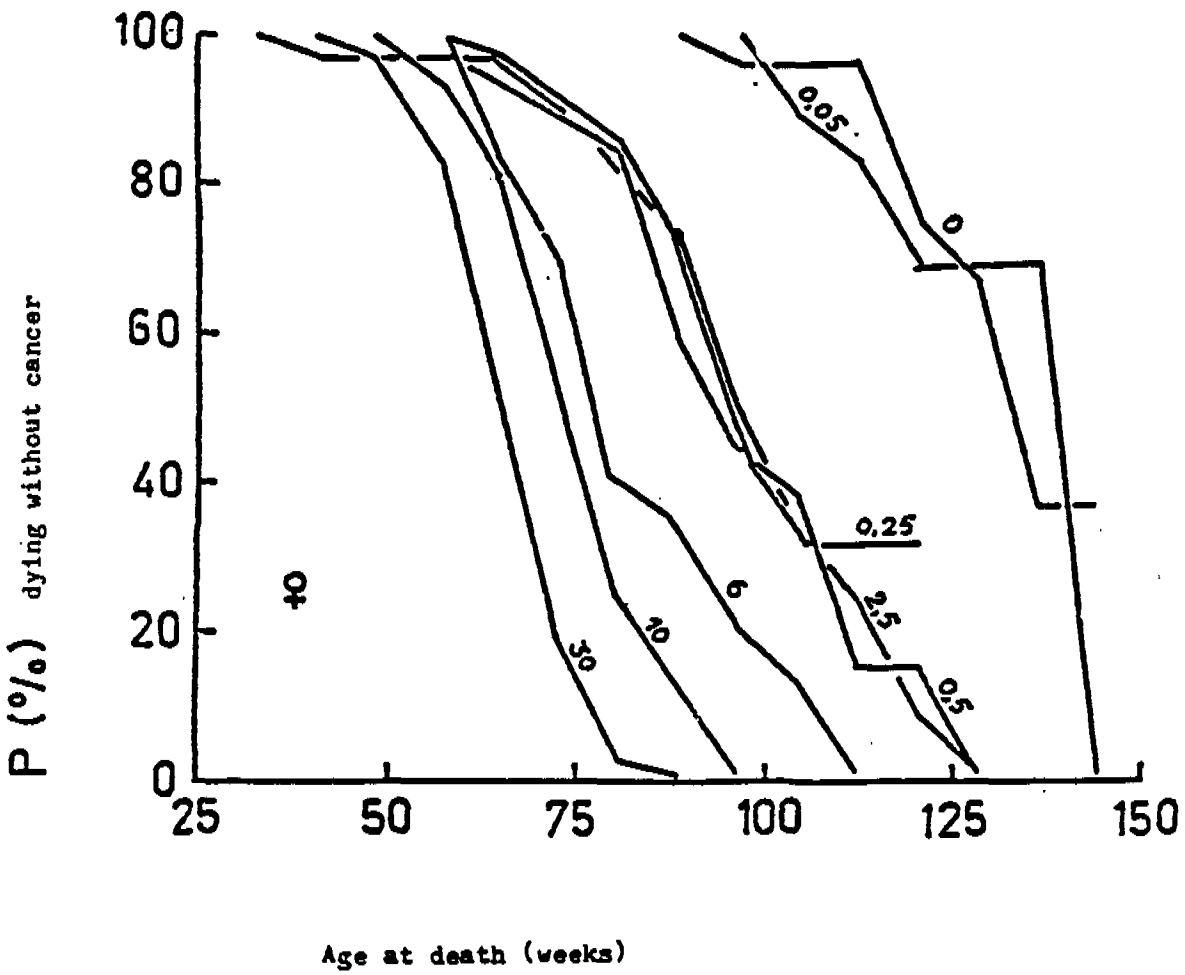
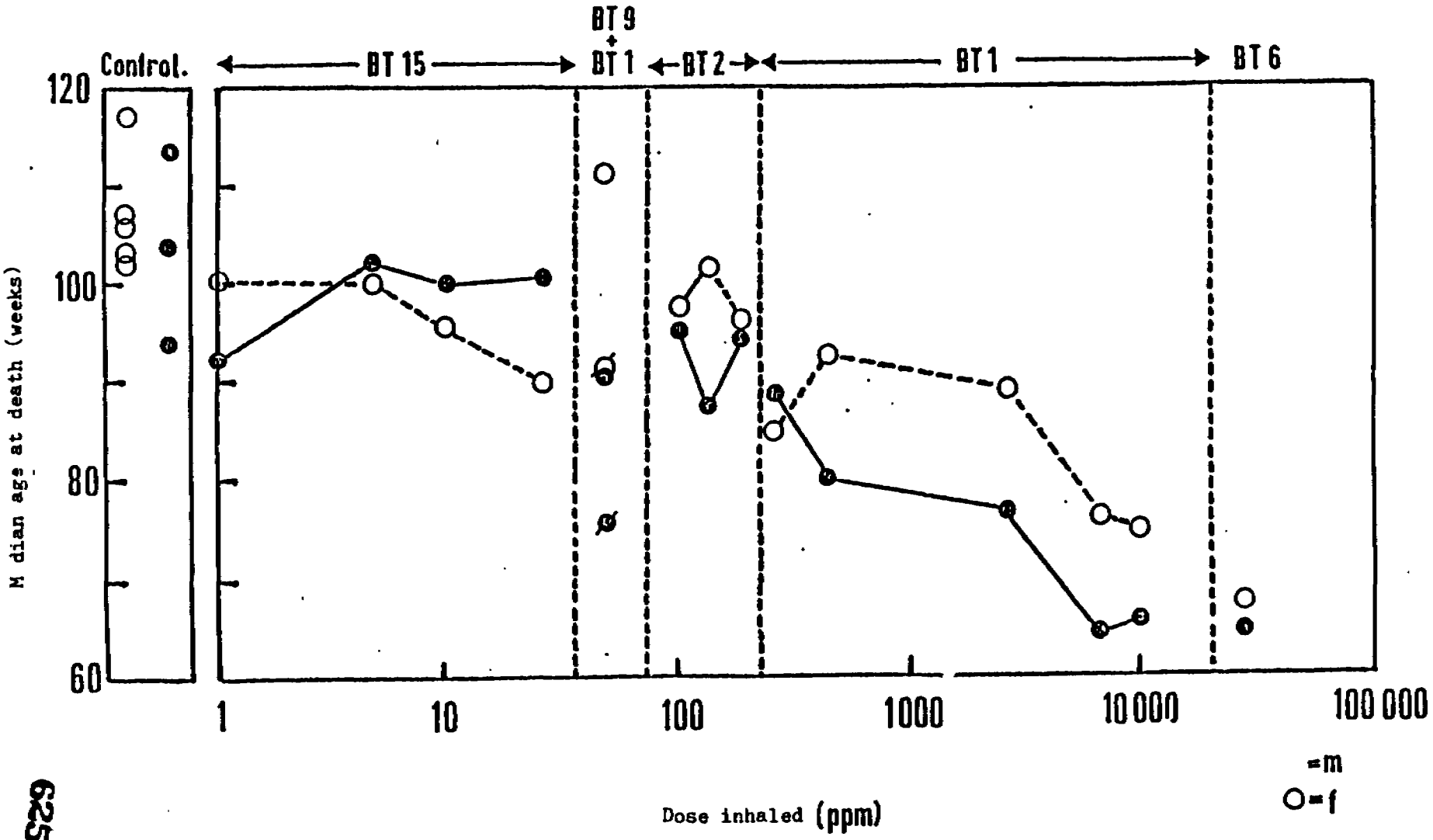


Fig.16: Actuarial method. Survival without cancer in the femal Sprague-Dawley rat exposed by inhalation to various doses of VC (expressed in 10^3 ppm, 4 h/d; 5 d/w for 1 year). Maltoni's data.

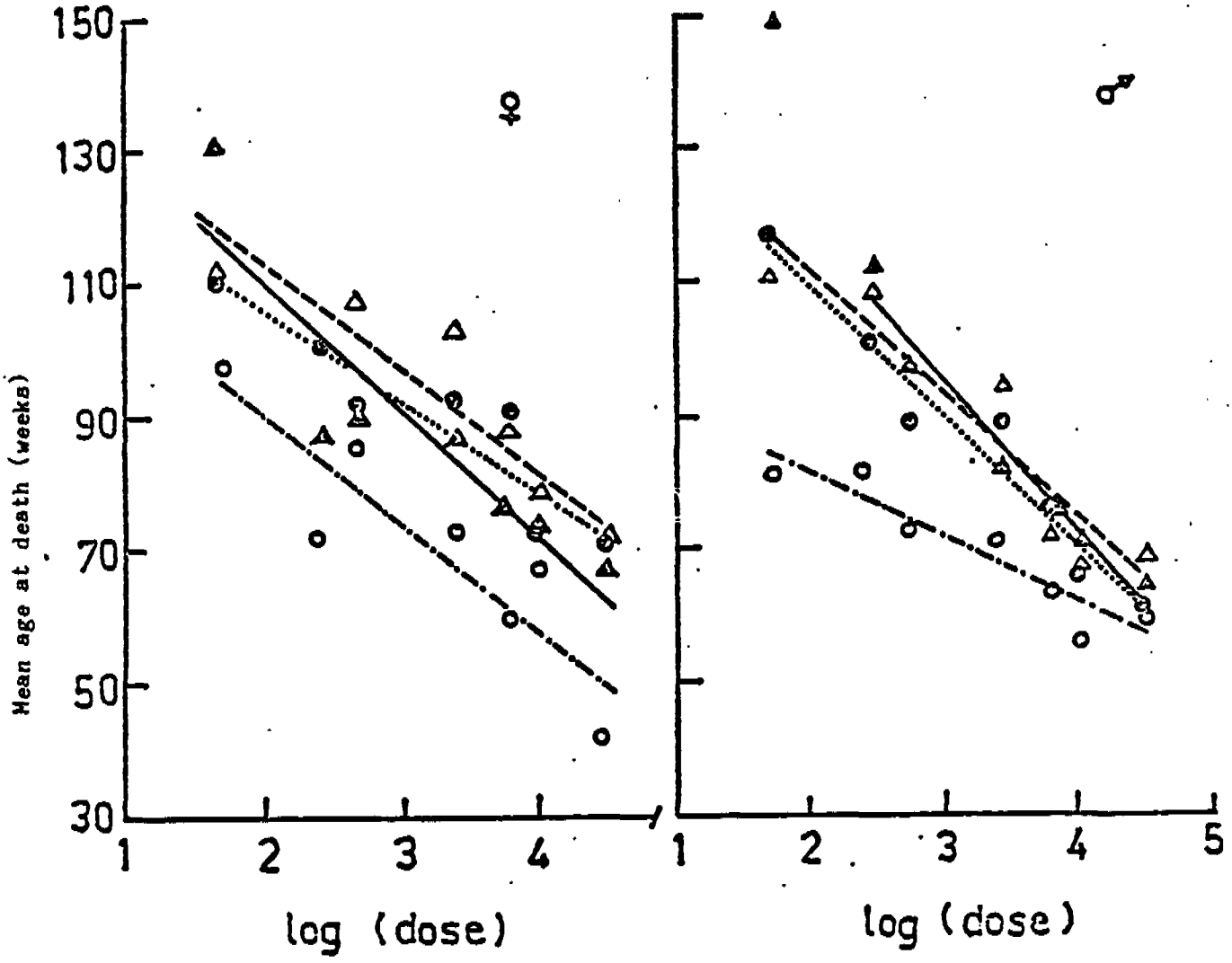
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Fig.17: Reduction in median life of the rats as a function of the dose

Fig. 18

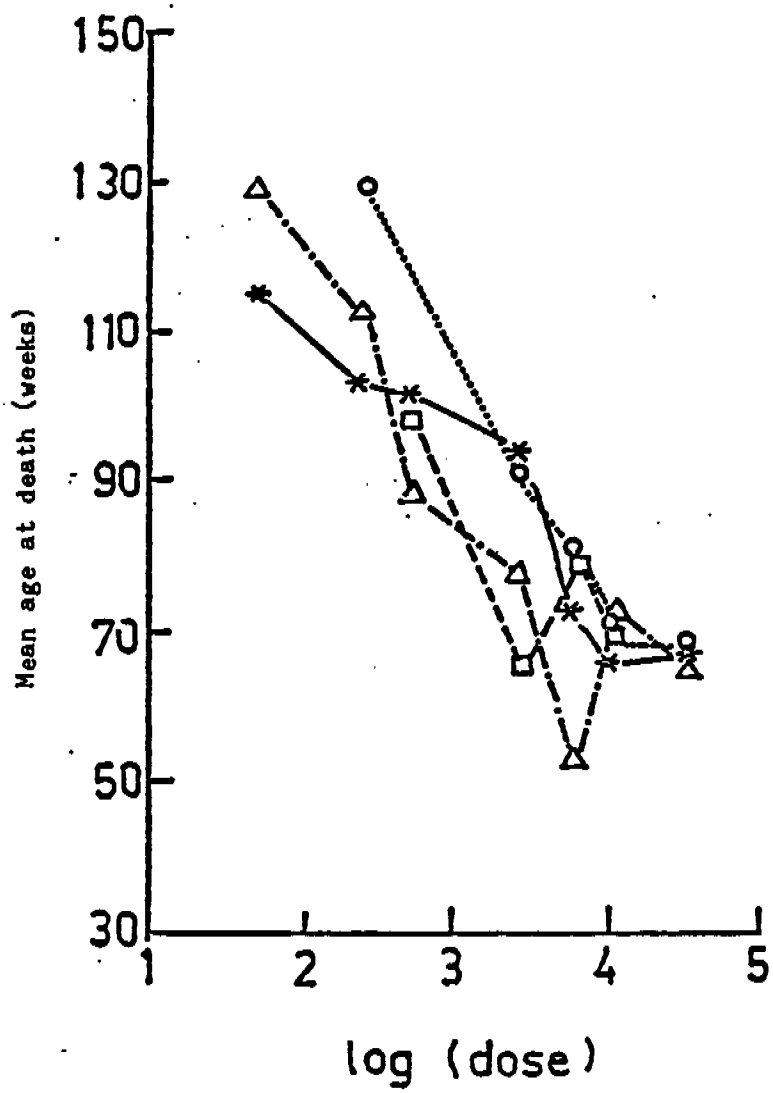


Reduction in the life of the Sprague-Dawley rats as a function of the dose. The systemic toxic effect is independent of the type of tumour(s) present at death. Note that the animals completely free from tumours have the shortest lives (significant only for the females, 0.05 p 0.01, one-way analysis of variance).

o-----o animals dying without tumours
-----● animals dying with benign tumours only
animals dying with benign and malignant tumours
Δ-----Δ both present

625221

Fig. 19



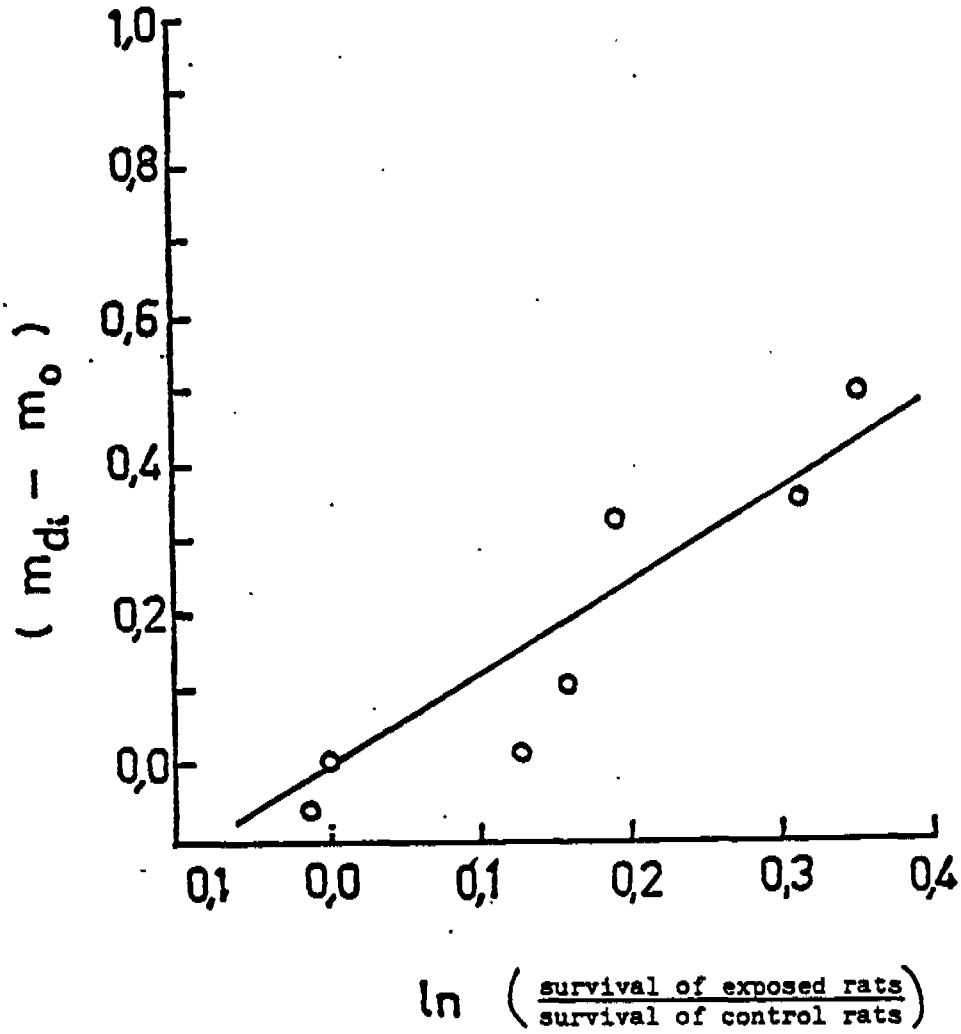
Changes, as a function of dose, in the mean survival time of rats affected by

o------o hepatic angiosarcoma
Δ------Δ malignant tumours not specific to VC
□------□ cancer of Zymbal gland
------ benign tumours not specific to VC

The effect of the dose is very significant (one-way analysis of variance)

625222

Fig. 20



Correlation between increased mortality and increase in tumours due to VC ($r = -0.94$). m_{di} is the mean number of tumours per animal exposed to the dose d_i; m_o is the mean number of tumours in the controls. A straight line passing through the origin has been fitted.

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MALE SPRAGUE-DAWLEY RATS (BT 1+6)

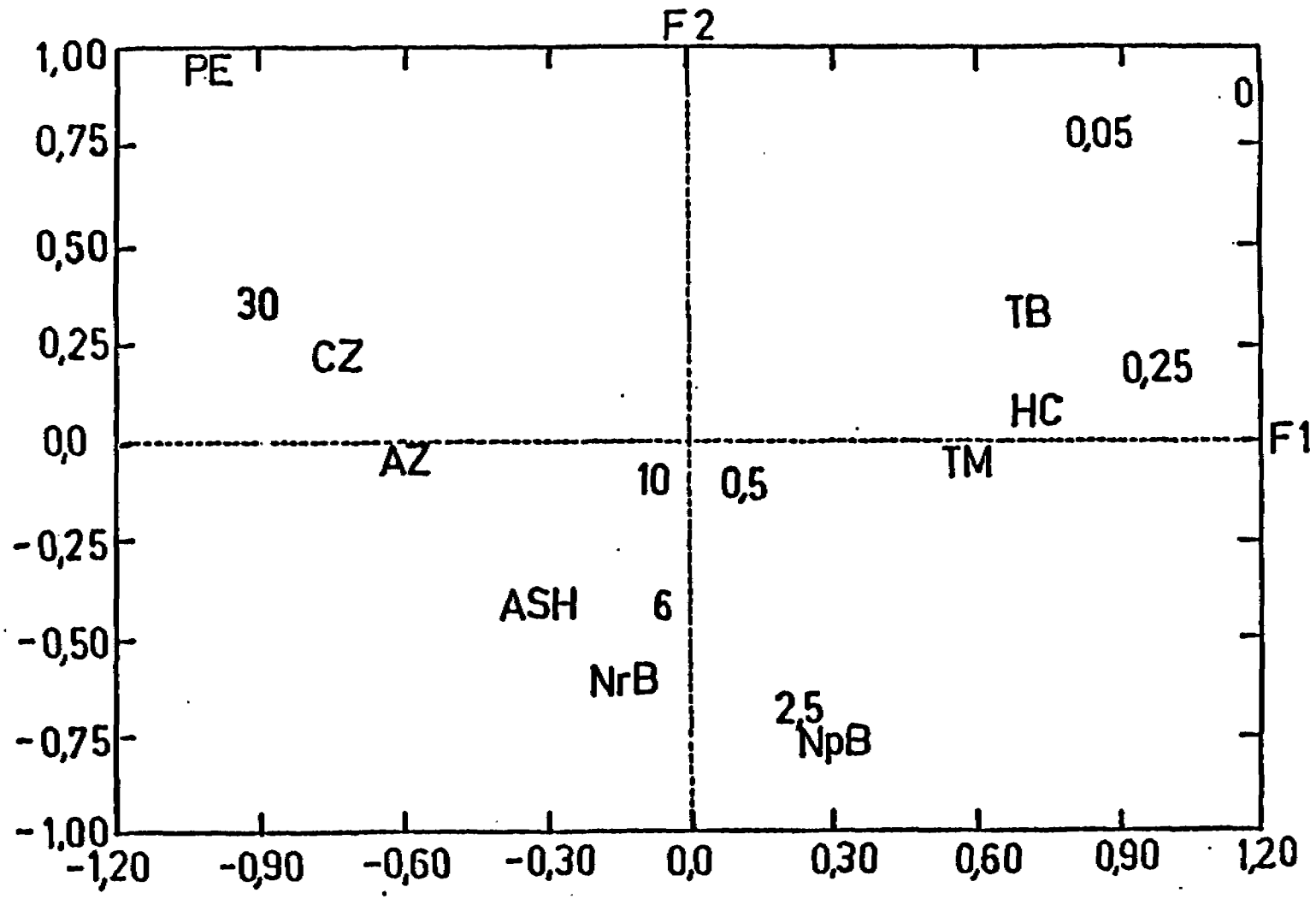


Fig. 21

Fig.21: Factorial correspondence analysis [26] between the image points of the doses and the image points of the tumours.
ASH = hepatic angiosarcoma. AZ = adenoma of Zymbal gland. CZ = carcinoma of Zymbal gland; HC = hepatocarcinoma; NpB = nephroblastoma; NrB = neuroblastoma; PE = forestomach papilloma; TB = all other benign tumours; TM = all other malignant tumours. The doses are expressed in 10^3 ppm. 4 h/d. 5 d/w for 1 year.

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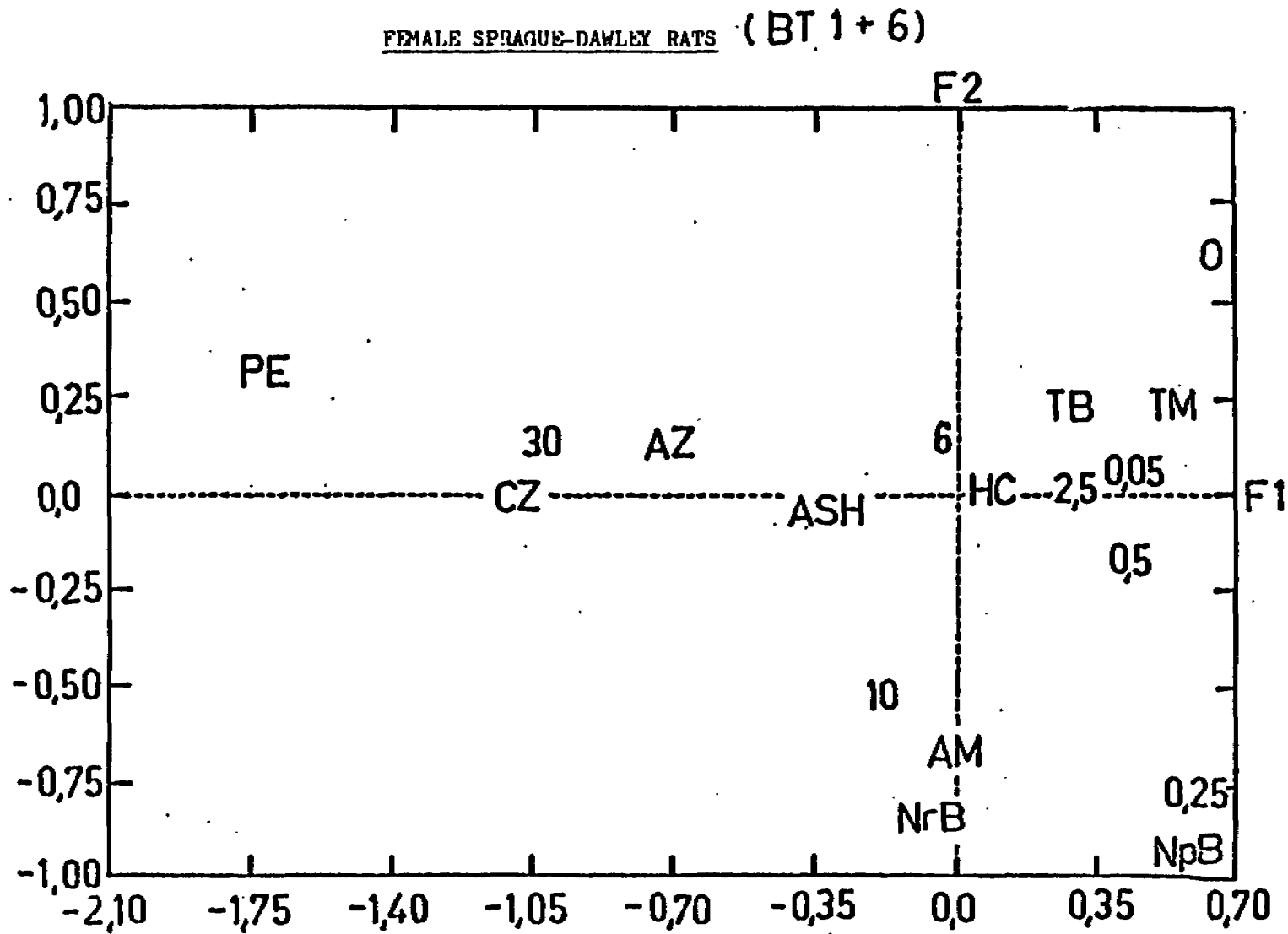
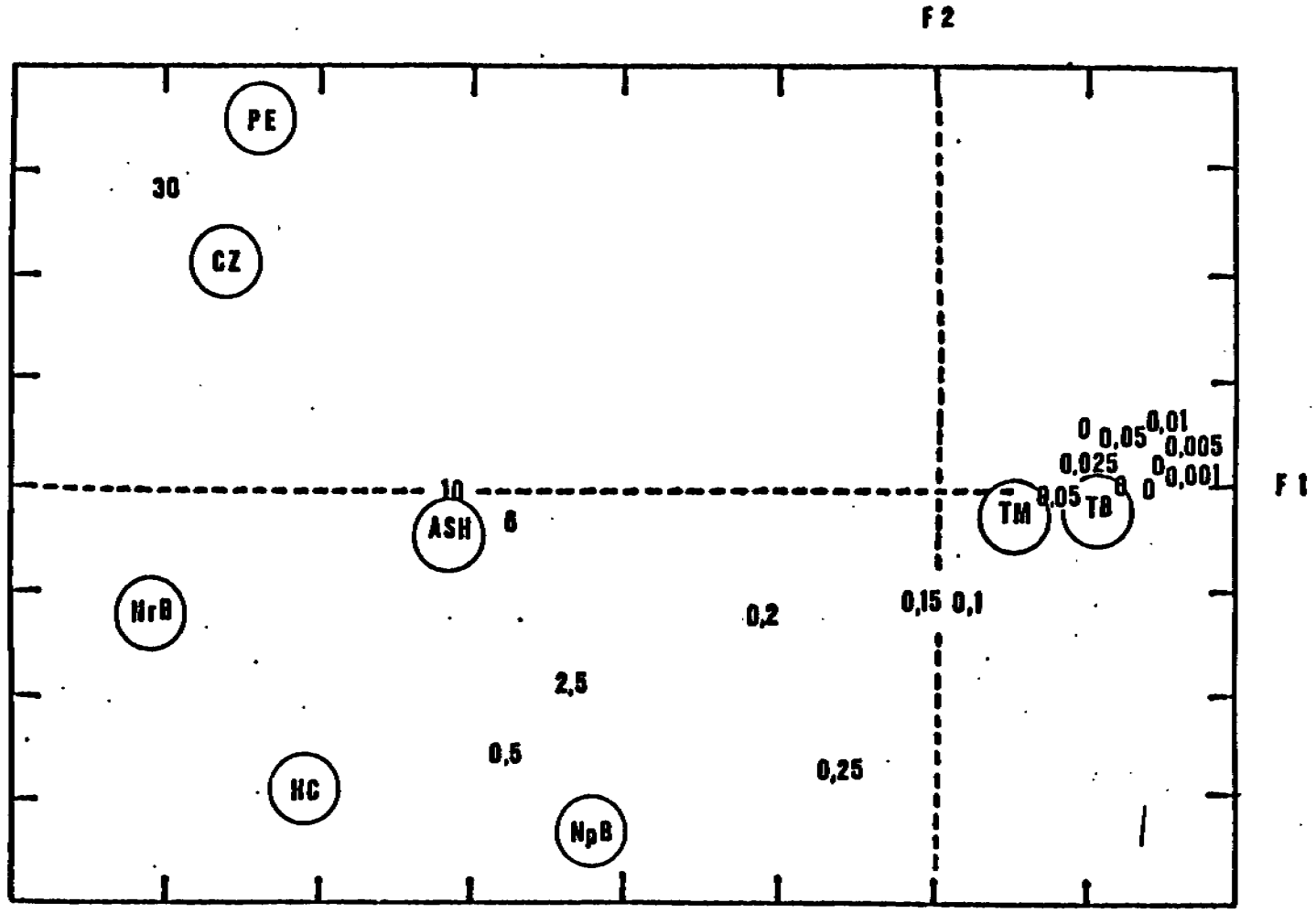


Fig. 22

Fig.22: Factorial correspondence analysis[26] between the image points of the doses and the image points of the tumours.
AM = mammary adenocarcinoma; ASH = hepatic angiosarcoma; AZ = adenoma of Zymbal gland; CZ = carcinoma of Zymbal gland; HC = hepatocarcinoma; PE = forestomach papilloma; NpB = nephroblastoma; NrB = neuroblastoma, TB = benign tumours, TM = malignant tumours. The doses are expressed in 10^2 ppm, 4 h/d, 5 d/w, for 1 year.

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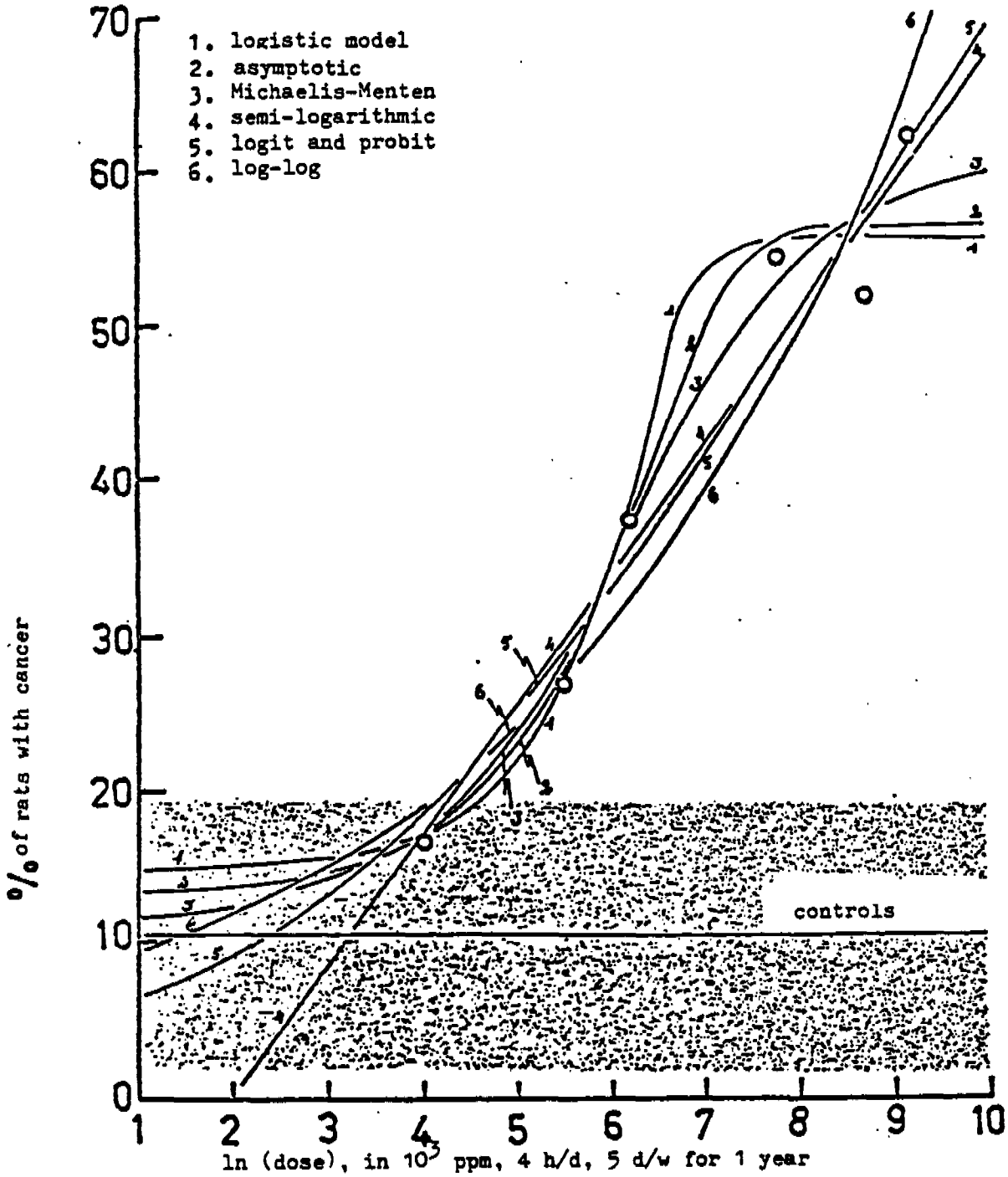
Studies BT 1, 2, 6, 8, 15

Fig.23:

Correspondence analysis between doses (represented by the concentrations in 10^3 ppm) and tumours. Male rats. The separation of the benign and malignant tumours (on the right) from the cancers "specific" to VC (on the left) is, perhaps, a reflection of the change in biochemical kinetics at about 200 ppm.

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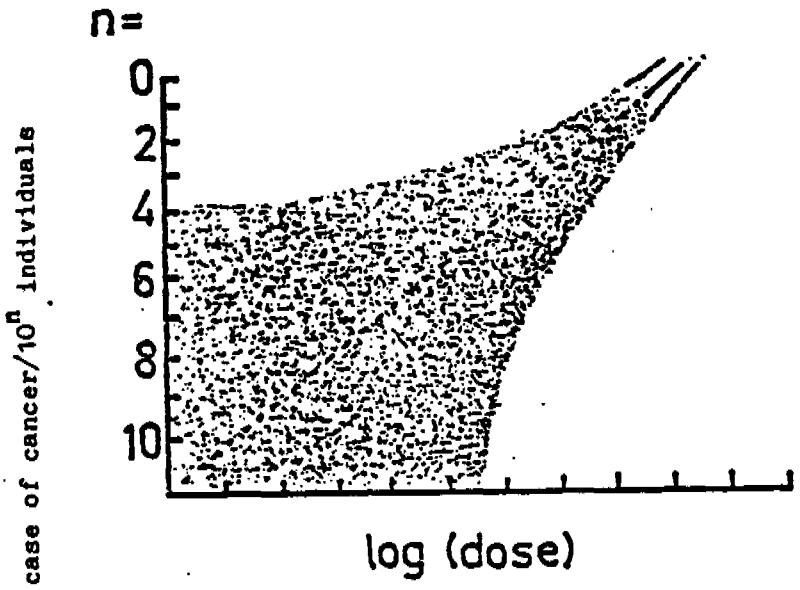
Fig. 24



Examples of models of dose incidence relation applicable to the data of Maltoni's study BT 1 on Sprague-Dawley rats. The shaded area shows the 95% confidence limits for the proportion of rats with spontaneous cancers.

625227

Fig. 25



Extrapolation from a regression line defined for an incidence of 10 to 100% of animals with cancer. The shaded area shows the 95% confidence limits. From Shubik and Clayson, 1976

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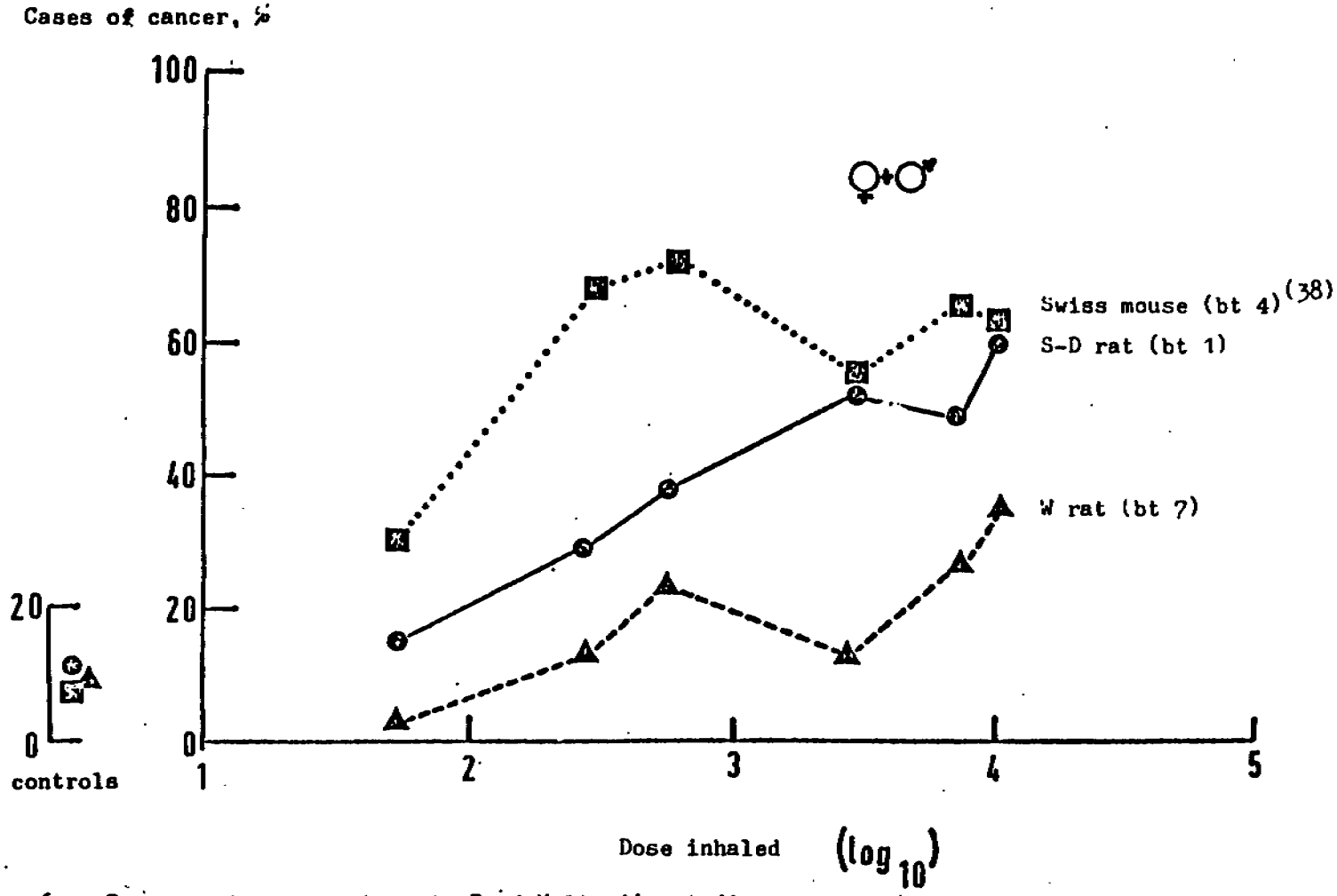


Fig.26: Interspecies comparison in Prof.Maltoni's studies

625229

C. Discussion of papers

Prof. Latarjet

I am very interested in what has just been said, and, even, in what has n t been said. We are touching on fundamental problems there, like that of the threshold and the dose/effect relation - whether or not it is linear. This statistical analysis has enabled us to profit from Maltoni's exceptional experiment (39) to come close to answering these questions which are fundamental because they go to the very root of any legislation. (sic ! ?)

There is one concept here which is dear to me, the concept of dose. The "ppm" have never been doses, they are concentrations. The doses are proportional to the ppm when the exposure-time is constant and the inhalation conditions are constant, but if the animal is exposed for its whole life and if survival varies with concentration, the dose is no longer parallel to the concentration. What we have seen, then, are concentration/effect curves, not dose/effect curves;

this is my main interest in this paper (40) and it is absolutely necessary for cancer specialists, chemists and toxicologists to understand that there is a rigour of expression which is not always observed in the Anglo-Saxon literature but which has become indispensable. We must be extremely strict, because considerable philosophical, social and legal consequenc s are involved.

Mme Hurst

To try to make a comparison with other known carcinogens, I should like to ask a definite question : In ingestion experiments with rats, what is the dose which caused the highest percentage of malignant hepatic tumours, and, under these conditions, what was the shortest latency period ?

625230

Prof. Maltoni

The dose which gave us the greatest response is 50 mg/kg body weight. In 80 animals we obtained 17 hepatic angiosarcomas, or an incidence of 21%. We also observed in animals not bearing angiosarcomas, 5 dysplasias and 7 hyperplasias of the sinusoidal cells. The mean latency period of the angiosarcomas was 78 weeks, but tumours certainly appeared sooner.

Mme Hurst 50 mg/kg body weight was the total dose?

Prof. Maltoni No, once a day, 5 days a week for 52 weeks.

Prof. Viola I should like to add that Maltoni's experiments are magnificent but that extrapolation from animals to man is still, I think, difficult, for many reasons. At different concentrations there are different cellular responses. There are all sorts of enzymes which no one has properly studied yet.

If we are speaking of quantitative extrapolation, 10 or 50 ppm in Maltoni's work, we obtain our answers from animal experiments which have nothing to do with human beings. If 50 ppm is significant for humans then I wonder why only 100 people have died up to now.

I am well aware of the exposure situation 20 or 30 years ago with 1,000 - 3,000 ppm every day. Outside these concentrations, there are thousands of people who breathed 100 ppm of vinyl chloride and 300,000 who breathed 3 or 4 ppm. So I think a quantitative extrapolation from 1 ppm, from 1,000 ppm is a reflection of research restricted to animals. When, for the first time, I went to USA to discuss all the problems of vinyl chloride, I said : "there are fundamental principles we must, above all, study and investigate. Is there or is there not a safety threshold?" This was 10 years ago and research on vinyl chloride has today become a research method in cancer r search. I must say that the analysis

625231

Dr Tassignon

I should like to reply to Prof. Viola because the questions he raises, the d se/effect relation in animals and extrapolation of the data from animals to man are very important for this afternoon's discussion.

The choice of a model is already very difficult. There are thousands of them. (See the examples in Fig. 24). When you have this small dose/effect relation[41] (Fig. 25) in the dose-range examined and you wish to extrapolate the doses which are very low but which correspond to the manner in which human beings are permanently exposed in the environment or in their food, you are taking a terrible leap, and since any regression set up has confidence limits your confidence limits become extremely wide insofar as you leave the range of the experiments. M reover, which of the various animal species is the right model for man? (Fig. 26).

Prof. Maltoni

The neoplastic response depends on the basic tumorigram[42], the enzyme profile, and, of course, the dose.

We know that for both man and animals there is a relation between the dose and the neoplastic response. This dose/effect relation has certainly been verified in animals in the case of carcinogenesis by vinyl chloride.

As to the exact extrapolation of the quantitative data from animals to man, it is necessary to have comparable information on the susceptibility of response (of which the basic tumorigram[42] is an expression), and the enzyme profile for animals and man.

Parallel experimental and epidemiological investigations on man might make an extraordinary contribution to the extrapolation of the data from animals to man not only in the case of carcinogenesis by vinyl chlorid but for carcinogenesis

625232

4. HUMAN EPIDEMIOLOGY

M Latarjet called upon M Bonnefoy (Solvay) to address the meeting.

A. The VCM and PVC industry (Paper 4 - Mr M Bonnefoy)

I should like, on the occasion of this meeting, to raise some ideas which seem to me to be important both on the industrial level and on the human level in the PVC industry.

It may be useful, in the first place, briefly to recall the outline of PVC production (Slide 1).

- Two raw materials
  - ethylene of petrochemical origin
  - chlorine obtained by electrolysis of salt, an industrial peration which produces, in parallel, caustic soda, the basic alkali of the chemical industry.

- The synthesis of VCM, a continuous process under pressure, which requires gas-tight circuits. The plants built in the open are of the petrochemical type. The staff is small.

- The polymerisation of vinyl chloride to PVC. This is a discontinuous operation comprising numerous manual operations. It is there that there used to be the greatest hazard of exposure to vinyl chloride, in particular when the cleaning of the polymerisation reactors was effected manually.

- Finally, downstream, the conversion of the PVC resin to finished products, either directly or by the intermediary of compounds ready for use.

625233

What is the importance of PVC in our present society? A society which is by nature technical, industrial, and based on th use of artificial materials, whether they are steel, cement, glass or plastics.

The world consumption of PVC in 1976 was 9.2 million tonnes, that of Western Europe 3.4 million tonnes (Slide 2).

To illustrate these figures let us express the consumption of PVC as a fraction of that of other materials which may be more widely known. In the EEC, PVC represents

- $\frac{1}{4}$ of all plastics
- as much as all rubbers, including car tyres
- more than the primary consumption of aluminium.

Upstream, it must be stressed that 30% of Cl_2 production is fixed in PVC, thus putting the same proportion of NaOH at the disposal of industry. Now, on the market, if the Cl_2 is in excess there is a shortage of caustic soda.

PVC therefore plays an indispensible part in the balance of several industrial sectors which consume caustic soda, some of them being of strategic importance for our economy.

Downstream, PVC turns up in numerous applications where its various properties - mechanical properties, non-flammability, resistance to ageing, economic competitiveness make it a prized, often irreplaceable product. I shall quote two examples as an illustration.

- In the building sector:
  half the plastics used are PVC, thus:
  - in France, half the pipes are of PVC

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- Another example, food packaging, particularly bottles:
  - in France, 2 wine-bottles in every 25
    20 water-bottles in every 25
    17 oil-bottles in every 25
    20 vinegar-bottles in every 25 are of PVC.

These few points of reference are quoted to stress that PVC is not a trifling novelty but a basic raw material. It is therefore socially inconceivable to ignore it, still less to prohibit it.

If production presents risks, it is up to the social partners(43), firms, workers, scientists, the authorities to take steps to master and eliminate them.

What is the population directly involved in the production of PVC? It is evidently difficult to make an exact census - those present at this meeting wh are presenting epidemiological surveys will explain to you the obstacles one runs into in this field - but it is possible to make an estimate.

At present, in Western Europe, the personnel employed in the production f VCM and PVC is of the order of 16,000 people. On a world scale, extrapolation based on PVC production gives a figure of 40,000 people.

To represent the total population employed or formerly employed in PVC production we need to take two further factors into account:
- The increase in the number of people employed in PVC production with time
- The turnover in the personnel.

The graph (Slide 3) from a survey carried out in Great Britain by the Empl yment Medical Advisory Service is a good illustration of these tw aspects.

625235

1 Beginning of the PVC industry in the years 1940-1950; exponential growth of the personnel employed up to 1973-1974, and, not apparent here, a smaller increase in numbers during the last few years because of the economic crisis and the slowing down of PVC production which this has caused.

2 The number of former employees is substantially equal to those currently employed. On this basis we may, as a crude approximation, estimate that the population having worked or working in the VC and PVC production sector is of the order of 80,000 people for the whole world.

I should like, and this is a delicate aspect, to talk of the cases of death from hepatic angiosarcoma, a condition whose relation to exposure to high doses of vinyl chloride is clearly established.

This graph (Slide 4) shows the curve for the growth of the number of cases identified as a fraction of time. We see a rapid growth from the years 1967-1970, culminating in 1976, and what seems to be a stabilisation in 1977 and 1978.

I should like to make a few remarks on this subject illustrated by this other, strictly qualitative graph (Slide 5)

- The first curve is that of the preceding graph. How is it going to develop in future years?
- The second curve is an attempt to answer this question. It shows the frequency of cases actually occurring,that is, the number of effective cases each year in relation to the population exposed. We can show:
- in (1), an underestimate for the years 1940-1950, for detection was certainly incomplete
- in (2), a more moderate increase in the 60s, having regard to the rapid increase in the population exp sed

625236

- in (3), the hoped-for effect of the reduction in exp sure-levels in the 60s

and beginning of the 70s, the first results of the efforts connected with the prevention of acro-osteolysis, on which Dr Berrod said a few w rds to us this morning

- finally, in (4), 15 to 20 years after the putting into operation of the drastic reductions in exposure since 1974-1975, a tailing off of the cases.

Does the stabilisation of the number of cases observed in 1977 and 1978 justify the hope that we have now reached zone (3)?

That is the question.

I wish to conclude by putting forward some ideas.

- Animal experiments - the discoveries of Dr Viola and the remarkable work of Prof. Maltoni are an illustration of this - have played a fundamental part in the story of vinyl chloride toxicity.

They have enabled us to demonstrate its carcinogenic effect, to identify, in animals, its target organs, and to confirm the hypothesis of a relation between the dose and the effect.

Animal experiments, unfortunately, possess their own limitations.

- The animal populations exposed are too small in numbers to permit statistical exploitation(105) of the results at low doses.
- Above all, quantitative extrapolation is impossible at present between different animal species; still less is it possible from animal to man.

Human epidemiology - and I beg you to excuse this anticipation of this afternoon's topic - makes up for the weaknesses of animal experiments. In the case of vinyl chloride the fact is that unfortunately the populations exposed have been large. But above all, human epidemi logy analyses the behaviour of man - a complex being in a complex environment - directly. This study is, to my mind, basic.

625237

Animal experiments and human epidemiology are, however, only a posteriori methods of study. In both cases we analyse actual situations and discover results.

As a former works engineer I ask the question: Is it not equally suitable to direct scientific research effort towards a better knowledge of the carcinogenic function of vinyl chloride, towards the study of the various stages of development of the tumours : why and how does vinyl chloride act?

We are cruelly lacking in knowledge of how to detect the early symptoms of the development of the disease in those who have been exposed in the past and in therapeutic means when a case of angiosarcoma is confirmed.

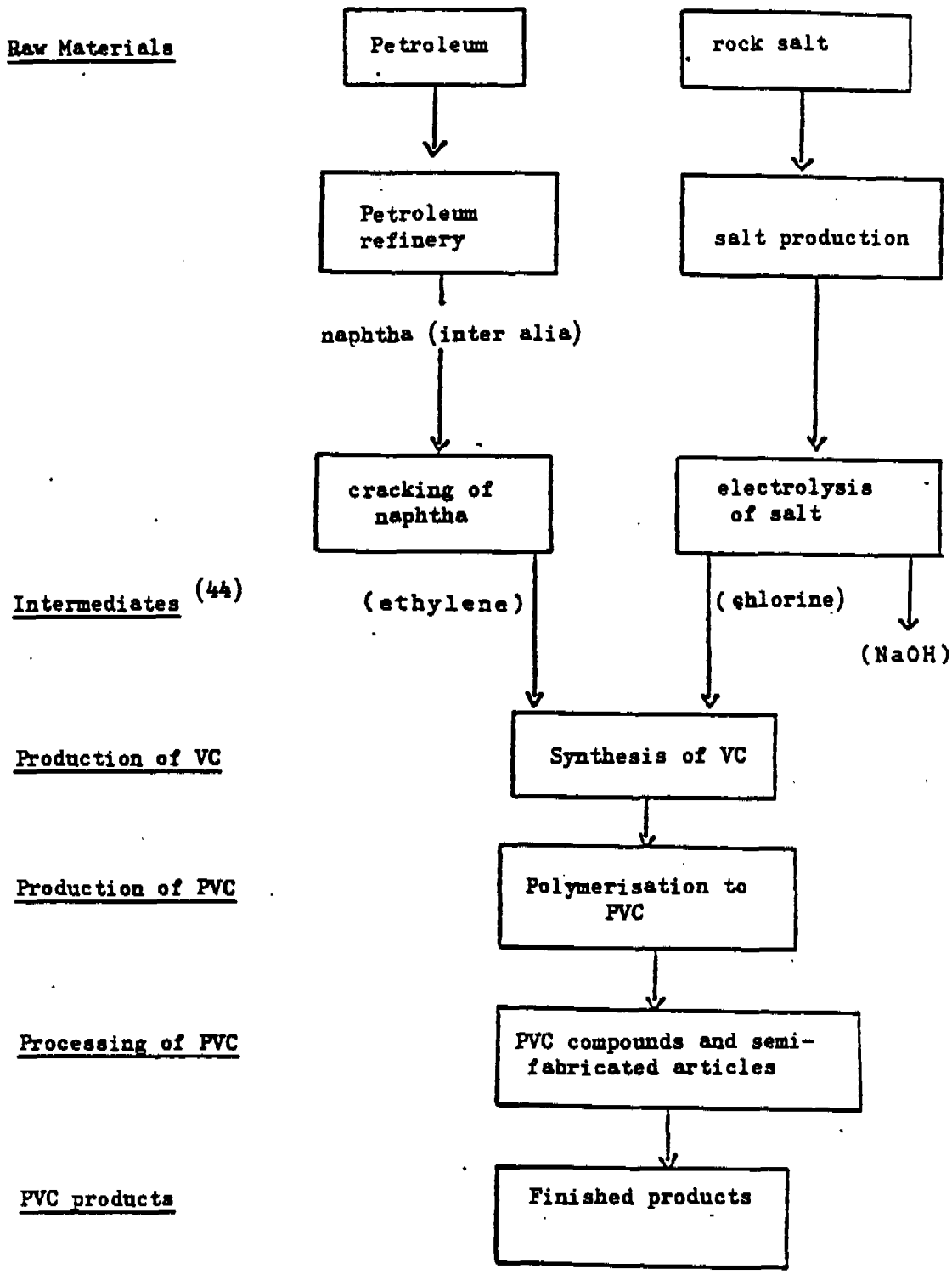
From a more industrial aspect, it is certain that the various forms of exposure to vinyl chloride have been reduced to very low levels by a considerable effort by the industry. At this stage it becomes important for the community to assess the reality of the hazard associated with exposure to vinyl chloride accurately in relation to other social risks, so that the resources of the community are used where the action will be most effective.

From this point of view, also, fundamental research on the mechanisms of action of vinyl chloride must contribute to supplying an answer.

These are the questions I ask the distinguished scientists of your Club de Cancérogénèse Chimique.

625238

Fig. 1


Raw Materials
Petroleum
rock salt
Petroleum refinery
salt production
naphtha (inter alia)
cracking of naphtha
electrolysis of salt
Intermediates (44)
(ethylene)
(chlorine)
(NaOH)
Production of VC
Synthesis of VC
Production of PVC
Polymerisation to PVC
Processing of PVC
PVC compounds and semi-fabricated articles
PVC products
Finished products

625239

Fig. 2 PVC

1 Consumption (1976)

World	9.2 million tonnes
Europe	3.4 million tonnes
EEC	2.9 million tonnes

2 Importance of PVC (EEC = 1976)

Plastics	12 - 13 million tonnes
PVC	2.9 million tonnes
Rubber	2.9 million tonnes
Primary aluminium	2.0 million tonnes

3 Industries upstream

PVC = 30% of the chlorine and NaOH

4 Industries downstream

Examples:

Building: 50% of the plastics used (EEC)

1 pipe in 2 (France, Germany, Holland)

1 window-frame in 2 (Germany)

Bottling: Wine = 2 bottles out of 25

Water = 20 bottles out of 25

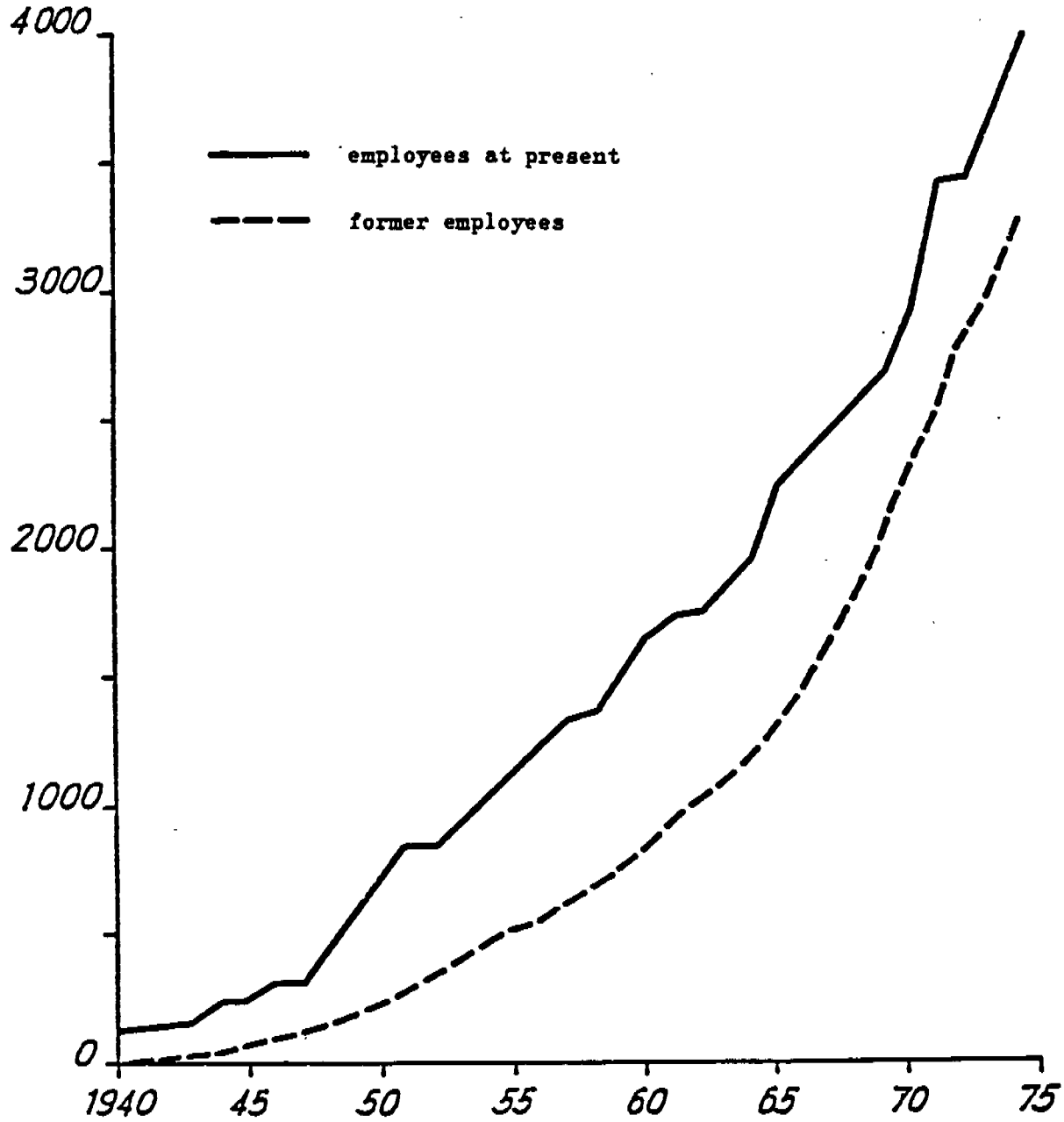
Oil = 17 bottles out of 25

Vinegar = 20 bottles out of 25

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Fig. 3

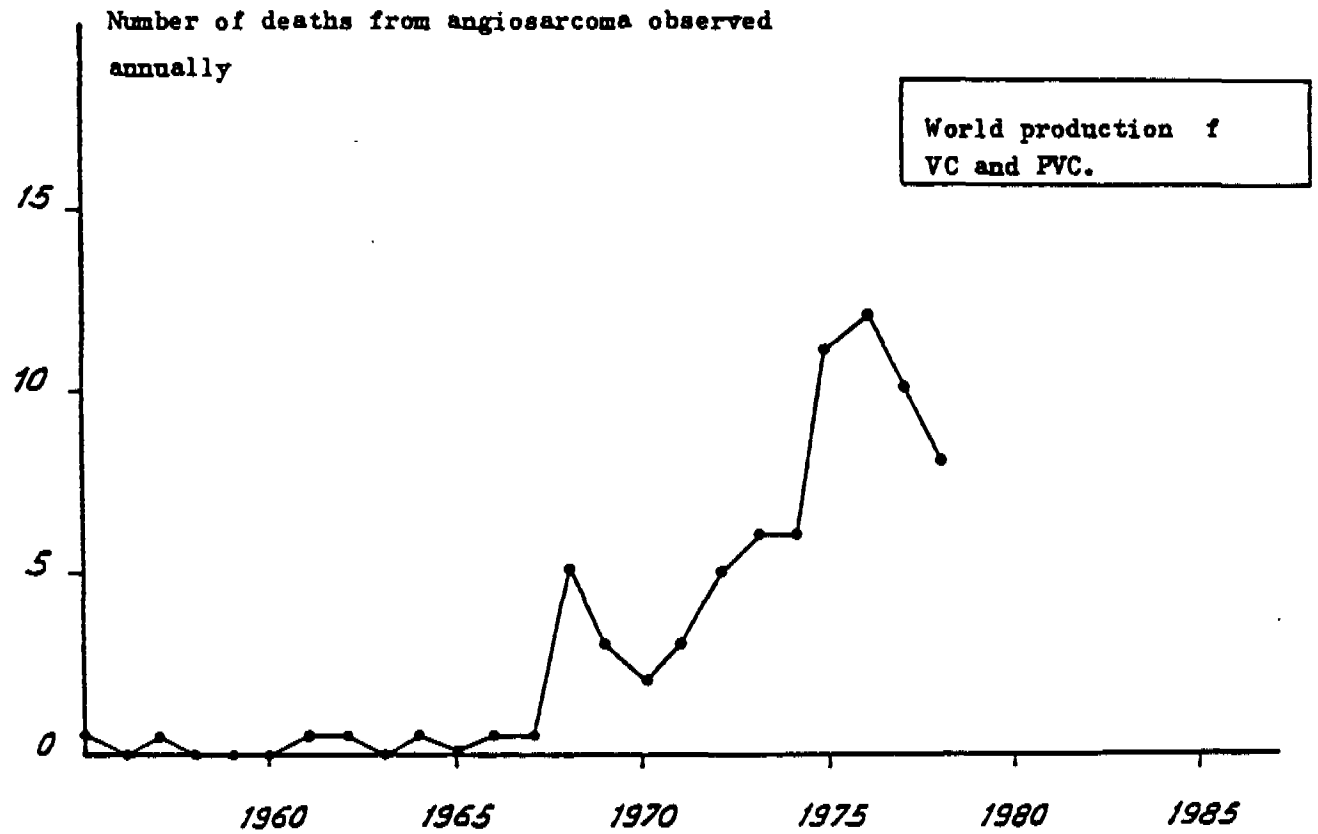
GREAT BRITAIN , VC/PVC



Number of persons employed at present and total number of persons who have left this industry each year since 1940.

625241

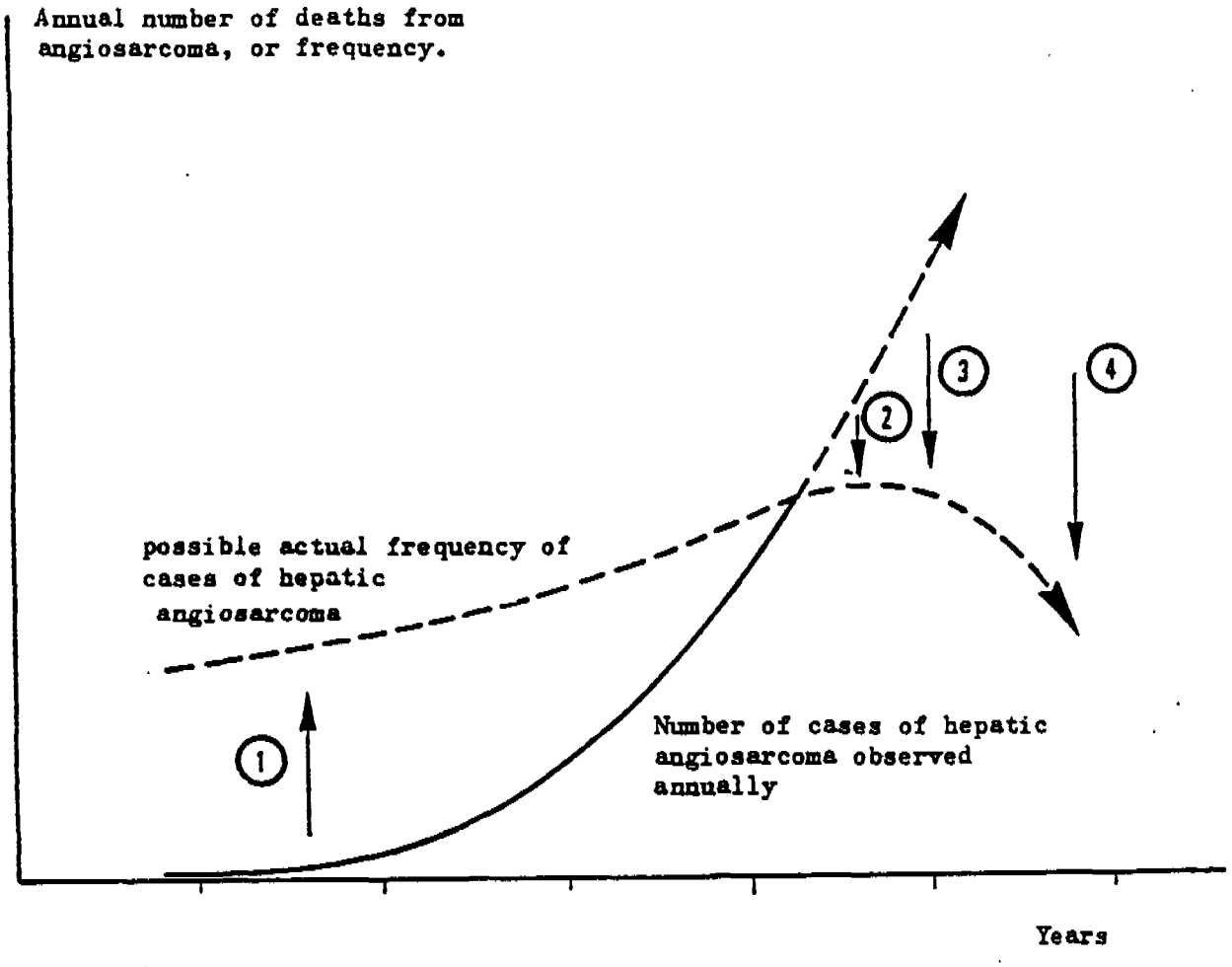
Fig. 4


Number of deaths from angiosarcoma observed annually
World production f VC and PVC.
15
10
5
0
1960
1965
1970
1975
1980
1985

625242

Fig. 5

World production of VC and PVC



(1) Detection incomplete

(2) Increase in number of people exposed

(3) Reduction in exposure-levels in the 60's

(4) Effect of the application of new safety standards.

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Prof. Truhaut

You have, M Bonnefoy, compared the data from animal experiments with the data obtainable from the epidemiology of exposed groups of humans. You said that the limiting factor was uncertainty. I should like to draw your attention and the attention of our audience to the fact that where we are concerned with long-term effects human epidemiology has a limiting factor which is the observation cycle. In the case of vinyl chloride, we have an example where animal experiments and epidemiological surveys are mixed. It was said this morning, in fact, that there had been three main stages in the detection of the risks associated with exposure to vinyl chloride.

At the beginning, we knew that it was a flammable, neuro-toxic substance, and consequently the toxicologists had fixed limits for industrial exposure. Then suddenly, in about 1963, there was the discovery by human epidemiology of the vaso-motor effects at the ends of the upper limbs with perforations in the fingers - the acro-osteolysis syndrome. It is because Prof. Viola wished to try to establish by animal experiments the mechanisms of the production of this acro-osteolysis syndrome that, to his surprise, he demonstrated carcinogenic effects with various localisations at fairly large doses. Then we went on t an experiment in depth, which is what Prof. Maltoni told us about this morning. All this is mixed, and it so happens that in this case the data on the carcinogenic effect from the animal experiments led the epidemiologists to have retrospective surveys made and demonstrate the production, in particular, of very special tumours, hepatic haemangiosarcomas(45). See how, in the field of cancer research- and I personally would not know how to separate the study of the carcinogenic hazards from the study of the toxicological hazards - there was necessarily a close liaison between the two disciplines of toxicology and cancer research as a result of experiments and epidemiological surveys.

625244

Prof. Latarjet called upon Dr Lazard of Rhône-Poulenc to address the meeting, stating that he was a works doctor, a rapporteur to the French Medical Committee on VCM and the French representative on the Commission Européenne des Fédérations des Industries Chimiques.

B. European studies (Paper 5 - Dr Lazard)

I shall be brief, particularly because after the volume of work on animal experiments we are going to pass on to the study of human epidemiology which is to be evaluated by Prof. Flamant who, as an epidemiologist, will also be able to criticise the data of the surveys now published.

After the first animal experiments by Prof. Viola showing that vinyl chloride was capable of inducing cancerous tumours, many research workers thought it necessary to carry out epidemiological surveys to determine in what proportions(46) vinyl chloride could be responsible for the increased pathological hazard, in particular cancer hazard, in the exposed workmen. Prof. Maltoni's papers, in their preliminary conclusions, specified the target-organs, and, more particularly, the statistically significant occurrence of hepatic angiosarcomas in the animals observed. These results led to a more precise investigation of the effect(47) of exposure to vinyl chloride on the number of hepatic angiosarcomas and, moreover, confirmed the necessity of statistical surveys of the populations exposed. These surveys, carried out in Western Europe, ran into numerous difficulties over ascertaining the duration of exposure, the years of exposure, the degree of exposure and each of them has been or may still be(48) the subject of lively(49) discussion.

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In the context of this meeting, we are proposing very simply to take stock of the epidemiological findings that a practising works doctor may come across[50], reporting for each of the European countries the essential published papers, paying particular attention to the conclusions of cancer mortality surveys. I must emphasise, in passing, the rôle of the medical committee of CEFIC responsible for the study of the pathology of vinyl chloride which, under the chairmanship of Dr de Boer, has centralised most of the European information and drawn general conclusions from it, and that of the Centre International de Recherche sur le Cancer in the field of centralisation of international research. In certain countries, in fact, for example Holland and Norway, the total population exposed to vinyl chloride hazards is too small for us to be reasonably able to draw statistically valid conclusions. The conclusions may differ greatly from survey to survey. The Swedish authors Byren et al published in 1976 a survey covering all the workers on a single polymerisation plant in the 40s. Of a total of 771 persons, 21 were lost for the investigations. The degrees of exposure, as is often the case, could not be accurately determined in the absence of systematic measurements of the VC content of the atmosphere such as we are familiar with in our plants today. The VC content of the atmosphere was at that time a rough estimate and not determined as it is now by gas-chromatographs which enable us to know the monthly, weekly, daily and yearly average exposure levels.

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In the group examined 4 or 5 times as many pancreatic tumours were noticed than in the general population, with two cases of hepatic angiosarcoma in 1967. The number of cerebral tumours and suicides did not differ from what was found in the general population. In contrast, cardio-vascular and cerebro-vascular complaints were significantly raised. The authors note that in the group concerned no exact investigation of the ways of life and the factors favouring chronic degenerative or cardio-vascular conditi ns had been made. In connection with[51] this work we must mention the work done by Elinder and Cederlof directed to the investigation of the

possible effect f VC on the environment. A survey of cancer mortality for the period 1961-1974 was carried out on the Swedish p pulation near a PVC pr duction plant compared with a population of the same size situated beyond risk of exposur . This work concluded with the finding of a 50% increase in standardised mortality ratio for cancers of the pancreas compared with the control population and the national population. No increase was found in other cancerous conditions and there had not, at that time, been any cases of hepatic angiosarcoma . No valid aetiological explanation can be given for this increase in pancreatic tumours.

In 1979, Holmberg et al., also in Sweden, noted[52] a survey relating to the employees of four PVC processing plants who had been exposed to the monomers for at least 3 months over the period 1945-1974. It was possible to follow up 1970 of the 2073 workmen, and this group was compared with the Swedish population in respect of the mortality for the various causes of illness and for cancerous conditions. Mortality as a result of coronary thrombosis was greater in the group considered and particularly in a sub-group of workmen exposed to the product for at least 2 years (11 cases, compared with 5 cases in the control population). We also note a tendency for an increase in illness and mortality caused by tumours of the digestive tract (although this finding is not statistically significant). This survey will have to be the subject of a follow-up by the authors in order to evaluate the changes in these percentages accurately for future years.

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In Great Britain, Duck and his co-workers published in 1975 a mortality survey on workers in a single polymerisation plant. In a population of 2,100 male workers exposed for a period of up to, in some cases, 27 years, the survey shows no excess in the specific causes of mortality, and the authors conclude that the survey does n t give any evidence for an increased frequency of deaths due to the most common cancerous conditions. But, in reviewing the evidence provided by this publication, we must note that Wagoner, Infante and Saracci at that time, in 1976, arrived at very different conclusions. They found an excess of deaths due to cancer, in

particular of the digestive tract and lung, which was closely related to the increased duration of exposure. Baxter and Fox, at the beginning of 1976, published a survey of PVC processing workers. This survey, which related to the mortality associated with every cause found between 1970 and 1972, suggested that cancers of the stomach and urogenital tract conditions were statistically responsible for a greater[53] number of deaths. The total number of deaths due to cancers of all sites observed is slightly higher than expected.

We had to wait until 1977 for a very important[54] British paper by Fox and Collier giving the results of a large[55] survey of over 7,000 workers, representing the whole of the personnel in Great Britain between 1940 and 1975 exposed for periods of some length. This survey is still, so far as we know, the largest in Europe in terms of the number of people concerned. It was possible to follow up about 99% of the workers, and the conclusions of this paper suggest a significant reduction in standard mortality ratio compared with the national percentage for deaths due to cancer in general.
The survey does not enable us to demonstrate a significant increase in the total number of cancers except for cancers of the liver and angiosarcomas. The authors insist, however, on the fact that the total impact of the effect of VCM will probably only be capable of a full evaluation if epidemiological surveys are carried out for several years.

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In October 1978, Frentzel-Beyme, Schutz and Thiess in the German Federal Republic published their observations on a mortality survey of 1,618 workers exposed to VCM and PVC in a BASF works at Ludwigshafen. The methodology and analysis of this survey were based on the usual international methods, enabling comparisons to be made. Since insufficient details of the degree of exposure were obtainable the mortality of the group studied was determined by reference to exposure-periods of 5, 10, 15 and over 15 years. Two groups were set up,

their first exposure after 1960 and up to the end of the survey. This ties up with what M Bonnefoy has just shown us, 1960 being the year of advances in manufacture and so corresponding to shorter exposure-periods, while the years preceding 1960 could correspond to much longer exposure-periods. Control groups were also studied, comprising firstly the town of Ludwigshafen (180,000 inhabitants), and secondly, the population of a complete region totalling 3½ million inhabitants. Finally, a third group of workers from the same works, 1,960 workers on a styrene plant. At the end of this survey, less cirrhosis of the liver and less myocardiac infarction than expected were found. No hepatic angiosarcomas were found in this works. The number of cases of death from natural causes (international definition ICD 0796) is also smaller. The number of deaths from unnatural causes (ICD 800 999) is very close t expectations. Three conditions with a greater frequency were noted - pulmonary tuberculosis, malignant tumours of the colon and stomach and prostatic hypertrophy. The duration of exposure does not seem to have had a significant effect in increasing the percentage mortality after long periods of exposure. The authors, moreover, remark that the observations made in other surveys of a significant increase in cancerous tumours of the brain, lung and liver were not confirmed in their survey. They put forward the hypothesis that these differences are, perhaps, due to a dose/response effect, seeing that the level of exposure to VCM in their works has always been relatively low compared with works where similar surveys have been carried out.

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Reinl and his co-workers finished, in 1977, a survey of all the works in Nordrhein-Westfalen, which was published the same year and presented, in particular, at the 19th International Congress, Dubrovnik, in September 1978. This survey comprised 3 groups - a group of exposed workers, a control group, and a group of workers from the processing industries. The duration of exposure and the age-classes were taken into consideration. The results of this survey show conclusions rather different from the other surveys, in particular the British surveys of Fox and

Collier. In March 1979, however, Drs Reinl and Gresser, the authors of this publication, in the course of a meeting with Dr De Boer of CEFIC and Drs Adams and Paddle, modified the published Tables, and these changes will need to be the subject of a fresh publication. After these corrections, the conclusions of the survey appear as follows : firstly, the standard mortality ratio for all tumours is not significantly increased in Group I of the exposed subjects; secondly, there is no longer a significant increase in the number of cancers compared with the male population of Germany; thirdly, the standard mortality ratio for the tumours of the lymphopoietic system is increased in a fairly significant manner; and finally, the standard mortality ratio for the tumours of the digestive tract is higher overall and more particularly for the gastric tumours. For the hepatic tumours including angiosarcomas, it seems very definitely increased. A definite increase in cardio-vascular attacks[56] is noted, but this increase is found almost identically in the three groups compared. For the control groups, moreover[57], a significant increase in standardised mortality ratio due to malignant tumours of the liver and cardio-vascular conditions is noted. The standardised mortality ratio for all the tumours of an organ was not increased; nor was any significant incr ase in the number of tumours of the brain and respiratory system found in the production workers group.

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It was also at the 19th International Congress of Industrial Hygiene that Bertazzi, Villa and Foa and their co-workers presented an Italian epidemiological survey published earlier and covering 4,777 workers in 9 production works in various regions of Italy. This group represented ca. 86% of the personnel exposed to vinyl chloride. The population studied comprised workers employed at the time of the survey (1975-1977), workers who had been exposed in the past and transferred to other sectors and workers who had been previously exposed and had retired, having given up all activity in the industry. Three exposure levels were defined - low, medium and high. One part of the survey related to th results of clinical

and biological examinations for 4,713 workers. As to th mortality survey, the reference period considered is given by the date of start-up of production in the various works.

In the absence of adequate official registers in Italy the data can only be indicative. In the dead workers (64, rather over 1.3% of the total) the malignant tumours appeared to be responsible for death in 48.3% of the cases, 30% being tumours of the liver and bile ducts, 3 of which were angiosarcomas. This percentage, 48%, is about twice the expected percentage.

On the occasion of a meeting of the Medical Committee of CEFIC in Milan (29 May 1979) Dr Foa was kind enough to give us some comments on this survey. With particular reference to the study of clinical and biological mortality he indicated that the data obtained must be handled with care in view of the absence of a suitable control group and possible differences in the methods of examination and diagnosis. In the mortality survey more particularly in relation to cancerous tumours, an increase in standardised mortality ratio appears in certain works although the differences are generally relatively slight.

In France, nothing has so far been published, but it is a gap that is going to be filled. The works doctors in French VC/PVC production works have formed themselves into a study-group and are not letting this question slide but are patiently collecting, sometimes with great difficulty, the documents which will enable them to make a survey of the deaths occurring among vinyl chloride workers so as to make an assessment of incidence. They published, at the Dubrovnik Congress, in September 1978, the whole of the clinical information on the 10 French cases of angiosarcoma then known; they have contributed to the study material of which Prof Flamant and Mme Tirmarche are about to tell us; the mortality survey carried out by my friend Dr Pierre and Dr Tassignon at the Tavaux works is a good illustration of this effort.

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C. Solvay study at Tavaux (Paper 6 - Dr. Pierre)

At the Tavaux works in the Jura where the Solvay gr up have polymerised vinyl chloride since 1953, an epidemiological mortality survey was carried out on 1,482 workers exposed to monomers during their employment in the works between start-up in 1953(58) and 31 December 1976. The collection of data was carried out at the works by Personnel and Production Departments and the Medical Department. The object of our survey was to establish the effect which exposure to vinyl chloride in the course of employment could have on the health of the personnel exposed for 24 years of VC and PVC production in this works. The number of deaths appearing in the course of the period considered is compared with what would be expected in a control population having the same sex, the same age-group distribution and living in the same historical epoch and whose mortality-rate is judged to be normal. The most accurate(59) approach was to choose for each subject exposed to VC a control of the same sex, age, job, smoking and eating habits and socio-professional class and living near the first. To speed up the survey and produce it before the end of 1976, however, we made use, as in analogous surveys, of the mortality-rate of the French population published in the WHO world health statistics yearbook. The survey covered all male workers - manual workers, foremen, office-workers, salaried staff - who were exposed to the monomers in the course of their duties in the VC synthesis and polymerisation plant and in the compounding plant up to packaging and storing. The laboratory and polymerisation pilot plant(60) were also included. The maintenance teams and the personnel involved in the production of vinyl chloride/ vinylidene chloride copolymers(61) were also added. The works Personnel Department has records permitting an accurate statement of the persons exposed to be made.

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1,482 persons were recorded in this way. An individual record was set up comprising the name, forename, date of birth, where relevant the date of death, the dat and period f employment in the various departmentsof Plastics Division, the posts held, and, where relevant, the diagnosis of the cause of death. 6

observed in these cases. 5 women, including one death, were excluded from the statistical calculations because there were too few of them. Finally, 160 persons had to be rejected because it was impossible to discover whether they were alive or dead at the end of the survey (we shall return to these later). The deductions therefore leave 1,311 records which were used. The exposure was characterised by its intensity. In the absence of exact data for the individual VC exposure levels in the past these exposure-levels were estimated from the jobs held while working in a polluted environment. A detailed career history to within a month or so[62] was obtainable from the works Personnel Department.

A study of the development of job-definitions resulted in the isolation of six typical jobs, from the most to the least exposed:

1 Autoclave cleaner and emptier and latex/slurry filtration charge-hand[63]

2 As above, on more modern plant

3 Autoclave maintenance worker

4 Foremen and workers other than as specified above, working in the polymerisation halls

5 All foremen and workers working in the halls for the synthesis and liquefaction of VC from acetylene or in the charging and discharging of vinyl chloride tankers and autoclave workers in the IXANS (copolymers) section.

6 Finally, all other jobs not specified above.

In production, the task of reconstituting the exposure-levels that had existed in the past from 1953-1976 was undertaken, the technical development of the various shops was retraced with the dates marking changes in working procedures or

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technology (air-blasts[64] in the autoclaves, aut matic hydraulic washing, suction[65] on the autoclaves etc), thus defining 5 different periods. By taking account of these elements and of measurements carried out sporadically we were able to establish grids giving, by department and job, the probable changes in the mean VC content with course of time. The mean contents were subdivided into 3 degrees of intensity, grade 1 corresponding to a "slight" exposure, grade 2 to a "medium" exposure and group 3 to "severe" exposure. For a given job, the degree of risk has changed in the course of time (in the 5 periods defined) as a result of the improvements resulting from the technical precautions.

Exposure-index

The exposure of every worker was characterised by an index as defined in the paper by Tabershaw et al., 1974. This index has the dimensions of a time-weighted average which is not expressed in concentration-units but in degrees of intensity on a scale ranging from 1 (the lowest) to 3 (the highest level). This index- later called the exposure-index - is calculated by multiplying the number of months spent in a given job by the degree of intensity attributed to this job at a given time, summing these products and dividing the total by the number of months of exposure to VC in the course of the subject's career.

Duration of exposure

The exposure of each worker was characterised also by its total duration, defined as the sum of the partial durations of work in contaminated environments in the Division. The time in the individual's career which would be spent off production was systematically discounted.

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The drawing up of the alive/dead rec rd required a substantial effort in tracing those who had been discharged or had resigned, who had in som cases left th country. It was, nevertheless, carried out with remarkable efficiency by the works Medical and Personnel Departments. About 8% of the individuals were contacted by post, by means of a questionnaire. The vital status of 160 men who had been discharged or had resigned (10.8 % of the 1,482 individuals) could not be established.

These "non-respondents" are apportioned as follows:

Exposure-index	Duration of exposure $\leqslant 5$ years	$5 < i \leqslant 15$ years	>15 years[66]
< 2	119	21	2
$\geqslant 2$	10	8	0

Analysis showed that they had been, on average, exposed for a shorter period (3.1 years as against 9.5 years for the personnel studied). This group was excluded from the calculations, as in the epidemiological surveys already published. This "non-respondents" problem always turns up in this way in an epidemiological survey. Do they constitute a random sample indistinguishable from the personnel as a whole - and thus capable of inclusion therein - or is this group characterised by an abnormally high mortality from the fact that sensitive individuals would be spontaneously removed from the hazard - possibly in vain? In this case, there might be a segregation of the deaths in the group of those who had been discharged or had resigned who could not be found. This question remains unanswered in any epidemiological survey.

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List of data

The following information was known for each of the individuals involved in the survey : name, forename, vital status on 31 December 1976, date of birth, date of death (where relevant), date of first exposure, date of final exposure known on 31 December 1976, duration of observation (in years and months), duration of exposure (in years and months) and the index representing the mean exposure-level in the course of the career of the person concerned.

TREATMENT OF THE DATA

Man-years of observation and standardisation by age, sex and year

The presentation of the national mortality statistics necessitated transformation of the crude data collected at Tavaux. These statistics indicate the number of deaths occurring each year in the French male (or female) population taken as a whole or split into 10-year age-groups.

Each man-year contributed by a given individual is independent of the other man-years he contributed to the survey, and is thus considered as the experience of a year of life by a man (the same one, of course) whose exposure to the toxic material outside the year considered is simply ignored. This hypothesis, on which for a given individual the years of exposure constitute a cumulative risk to health is the null-hypothesis which the epidemiological survey is supposed[67] to reject or accept.

Up to 31 December 1976, each worker at Tavaux subjected to the survey contributed each year to the epidemiological survey by adding one year of life or one man-year.

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Each year, these man-years were distributed into age-groups so that we could compare the mortality in the population under observation and in the control population for equivalent age-groups. The age-group distribution is, in fact, very different in a working p pulation from that which exists in the national population. S as n t to reduce the numbers too much, we considered 10-year

Exposure-man-years

The total man-years of actual exposure to vinyl chloride is less than the total man-years of observation. On 31 December 1976 a man could very well have been "observed" to be alive, having ceased to be exposed to vinyl chloride for several years (discharge, resignation, transfer from the VC/PVC sector). During this period, while contributing to the man-years of observation he would n t any longer have contributed to the man-years of exposure.

Observed deaths, expected deaths and standardised mortality ratio

Every year, the deaths in the national population were totalled and compared with the man-years of life contributed by the various age-groups of the population. These mortality ratios standardised by age and sex are considered as standards in this study. The man-years of observation contributed by the Tavaux group were distributed in Tables of which the columns represented the 10-year age-groups. If, for example, a worker entered the survey in 1968 at the age of 32 and is still alive on 31 December 1976 he will have contributed about 8 man-years to the survey, of which 3 will have been spent in the age-group 25-34 years and the column 1935-1944 for the years of birth and the rest in the age-group just above this column[68]. The general and specific mortality-tables we took as our standard were set up in the same way on the basis of the national statistics. The figures are specific to sex, age-groups, and the historical epoch defined by the conjunction of the birth-year groups and the age-groups[69]. The statistics for 1956, 1961, 1968 and 1974 were selected. Multiplication, case by case, of these two types of Table gave the expected number of deaths, that is, the number there would be in the group of workers studied if the risk-factors threatening them were no different from those affecting the general population. The ratio of this value to the expected deaths, multiplied by 100,[70] constitutes the standardised mortality ratio.

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Sub-groups

For better interpretation of the results as a function of risk due to empl yment, the group was sub-divided into sub-groups.

- firstly, by considering groups of individuals of exposure-index less than or greater than (or equal to) 2
- secondly, by considering groups of individuals contributing durations of exposure less than or greater than 5 years, or less than or greater than 15 years.

Statistical analysis

The comparison between the observed and expected values was made by assuming a Poisson distribution whose mean is equal to the expected number of deaths. (Geigy scientific tables).

Results

Characteristics of exposure to vinyl chloride at Tavaux

The results of the survey covered 1,311 men, totalling 15,458 man-years of observation and 12,470 man-years of exposure to VC, at various degrees of intensity (81% of the man-years of observation). The most-exposed jobs (1-3) contributed 11% of the man-hours of exposure, and the least exposed jobs (4-6) contributed 89%. Job no. 6 above, which only ever involves minimal exposure to VC, contributes 69% of the man-hours of exposure. The mean duration of exposure was 9.5 years, and we calculated for each standard job the distribution of these years of exposure for a hypothetical average worker. It emerged once again that the group examined at Tavaux works was, as a whole, in essence made up of individuals holding low-or medium-risk jobs.

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According to the intensity of exposure we find that only 7% of the exposure man-years are spent in highly contaminated environments (degree of intensity 3) against 18% in a moderately polluted environment and 75% at a low exposure-level (degree of intensity 1). Degree 3 apparently corresponds to a time-weighted average

concentration of 200-500 ppm in the air; d gree 2 to concentrations of 50-200 ppm; degre 1 to conc ntrations of less than 50 ppm and, more often, less than 10 ppm. These figures are proposed as the order of magnitude of the mean concentrations representative of the 3 arbitrary degrees of intensity which had been selected for estimating the exposure-intensity.

As the health hazard depends both on the duration of exposure and its mean intensity, we distributed the group in accordance with these two parameters. We found again that the low exposure-indices were preponderant (81% of the personnel had an exposure-index of less than 1.5).

During the analysis of the observed mortality it will therefore be absolutely necessary for the mortality of distinct sub-groups to be specifically isolated so that the mortality specific to highly-exposed individuals can be assessed in isolation.

Causes of death and analysis of mortality

25 deaths were observed, including 8 cancers, one of which was a hepatic angiosarcoma. The Table sets out the causes of death classified by the corresponding number of the International Disease Classification (Classification Internationale des Maladies, CIM), revised in 1965.

Of the specific causes, 2 diagnoses were not analysed : septicaemia and acute food-poisoning. The reason is that the corresponding heading of the CIM, numbered B 18 in the 1965 edition, was defined differently before 1965, so that statistics comparable at different (71) periods cannot be reconstituted. It is most improbable that the diseases of heading B 18, "all other infections and parasitic diseases" have any point in common with VC.

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The standardised mortality ratio for the complete personn l is only 51 (25 deaths observed, as against 49 expected), which is very significantly less than

cases observed as against 9 expect d, but one of the cases is a hepatic angiosarcoma. The number of suicides is slightly greater in the personnel as a whole, but the difference is not significant. Necrotic[72] enteritis is such a rare cause of death that the case which occurred at Tavaux definitely deviates from the normal; it is unconnected with VC.

If we take into account the sub-groups sub-divided in accordance with exposure-index and duration of exposure we see that the hepatic angiosarcoma occurred in the group most highly exposed (index ≥ 2) for the longest time (> 15 years). There is a slight excess of suicides in the group given a slight exposure for less than 5 years, but the difference is not significant at the 0.05 level.

Firstly, the personnel are relatively young with a mean age of 34. There are only 25 deaths for over 100 persons. In the survey by Biren et al, 1976 which my friend Lazard quoted, there were 58 deaths in an exposed group of 771 persons Ott et al., in 1975, found 88 deaths among 594 persons exposed to PVC[73]. The age-structure of these populations was older and gave a greater number of deaths.

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Secondly, there is a low overall mortality. The standardised mortality ratio of 51 for the Tavaux group is a familiar observation in industrial epidemiology. Several factors are combined in this result. Industrial work is selective, requiring more robust health and rejecting the handicapped and sick from the start; work in a potentially toxic environment, moreover, presupposes medical selection for the job. The mortality-deficit thus artificially created was called the "healthy worker effect" in 1976. It should be noted that the death due to hepatic angiosarcoma occurred in a 42 year old factory-worker employed directly in the autoclaves since 1957. As to the other cases of death, in one of the two cases of cerebral cancer observed the exposure to vinyl chloride was characterised by an index of 1, the lowest possible, and in the other case, in contrast, the exposure had been heavy. The two cases of Hodgkin's disease proved

in the Tavaux group, there is n thing to confirm the much discussed[74] idea that the VC would cause an excess of cancers other than hepatic angiosarcoma. This conclusion must be tempered by the fact that the population studied was relatively young. It is now evident, thanks to world-wide epidemiological surveys as well as those carried out in our group, that hepatic angiosarcoma is not a uniform threat to the whole personnel working on monomer synthesis or polymerisation. The risk is greater for personnel exposed for a long time to high doses in the past.

D. Discussion of papers

Prof. Truhaut

My question is an extension of[75] the question I asked M Bonnefoy. I should like to know what you mean by "mean exposure index"?

Dr Pierre

The mean exposure index was arbitrarilyfixed between 20 and 200 ppm, given that we did not analyse the atmosphere at that date.

Prof. Truhaut

Is it a time-integrated average?

Dr Pierre

It is a time-integrated average.

Prof. Truhaut

Are the deviations from the mean likely to be very large, or not?

Dr Pierre

Unfortunately we were completely unable to study the deviations at this period.

Prof. Truhaut

This morning we heard Prof. Maltoni lay down(76) the exposure-levels for us in a very precise manner. It is evidently very important to try to determine(77) the dose/effect relations in a quantitative context, and this is the principal object of the epidemiological surveys.

Dr Pierre

In historical surveys that was not possible, and the exposure-indices would only be established by a study of the jobs held at different periods.

Dr Chalvay

I have no experience with vinyl chloride, but I can give you a personal experience with tar. You take people in the same job, they have the same dirt on their feet, hands and face. Some of them clean their hands with moist earth, like peasants do, and others, more knowledgeable, wash their hands in petrol, which is the painting technique used for the experimental stimulation of skin cancers. The results are falsified. Vinyl chloride is a liquid when stored, but boils at -13°C. It is extremely volatile, and we can estimate that the people who go to the cloakroom are completely free of it.

Someone just spoke of cleaning the autoclaves. Are they ventilated, and how? And where do you send what comes out?

Dr Pierre

The autoclaves, before opening, are subjected to reduced pressure to purge them as completely as possible of residual traces of vinyl chloride. Moreover, now we know of the toxicity of vinyl chloride, the people, as a supplementary precaution, enter for much shorter periods since cleaning has been automated, and they no longer enter without a self-contained mask.

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Question (?)

M. Pierre, you skated over the problem of smoking habits. Given the dose of carcinogen absorbed annually by every smoker inhaling a packet a day, I ask you : Do you, in your statistics, make a distinction between smokers and non-smokers?

Dr Pierre

We did not do so in our first statistical work, but it is really necessary now, given the precautions taken for doses which are small in comparison with the enormous doses derived from cigarette smoke. I think drinking habits and the various stresses of industrial work would have to be taken into account.

Dr Lazard

As for France, all the cases of hepatic angiosarcoma have been collected as they are found at the Comité Français. A report is then made through M. J.-C. Thomas to APME and at European level on the details relevant to duration of exposure, age, and the nature, causes and circumstances of the diagnosis. The APME is the Association des Producteurs de Matières Plastiques, which is affiliated to the Fédération des Industries Chimiques Européennes, which we have mentioned before. Dr Stafford, who is here, keeps a very accurate record of all cases of angiosarcoma in the world. He is in contact with correspondents in all parts of the world.

E. Protocol for French National Study (Paper 7 - Prof.Flamant and Mme Tirmarche)

Prof. Flamant

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As an epidemiologist of long standing, I am delighted to hear it said that epidemiology is going to have to provide the solution to a whole series of problems, but at the same time, I am afraid there are numerous difficulties. The participation of Mme. Tirmarche and myself in this field of research is fairly recent - it goes back just over a year. I must tell you that our present contribution is extremely modest, being limited to the results of an historical surv y, but it was built on our (78) plans and hopes for the future

I sh uld like first to recall a few principles of epidemiological surveys.

Whatever the survey technique the result may always be summarised as in the following Table.

	Exposed	Unexposed	
Ill	a	b	a + b
Not ill	c	d	c + d
	a + c	b + d	N = a + b + c + d

It is composed of four cases with four groups of individuals:

1 People who have been exposed to the hazard (here, vinyl chloride)

2 Unexposed people

3 People we call "ill"

4 People we call "not ill", who do not have the disease studied.

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It is tables of this type that statistical analysis eventually has to deal with, whatever the method used to collect the information. Every effort will be made, with these data(79), to measure the exposure to the hazard with all the difficulties already mentioned and common to all surveys (when we make smoking surveys it is difficult to know how much people smoke, but still more difficult to know how much they drink). A certain imprecision is tolerable if there is no relation between this approximation and the pathological condition we are going to measure. If we measure the exposure to the hazard by the fact that the people are or are not ill, or if we say that they are ill because they have been exp sed, we are going to have the result before we have even commented on the survey. That is when this great idea of bias comes in; bias is nothing more than a systematic error which ass ciates a priori the exposure with the hazard and the pathological condition we are measuring, which obviously falsifies the results.

There are several ways of classifying surveys.

The first way concerns the chronological aspect. The survey is retrospective if it is set up at a time when the pathological condition has come to light (this is the case with people who have a pathological condition of the liver which we compare with controls); it is prospective if it is set up before the disease is found (we then take people of whom we do not know whether they are ill or not, measure this exposure to the hazard, and, eventually, they will separate of their own accord into ill and not ill).

The other way of characterising surveys takes into account the methods of setting up the groups we are going to study.

- Firstly, there is the representative sample of a population. For example, in surveys of smoking, the whole body of English doctors was taken, accepting that if a relation between smoking and cancer is found in doctors this relation holds for the rest of the population. In an American survey, a million people were taken, the smokers and non-smokers being distinguished, and they were followed up for several years to see if they were ill or not. In the particular case of a survey on vinyl chloride the trouble is that there will probably be very few people exposed to the hazard.
- There is another way of tackling the problem, which is to take exposed and unexposed people, providing we can define "exposed" and "unexposed", and either consider them retrospectively or pick up the pathological condition prospectively.
- The final, well-known type is the type of the control-case survey where we take people who have, for example, a pathological condition of the liver, whether they are hospitalised or not, and look for controls, with all the difficulties which that involves.

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Mme. Tirmarche is going to t ll us in a moment about investigations of documents of the historical type. These are not surveys, properly speaking. The subjects being already dead, we cannot anyhow try to reconstitute their history. But we never know why any given person drops out of sight. It is very difficult to investigate past events, and, in addition, information noted in a file can never have been completely independent of the event we are studying. There may be an association between the exposure to the hazard and the pathological condition. These are therefore tasks which are booby-trapped at the start and may give indications but must be examined with great care. We are therefore going to begin there and Mme. Tirmarche is going to give us some indications of the analysis of the files that she has been able to make.

Mme. Tirmarche

We are faced with the causes of death collected by the works doctors at different works. These dead people had all, in the past, been exposed to vinyl chloride(80). We had their duration and degree of exposure, but it was impossible to weight the exposure as a function of the number of years. In fact, it often happens that a person has had a job with a high exposure-level for a very short time and is therefore coded 3 + (maximum exposure) while for the rest of the time he has been subject to much lower exposure.

I attempted to make two separate studies, taking either degree of exposure or duration of exposure into account. We were then faced with two groups of people; those who died of cancer and those who died of other causes. I have classified the two groups by age-group, and I have picked at random from within the groups of people dying from causes other than cancer one person of the same age-group (± 5 years) as the person having a cancer of known localisation.

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STUDY OF THE CONNECTION BETWEEN DEATH FROM CANCER AND EXPOSURE TO VCM/PVC

Each subject dying of cancer is matched according to age with a subject dying of another cause.

- Liver cancers	Significant difference $p < 0.05$
- Hepatic angiosarcomas	Significant difference $p < 0.05$
- Lung cancers	Significant difference $p < 0.05$
- Cancers of the digestive tract (stomach, intestine, rectum)	Difference not significant
- Cancer of the upper respiratory/digestive tract (larynx, oesophagus)	Difference not significant

(Wilcoxon test on matched series)

Of the 6 cancers of the liver, I was able to observe a significant difference in the duration of exposure; the liver cancer cases had been exposed for significantly longer than the group serving as their control. The same results were obtained for the hepatic angiosarcomas (11 at that time) and, a rather surprising thing, we also observed a significant difference for the lung cancers. In contrast, for the cancers of the digestive tract, including the stomach, intestine and rectum, I was unable to show any significant difference from the controls, and the same was true for the cancers of the larynx and oesophagus combined. Cancers located elsewhere were not studied because the cases were too few. These results it is true, have only an indicative value which must be open to dispute[81] because we know nothing of the other aetiological factors for these cancers. We do not know whether the distribution of smokers was the same between the controls and the cancer cases, what was the quantity smoked, or the alcohol consumption. Moreover, since all these people were from an industrial environment they had certainly been exposed to other products which may also have a carcinogenic action of which we are unaware. I should like to say that we have here a type of "ultimate" retrosp ctive survey, given that we are trying to recover simultaneously

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the durati n and degree of exposur . As for the degree of exposure, I observed no significant difference between the cancer-cases and the controls, whatever the localisation.

I repeat that this study can have only an indicative value and give us lines of research for a later survey. The biases of a retrospective survey may be very large. Faced with a person dying from hepatic angiosarcoma we are forcibly led to a thorough investigation of the duration and degree of exposure of this person. Are things the same for the person killed in a road accident or dying from some other cause? I think this type of study never gives an exact answer to the questions we may ask, and it would now be advisable to launch a prospective survey, which M. Flamant is going to talk to you about.

Prof. Flamant

Our plan is to conduct a survey, the draft of which, now being edited, will have to be the subject of discussions at the end of this month, the intention being to start the survey at the beginning of 1980. This survey will, in principle, be carried out in 10 or so works currently handling vinyl chloride as the monomer or polymer, in very close collaboration with all the works doctors of these works. The first major problem discussed was the choice of the population on which to carry out the survey. We had to find a population which was or had been exposed relatively severely (whereas now the exposure is reduced to very low levels) so as not to have to wait many years for the results. We had to try to profit from this unfortunate circumstance which led to people having suffered relatively severe exposure and so take a rather older age-group which had the advantage of being close to the age-groups for which the incidence of cancer is greatest. For the moment, we have chosen to work on a population of men aged 40-55, not too near retirement, to avoid the difficulties of tracing people who have left the works or left the area. Of the three survey methods we are moving towards(82) a study of the "exposed/unexposed" type. What we should

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interrogated and examined und r the same conditions by the same doctor. It would als be necessary for these people to be empl yed in the same works as the people exposed. We think these controls would be better than people taken at random from the general population. There is a whole series of important factors, apart from thos e studied, which a priori differentiate a factory population, often very localised in a given region, from the general population as a whole.

There will be the problem of exposure to chemicals other than vinyl chloride which it would be better to try and avoid insofar as we want to find an unexposed control population, but we must not deceive ourselves too much; I believe the simplest thing will be to note this exposure carefully if it exists, and takeit into account in the statistical analysis.

Here, in outline, is the problem of the choice of the population to be studied. As to the collection of the pathological data, there will, of course, be the possible deaths and their causes, but the survey would need to apply itself to specifying a certain number of morbidity data with the co-operation and active assistance(83) of the works doctors. The examinations will be made, as is already the case, by the works doctors, with precisely the same(84) attitude whether they are dealing with exposed or unexposed people. A questionnaire will be filled in at each examination with

- 1 general information of the type: age, civil status, place of residence.
- 2 a measure of the exposure to the hazards, that is, the different stages of the industrial career, making every effort to take the chronology, the duration and intensity of this type of exposure into account in the hope that it will be possible with, all the same(85), maximum precision for past exposure, to arrive at a valid codification(86) of this exposure to vinyl chloride;

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- 3 a standard questionnaire on the consumption of tobacco and alcohol; there, again, we shall have to wait and see how things turn out, it is not always easy;
- 4 The various pathological events which may occur with each of these individuals.

All in all, we shall need to continue, in spite of the difficulties this may cause, to follow up the people even if they leave the works for any reason. Only a trial period will be able to tell us whether we can eventually meet these objectives or not.

To conclude, I feel that we can only accept the results of the work on this subject which has already been done as being of indicative type (87). Apart from the special case of angiosarcomas nothing is yet settled one way or the other. If we now wish to make a substantial contribution which marks a decisive step we shall inevitably have to proceed by way of this type of survey which is very difficult to conduct, which is probably why there have not been many of this type done (88).

F. Discussion of preceding paper

I think we can say that the great difficulty of epidemiological surveys is to group all the factors which may be involved, if only for the question of exposure. You are, perhaps, going to have information on the possible content of the air breathed, but I believe that that will not be enough, and this morning, our attention was sharply drawn to the difference between dose and concentration. We had arrived at the dose/effect concept and it would have been interesting to calculate from the inhalation what was the weekly dose which had no effect. By taking the air consumed by the animals into account we might, perhaps, have calculated that. In the case of man, we know that he consumes about 15-20 m^3 of air per hour, but when at work on an intensive job he greatly exceeds this quantity, so we have to allow for a much larger consumption.

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Prof. Latarjet

When I presented proposals to the Conseil Supérieur d'Hygiène to limit the d se of ethylene I distinguished a bracket ranging from the individual working in an office to one doing a physical job whose pulmonary ventilation is increased. That is why the doses proposed allowed a factor[89] of 2½ so as to give reasonable coverage of the conditions obtaining. This is a factor to take into consideration.

5. CONCLUDING DISCUSSION

I think it is the Chairman's job to open this discussion; if you will allow me, I wish to begin the questions by recalling a phrase Prof. Maltoni used this morning which I consider very important. He said that in these problems of chemical carcinogenesis the qualitative aspect becomes less and less important and that it is the quantitative aspect we must consider. It[90] is certain that the qualitative aspect retains some importance, for example when we produce new substances and have to know if they are or are not carcinogenic. You are aware of the proliferation of methods based on simple microbiological tests designed to give rapid presumptive evidence of any carcinogenic capacity, but it is very evident that what matters is not to know in this way whether a contaminant is carcinogenic but to know the quantity already present and, ab ve all, what are the additional quantities allowable when it is an indispensable contaminant, that is, a contaminant whose benefits seem to outweigh the hazards. One of the reasons why this quantitative aspect is becoming more and more important is the increasing accuracy of the methods for detecting carcinogens. These methods are becoming so sensitive that practically everything becomes carcinogenic. We now know how to detect benzpyrene in a puff of cigarette smoke. I do not think that if the whole population were forced to take a single puff at a cigarette in the course of their lives we should have lung cancer. Equally, we find benzpyrene in bread; we are not going to ban bread. This stress on the importance of the quantitative was repeated this evening by M. Bonnefoy, who insisted on the

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importance and even the necessity of comparing a given hazard with other hazards. Quantitative comparison becomes indispensable so as both to obtain the maximum protection for a given effort and to be in a position to study the total hazards resulting from joint exposure to several geno-toxic substances, that is, mixed exposure. In this connection I should like to contribute very rapidly to the discussion a finding which results from a different approach and again raises problems of extrapolation.

You will know that in certain laboratories, including ours (Dr Averbeck), attempts are being made to determine on the basis of the lesions produced equivalences between a dose of ionising radiation expressed in rads and a dose of a geno-toxic chemical. Substantial studies of VCM have been made. It is evident that the equivalence found is based on various tests which are always genetic tests, in particular the induction of mutations in bacteria, yeasts and human cells in vitro. The equivalence found depends greatly on the system considered, but by comparing the values found for these various systems we arrive at an average value, a sort of centre of gravity. (Please refer to Averbeck's report in the Appendix[91].

If we adopt this equivalence as an approximation[92] we come to the conclusion that a worker exposed for 8 hours a day, 40 hours a week and 40 weeks a year to an atmosphere limited to 5 ppm (which is a currently accepted rule), or 5 ppm for 1,600 h, receives the equivalent of 40 rads.

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I remind you that the law allows 30 rads per annum for workers exposed part-time[93] and 5 rads when continuously[94] exposed. You see that the permitted annual dose of 40 rad-equivalents for VCM is close to what is currently allowed for radiation. We may say, then, that the limit of 5 ppm which the workers are permitted appears reasonable in practice and scarcely open to criticism. If we went down to 1 ppm, or 8 rad-equivalents per annum, we should be able to consider

recall that the doses allowed for radiation have been the subject of detailed discussion for 25 years and that they currently correspond to a philosophy we can call conservative, meaning that when ver we are in doubt we err n the safe side. The limits currently allowed for radiation are very safe; to take equivalent doses for a chemical is a philosophy of safety. I have one reservation, however, which is that all these philosophies have been accepted with the idea of exposur to radiation only. But it is quite evident that when we are dealing with mixed exposures we must consider the additive or potentiating effects, and sometimes antagonisms, for they do exist, but that is another problem.

Messieurs, the discussion is open.

Prof. Latarjet

Ah well, if nobody is going to attack, I am going to continue on another topic.

I was very interested in the curves M. Tassignon presented this morning, particularly one showing a definite threshold, which is very important, then, at very large doses, a drop. This drop is a phenomenon which geneticists are familiar with and which caused much surprise at first. A bell-shaped curve was found for the first time in 1945 in plotting curves for the induction of mutations in Neurospora by UV. I remember, also, obtaining a bell-shaped curve for the first virus mutation with UV, carried out in 1949. Since then these curves have become well known. Two phenomena may be involved. The mutant may be more sensitive to the agent than the original type and therefore be eliminated as soon as it is formed.

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Moreover, there may be inducible enzyme phenomena, with either the chemical inducing metabolic enzymes which transform it into an active form or the lesion produced in the nucleic acid inducing the synthesis of repair enzymes which make mistakes at the origin (95) of the mutation. The bell-shaped curves found with vinyl chloride undoubtedly indicate that this compound is involved in an inducible

It seems today that we are moving towards legislation which seems to give guarantees of harmlessness, perhaps not total, but satisfactory in relation to the benefits expected from this industry. We must not look for zero risks, we must look for safety. Safety is never anything else but an accepted risk. I have seen curves stabilise, if not fall, from 1976. Do you think these reductions, which now are resulting in concentrations of the order of a few ppm, should be considered as satisfactory, or, on the contrary, no longer (96) convincing?

Prof. Truhaut

The fact is that we call risks socially acceptable which are not major risks in the context of the general benefit/risk concept, although, of course, the benefits are benefits to the community and not to one part of the community.

M. Tassignon

We have the epidemiological experience of another industry, the polymer processing industry, in very practical applications (PVC-insulated electric cables, polymer articles etc), this industry employing tens of thousands of people all over the world. Thus hundreds of thousands of people have, in fact, been exposed to vinyl chloride, because in the past the finished PVC (97) contained a much higher concentration than now of residual VCM. This vinyl chloride contaminated the processing shops and the places where the bulk polymer or polymer already prepared for processing was stored, which meant that there were low concentrations of the order of 10 ppm in these shops, in spite of which no angiosarcomas have yet appeared in the personnel exposed in this way. Is this already a proof? We know that the latency-period is shorter for severe exposures, but in spite of that, there is this positive fact that we still have no angiosarcomas in processing workers.

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Prof. Truhaut

This morning, if we had had the time, I would have asked M. Tassignon and M. Maltoni some questions, stressing the biochemical aspects. I think, M. Tassignon, that you stressed the importance attached to the "toxification" phenomenon, and you were thinking, of course, of the formation of the epoxide(98). But besides this formation, which corresponds to the toxification of vinyl chloride, there are detoxification mechanisms, since the epoxides(98) themselves are, as you know, eventually destroyed, this destruction involving, inter alia, compounds with sulphydryl groups(99), and M. Maltoni must certainly remember that work had been carried out in the USA which tended to show that vinyl chloride only began to act on the receptors if at all, from the moment when the "scavengers", acting somewhat like moppers-up of vinyl chloride, had exhausted their means of action and the vinyl chloride was free to act again.

One important point was raised this morning, the choice of equivalent(100) species for subjecting a given chemical to experiments for extrapolation to man, particularly substances having a long-term effect. We are limited for observations on man by the fact that we need a certain observation-cycle , which means that of the parameters we take into consideration the biochemical parameters are of primary importance. They are primary in respect of the metabolic fate and also primary in respect of the mechanisms of action, for there are(101) cases where animal species metabolise a compound in exactly the same way as man although not themselves sensitive to the toxic action; this is the case for example, with tri-o-cresyl phosphate(102), which in the rat is metabolised as in man, although the rat is not sensitive to its paralysing action, and, as you know, we have to use hens as the equivalent species. We still discover equivalent species by lucky accident(103), but one day, we hope, we shall have parameters for selecting the equivalent species, and instead of experimenting with 6 or 7 species, we shall begin from the start by selecting, on the basis of biochemical parameters, the species most nearly equivalent for extrapolation to man under conditions which will no longer be conditions of such great uncertainty as at present.

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Prof. Maltoni

As has just been said, it is essential for the planning of experimental studies in carcinogenesis to take metabolic parameters into consideration, but it is also necessary to evaluate the susceptibility of the animal expressed in a general way by the basic tumorigram (42).

Prof. Truhaut

Nothing prevents us thinking, my dear friend, that the basic tumorigram(42) is itself conditioned by biochemical factors.

Prof. Flamant

I was struck this morning by the insistence with which Prof. Maltoni spoke of non-cancerous lesions which he has systematically investigated, saying that they could be pre-cancerous lesions. Is there a correspondence with human pathology? Might one, on an epidemiological level, look for "infra-clinical" symptoms, if I may call them that, in any case well before the appearance of a cancer?

Prof. Maltoni

I think that the systematic search for precursors in the tests for carcinogenicity is an important source of information(104) which should always be determined and evaluated.

This type of investigation depends on our knowledge of the pre-cancerous lesions. Many of these "precursor" lesions are known, both in animals and in man. I think we now need fundamental research in this sector.

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In the case of the vinyl chloride angiosarcoma we have identified pre-cancerous lesions which are, surprisingly, similar for animals and man, and of the same type as the cells we can observe in human liver after exposure to other agents (arsenical pesticides and thorotrast) which can cause hepatic angiosarcoma.

Prof. Latarjet

We have been exposed for over 6 h urs to a very high concentration of VCM, I do not know how many ppm there have been in this hall, but certainly a very high concentration. I do not think that the risk we have run is very high, but I am certain that the benefit/risk ratio is broadly positive.

I thank all those who have contributed by their papers and their interventions in the discussions, and I thank the organisers for having given us the opportunity to take part in this very interesting meeting.

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TRANSLATOR'S NOTES

1 "en processus industriel". What is m ant here is completely obscure.

2 "Cette polymérisation ... doit s'accompagner", which suggests that th additives must be added to the reactor, which may not be what the author intended.

3 The French can only be read as saying that the explosive limits for vinyl chloride are 4-20% V/V of air in the vinyl chloride, which seems improbable.

4 "asphyxie des extrémités"

5 "avec localisations diverses".

6 "qu'il en était au point de vue animalier"

7 "mesures d'ambiance"

8 "au courant du suivi qu'il a".

9 "intervention"

10 "masques à adduction d'air"

11 "dégazage". Whether this refers to forced ventilation of the reactor or stripping of the polymer is not altogether clear in the context.

12 "cheville ouvrière"

13 "multiples"

14 "la pathologie"

15 "s'atténuer"

16 "exemplaire"

17 "fondamentalistes"

18 "contraignantes" or "which will, perhaps, be binding on them"

19 "direction générale des polymères"

20 "n'etaient pas de mise en regarde"

21 "des ouvriers et des travailleurs"

22 "déroulement de l'expérience"

23 "code"

24 "listing"

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25 "probable" seems to b required to make sense.

26 "analyse des corresp ndances" (On this first occasion, by a clerical error, this appears as "correspondantes"). In the Solvay report(TR 15925) this was translated "correspondence analysis".

27 "bute ... sur"

28 "en avançant dans .."

29 "papillome du pré-estomac". It is not clear what the "pré-estomac" is from the dictionaries consulted.

30 "très vite émoussée"

31 This seems to be the sense, although the grammar is messy.

32 "informatique"

33 "S'exprime mieux "

34 "dépassées"

35 "avoir des chiffres ou unquantification"

36 These seem to be blocks and sections of data, not of tissue, were it not for the reference to "sections" in para 4 of 1 on p8, and for what looks like a slide-tray in the drawing.

37 "S'agit-il"

38 The meaning of "bt" is not given, but is presumably Maltoni's "BT".

39 "expérience", of course, can also mean "experience"

40 "je vous prie de voir là tout l'intérêt que j'ai porté à ..". It is not clear what is meant.

41 What "small" means is not clear, unless it is "slight", possibly referring to the fact that quite different mathematical models give equally good fit.

42 "tumorigramme de base".

43 "agents sociaux".

44 "matières premières", strictly "raw materials", although this had already been used for "matières de base" at the top of the Table.

45 Presumably not a special sub-class of angiosarcomas but a slip on the author's part.

46 Whether this means "the extent to which vinyl chloride .." or is referring literally to the concentrations is not altogether clear.

47 "incidence", here used in a sense other than that used elsewhere in this document.

49 "passionnées". The m aning here can be anything from "lively discussions" to "passi nate disputes".

50 "percevoir". The meaning also includes the more active "collect, gather", but apparently only in relation to taxes and the like.

51 "en correspondance avec". The question is whether this means the vague "in connection with" or "on a level with", the rather more definite "corresponding to" or the still more definite "in agreement with".

52 "font état". The meaning here may be "reported".

53 In relation to what is not clear.

54 Or "large"

55 Or "important"

56 "accidents"

57 " par ailleurs" normally means "elsewhere, in another connection", and it seems that "d'ailleurs" was meant here.

58 The French text has "1963", but in view of the "1953" earlier in the sentence and the reference to "24 years" this has been taken as a slip.

59 "fidèle".

60 "le hall d'essai des méthodes de polymérisation"

61 "copolymères du chlorure de vinyle et du chlorure de vinylidène". Although this could refer broadly to all VC copolymers and all VDC copolymers presumably the narrower meaning is intended here.

62 "au mois près"

63 "préposé"

64 "soufflage dans les autoclaves"

65 "aspiration"

66 The "greater than" sign was missing in the French text.

67 "sensée". This has been read as "censée".

68 This is not too clearly worded, but evidently the age-group column is meant and not the birth-year column.

69 What is meant by "conjunction" here is not clear.

70 This, again, is badly worded and has been heavily revised.

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71 "different" inserted for clarity ("dans le temps").

72 Or "necrosing" ("necrosante")

73 "VC" may, of course, be meant.

74 Or "disputed"

75 "Ma question prolonge.."

76 "fixer".

77 "fixer".

78 "elle est faite de projets .."

79 "Ces informations vont s'efforcer de mesurer.." How the data are going to make every effort to measure is not clear.

80 Simply "vinyle" in the French

81 "qui doit être discutée". Or "which must be discussed".

82 Or, perhaps more definitely, "we are preparing to undertake" ("nous nous sommes orientés vers").

83 "activité"

84 "identique et parallèle"

85 "quand même". The force of this here is not clear.

86 "codifier". The meaning here seems to be "definition".

87 "as being" inserted for clarity.

88 "qu'il n'y en a pas eu beaucoup de faites selon ce type".

89 "intervalle"

90 Or, perhaps, "He is certain".

91 Not supplied for translation.

92 "ordre de grandeur"

93 "partiellement" } This may refer not to the time but to

94 "en totalité" } parts of the body and the whole body.

95 This is presumably referring to the enzymes "mis-reading" the damaged nucleotide sequence.

96 "plus". Presumably the negative is implied here.

97 "chlorure de vinyl " in the French.

98 "époxine"

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99 The French text has a gap before "groups"; these have been assumed to b sulphydryl groups.

100 "adéquate".

101 "il est des cas". Presumably "il y a" was meant.

102 "tri-orthocrésine phosphate".

103 Nous n'avons pas fini d'être surpris par les découvertes des espèces adéquates". Or perhaps "We have not come to the end of the surprises in the discovery of equivalent species" or "We never cease to be surprised..."

104 "donnée". This passage is not too clear.

105 It is possible that "exploitation" in the French text was a clerical error for "extrapolation", which would give " . . . extrapolation of the results to low doses", in view of the following comment.

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