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ORGANIC SOLVENTS AND PRESENILE DEMENTIA (THE PAINTERS' SYNDROME). A CRITICAL REVIEW OF THE DANISH LITERATURE

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ABSTRACT

Since 1971 a series of Danish medical articles have been published which concludes that the occupational inhalation of organic solvents can induce a chronic cerebral disease manifesting itself in a presenile syndrome. As the articles have mainly dealt with the exposure of painters, the disease has also been called "the painters syndrome". The publications have brought about, by law, an almost exponential recognition of "the painters syndrome" as an occupational disease. It has therefore become necessary to undertake a critical scientific analysis of the Danish publications which appeared between 1972 and February 1983. The conclusion of this evaluation is, that the Danish articles do not prove that occupational exposure to organic solvents produces a presenile demens. The indications that it does are very slender. The importance of adhering strictly to present regulations of working conditions is emphasized.

Among the medical profession, as well as the general public, attention has increasingly been focussed on the problem of whether exposure to organic solvents, including alcohol (ethanol), can induce, particularly under working conditions, a chronic cerebral disease manifesting itself in a presenile syndrome (also called the psycho-organic syndrome (p.o.s.)). Since this syndrome was first described as an occupational disease among painters, it has become known as the "painters' syndrome".

Prior to 1970 there had only been a few papers on chronic solvent poisoning (often in the form of individual case reports) and one thesis on the hazards of spray painting, with special attention given to its effect upon the blood cells [1]. The present debate originated from two reports: one from Aarhus in 1971 and the other from Copenhagen in 1972 [2, 3]. These are not scientific papers, but political discussions. It is pointed out in the Aarhus report that the aim of the Directorate of Labour Inspection, and thereby the State, is to secure the capitalist system of production and thus preserve the capitalist social system. The "Painter Report" from Aarhus was carried out by the "Occupational-medicine Group of the Students' Front" at the request of the painters' union in Aarhus. The report is based

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upon unstructured interviews with 20 painters supported by a questionnaire. The group did not trust a questionnaire alone, as a previous questionnaire investigation had demonstrated that the answers were "not in agreement with reality". Apart from that, the report consists of interviews with a large number of authorities, organizations and concerns, including the technicians and doctors of the Labour Inspectorate.

One year after the Aarhus report, the "Painter Report Copenhagen 1972", also called the "Poison Report", was published by the painters' union. It was prepared by a group of 17 persons, eight of whom were medical students, three engineering students, three cultural sociology students, one training to be a social worker and two house painters. The report comprised a total of 511 questionnaires completed by painters; the formulation of the questionnaires had been influenced by the painters. The study was introduced by the above-mentioned members of the group at club meetings at the various workplaces, creating, to a marked extent, a basis for bias. A further ground for bias was that additional group-interviews had been conducted, instead of individual interviews.

Both reports are devoid of scientific value as they are based upon interviews and questionnaires without an objective aim and without control groups; no regard was paid to previous or present disease among the subjects, their alcohol intake, or details of their exposure (duration and concentration) to organic solvents.

In 1976, Mathilde Lajer, a medical student, published a study on the nature and extent of acute and subacute symptoms in house painters engaged in painting new houses with paint containing organic solvents [4]. This was a questionnaire study involving 44 painters and a control group of 38 electricians working under similar conditions, but without exposure to painting materials. There was no relationship between the number of symptoms and the number of years the painters had been in the trade or their age. A special, but irrelevant, analysis of the incidence of coughing and expectoration was carried out. These symptoms were more common among the painters than among the electricians during workdays, but less common during weekends and holidays. The author emphasized that there was no relation between coughing, expectoration, and smoking, but no data are given as proof of this. No physical examination was carried out to substantiate the results from the questionnaires. Moreover, the investigation of the two groups was carried out at different times. The symptoms listed in the questionnaire were not thoroughly defined, for example what is meant by "visual disturbances", "slow reaction" or "difficulty in controlling small movements"? The lack of objectivity negates the scientific value of these symptoms. In the introduction to the paper it is stated: "In the course of the past years *painters* have made many complaints about this type of paint". This prejudice, as well as the vague formulation of the questions, creates a marked degree of bias. Previous diseases, drinking habits, smoking habits and use of drugs were not analyzed. On the whole, the paper must be considered inadequate and devoid of scientific value with regard to the painters' syndrome.

In 1978, Mikkelsen et al. published a review of the literature in order to elucidate the effect upon the central nervous system of industrial exposure to organic solvents [5]. Most emphasis was placed upon symptoms of chronic poisoning with a view to discussing whether permanent brain damage could be a consequence of long-term exposure. It is a characteristic of this review that it tries to convince the reader of the detrimental effect of organic solvents without elucidating the conditions under which exposure has taken place and which substances are concerned. Little mention is made of investigations which do not confirm the hypothesis and when they are mentioned they are not analyzed in any detail. The authors show such a lack of critical ability as regards research work that they actually state that there is no need to elucidate exposure conditions and other causal factors before using the results of the study for preventive purposes. On the contrary, they feel that to ascertain these conditions and factors adequately for presenile dementia is tantamount to a super-critical attitude to scientific work. The authors would have been expected to know that in medical science, as in any other science, there is no question of attitude to scientific work, but an analytical critical approach to work of varying scientific quality.

Gregersen et al., also in 1978 published a paper entitled "A chronic cerebral painters' syndrome. Cryptogenic or inhaled dementia?" [6]. Based on the concept that continuous occupational exposure to organic solvents is a probable cause of the development of organic brain damage, resulting in disabling presenile dementia, these authors tried to evaluate clinically the occupational syndrome in a group of patients, all of whom were painters. The group consisted of 35 painters aged from 27 to 58 years (mean 47 years), all of whom had ceased working or had changed to other work because of intellectual and emotional signs of dementia. The disease and the disablement were recorded on the basis of a retrospective analysis of the authors' own data and information from case records, including, inter alia, the declarations from 40 specialists to the Disablement Insurance Tribunal (now the Social Appeal Board) and the National Social Security Office/Accident Insurance. It was assumed that the painters' premorbid intellect had been normal, since they had completed schooling and their apprenticeship. The criteria for the exclusion of patients were entirely unacceptable from the point of view of medical research. Multi-infarction dementia was not included as an exclusion criterion and, a very serious research error, patients with diabetes mellitus, arterial hypertension, a history of myocardial infarction or intermittent claudication were included in the study. Moreover, two patients with birth trauma were included, one of them suffering from cerebral palsy. Qualitative or quantitative details of the exposure to organic solvents were not given. There was no information about alcohol consumption during working hours or in spare time. There were no control groups. No mention is made of protective measures, so that it is not possible to establish whether the painters had complied with the guidelines applying to the work. The description of symptoms is quite

unacceptable, since it was merely qualitative. The authors state that "the chronic state of insufficiency, predominated by irreversible psychopathology, developed in the 35 painters after 15—40 years in this occupation, with repeated episodes of poisoning". This claim completely lacks substantiation in the paper. In addition, there is no information concerning alcohol consumption prior to the cerebral insufficiency. In Table 1 of the paper [6] the reduction in intellect of 34 occupationally disabled painters was evaluated. As nothing was known about the premorbid intellectual state, there can be no question of a reduction in intellect, but, at most, merely an impaired intellectual function. The paper does not substantiate the occurrence of presenile dementia in painters as a consequence of occupational exposure to organic solvents.

Arlien-Søborg et al. (1978) have given an account [7] of toxic dementia in 46 house and spray painters who had been admitted, during the preceding 3 years, to the Neurology Department of Rigshospitalet, Copenhagen, for investigation of suspected chronic painter poisoning. On the basis of the investigations and a literature review, a detailed description of the painters' syndrome was given. There was an attempt to exclude patients with problems of differential diagnosis. Patients were excluded if there had possibly been alternative causes, such as major head injuries with prolonged unconsciousness, alcoholism, epilepsy or sequelae from birth injuries. Patients were also excluded if there was a suspicion that the changes could have been due to other diseases. This left 34 of the original 46 house and spray painters who exhibited acute as well as chronic symptoms. The criteria for exclusion from the study can be criticized. Among other things, no mention is made of the problem of multi-infarction dementia. Two patients had mild diabetes and were on dietary treatment. The authors do not mention whether arteriosclerosis was present in these patients and no data are given about their diabetes. Two patients had elevated haemoglobin and a markedly elevated haematocrit level. These two patients were not examined in further detail. One patient had polycythaemia, but what the actual diagnosis was is not mentioned. Three patients had a history of moderate, transient alcohol abuse, and with another two there was a suspicion of mild, also transient, alcohol abuse. Four patients had a history of, or active, liver disease, but no attempts were made to clarify the diagnosis. It is explicitly stated that painters with a high alcohol intake were excluded, and from this it was deduced that alcohol abuse could not play any aetiological role in the cerebral atrophy and presenile dementia. However, no attempt was made to substantiate this claim. Thus, the major role of alcohol in the development of presenile dementia and liver disease was entirely overlooked. This aspect will be dealt with in further detail in the discussion. In general, no information is given about the patients' drinking habits. All had a minimum of 7 years' schooling, and all except one were professional painters. Their premorbid intelligence was assessed as being within the range of normal in 33 cases, while one was on the borderline of mental subnormality. This assessment was completely unsubstantiated, and the

findings of Erik Høgh emphasize the doubts about its correctness (see [21] and below). In Table II of the paper [7] the authors give the degree of intellectual reduction on the basis of neuropsychological studies. It is wrong to use the term reduction, considering that their premorbid intellectual state was not known. The mean exposure time to organic solvents was stated to be 27 years with a range of 13—46 years; this is the only factual information given on the alleged aetiological factor in the hypothetical painters' syndrome. Nothing is stated about the nature of the substances, their concentrations in the air during work, the total time of exposure, nature of the work or working conditions (e.g. indoors or outdoors, ventilation, and protective measures). Of the 34 patients examined, 24 ([7], Table 1) had cerebral atrophy. In six it was exclusively cortical, in three central and in 10 both central and cortical. The cerebral atrophy was described as being of minor degree in 17, moderately severe in three and severe in four. It appeared that 10 had no atrophy. It is not clear for what purpose this information is intended, as no attempt was made to correlate the different locations of the cerebral atrophy to the severity of the dementia. Overall, the findings as regards the relationship between cerebral atrophy and a possible painters' syndrome provide no scientific proof, as there was no attempt to correlate them to the exposure to organic solvents, which is, in any case, unknown. In addition, no attention was paid to other aetiological factors which may lead to cerebral atrophy, primarily alcohol intake (which is not identical to alcoholism), but also silent episodes of transient cerebral ischaemia with possible thromboembolic complications.

Of the 34 painters in Table II of the paper [7], 27 were reported to exhibit intellectual reduction on the basis of neuropsychological tests. There was no attempt to correlate the reduced intellectual function to the exposure to organic solvents, the details of which are not given. Thus, the results of the psychological tests give no scientific information on chronic painters' syndrome. There was also no attempt to correlate the reduced intellectual capacity with cerebral atrophy. As a consequence, the results provide no scientific information with respect to the demonstrable cerebral atrophy or the alleged intellectual reduction in the attempt to define chronic painters' syndrome. The paper mentions that the investigations confirmed that most, if not all, of the painters repeatedly experienced acute symptoms of poisoning. This claim was entirely unsubstantiated due to lack of objective criteria, such as examination of the patients and information concerning their work and working conditions. There was no control group — a fundamental lack in any scientific study.

An overall scientific evaluation of the paper of Arlien-Søborg et al. [7] provides no evidence that occupational exposure to organic solvents caused presenile dementia in the painters concerned. The paper is entirely inadequate as regards precise data on fundamental issues. The paper must be seen by critics as one in which the facts presented do not substantiate the conclusions, and it can only be seen therefore as a tendentious intervention in the debate.

In 1974, Sabroe and Olsen published a study on changes in mental function in solvent-exposed cabinet makers [8]. This study was based upon questionnaires. No physical examinations were performed to confirm the answers. The authors point out that "in retrospect it is not possible to obtain data concerning the exposure of the lacquer workers to organic solvents". If only for this reason, the data lack an essential element, and this weakens the entire scientific basis of the account of the changes in mental function in the solvent-exposed cabinet makers. The 12 questions in Table IV of their paper, concerning changes in mental function, are so naively and badly formulated that they must be declared inapplicable to a scientific investigation. Additionally, the questions (except possibly question 10 about impotence) were put in such a way that a very serious risk of bias was introduced. While the statistical methods are considered applicable in the mathematical/statistical sense, the results are valueless because of the completely unacceptable, vague demands that the authors have made on the statistical analysis of the symptoms. It might be questioned whether this was due to the great difficulty in obtaining positive results on the role of organic solvents on mental function in exposed persons. Thus, the overall evaluation must be that this paper does not contain information of scientific value concerning a chronic effect of solvents upon the central nervous system.

Based on the files of the National Social Security Office, Nielsen et al. in 1979, published a study of 142 cases of workplace poisoning involving 140 workers exposed to organic solvents notified to the Directorate of Accident Insurance during the period 1961–1970. This study is reported in two papers, sub-titled "Exposure" [9] and "Disease, Disablement, Compensation" [10]. It is disturbing, in trying to understand the results of analysis of the data from patients, that in no case was there any information about measurements of the concentration of the substances concerned in the air at the workplace, and that the past and present risk of exposure was not stated in three-quarters and two-thirds of the cases, respectively. Because of this, the authors' view must be shared that it was impossible, or very difficult, to evaluate the duration and nature of the exposure. In Table I of the second paper [10], the acute and chronic symptoms of poisoning were listed in groups, but the symptoms were not correlated with other data, such as age, occupation, working conditions, and exposure to solvents. Also, no mention is made of other causal factors, such as diseases, alcohol intake, drug intake, etc. Indeed, it is pointed out in the paper: "But of course a study like the present one cannot rule out other or competitive causes of e.g. chronic respiratory disorder, persistent headaches and fatigue or the development of presenile dementia".

All that can be concluded is that the papers are so ill-based, scientifically, that they must be rejected as failing to qualify as medical research. Thus, they cannot be considered to provide evidence for the role of solvents in the development of presenile dementia in solvent-exposed persons, as stated at the beginning of the conclusion in [10].

In 1980–82, Mikkelsen published results concerning dementia and organic solvents [11–13]. Reviewing applications for a disablement pension, he found that in painters the relative risk of developing presenile dementia was ~2.8. However, in reviewing the application, he had carried out a so-called reclassification of the diagnoses. The reader cannot check the nature of this reclassification. The credibility of the results obtained by Mikkelsen is further weakened by the fact that they could not be reproduced in a study by Nielsen et al. [14]. In addition, the statistical analysis of the results in Mikkelsen's publication has been evaluated by Professor Erling B. Andersen, the University Statistical Institute, Copenhagen. He was unable to check the analysis from the data given in the paper. The analyses were poorly described, the conclusions were not well formulated, statistical tests were incorrectly used, there were errors in the tables, and there were numerous errors in the paper, so that he had to desist from further evaluation. Lastly, Andersen had to admit that it was not possible to find any profound statistical insight on the part of Mikkelsen's data (see Appendix II).

In 1982, Vinter published the results of a questionnaire study on organic solvents and presenile dementia [15]. Among painters, cabinet makers, carpenters, bricklayers, and labourers, the painters gave the highest percentage of answers and, according to Vinter, this might indicate a link between exposure to organic solvents and presenile dementia. However, this deduction is ill-founded because the questions were broad and poorly defined, and the questionnaire alone cannot be used to draw such a conclusion. In addition, the painters' answers were biased due to the intense discussion in the media about the possible detrimental effects of organic solvents. No specific information is given concerning confirmation of the painters' complaints or any information about exposure conditions (total time, concentration, workplace conditions, use of protective measures). Nothing is stated about alcohol intake, cerebrovascular diseases and other alternative diseases that could lead to presenile dementia. The paper provides no scientific basis from which to elucidate, let alone substantiate, a possible relationship between occupationally induced presenile dementia and organic solvents.

In 1983, Arlien-Søborg published a thesis entitled "Chronic Toxic Encephalopathy in House Painters" [16]. This thesis is based upon four previously published and one unpublished paper. The four original papers are discussed below.

Arlien-Søborg et al. published the first paper on the chronic painters' syndrome in 1979 [17]. In 50 painters the authors claimed that it was not possible to detect causes for the cerebral symptoms other than exposure to organic solvents. However, they did not mention cerebrovascular disease as a criterion for exclusion, and alcohol intake led to exclusion only if it exceeded 61 g day^{-1}. Hence, the role of alcohol in the development of presenile dementia is not even discussed, although the chosen arbitrary limit for harmful alcohol intake, particularly in relation to brain damage, is not in accord with current scientific knowledge. In addition, apart from

the possible exposure period, stated as a mean time of occupation as a painter of 27 years, no information was given about the working conditions (open air or indoor work), the concentration of organic solvents, or the use of protective measures. Results are confined to the neuroradiological examination of the brain (pneumoencephalography (PEG) or computer tomography (CT) scanning) and neuropsychological investigations. The figure in the paper illustrating the maximum width of the brain sulci is of no value, as the correlation with age was not given, either for the reference group or for the painters. In addition, the authors found a maximum sulcus width which differed only marginally but, according to them, significantly from that of controls. The significance of this marginal difference is rendered extremely doubtful, since the measurements from the scan, because of the small size of the scan, have to be multiplied by a factor of about three to obtain a result. Moreover, the number of sulci measured to obtain the observed and calculated sulcus widths is not stated for each painter. In relation to the neuropsychological investigations, Arlien-Søborg et al. did not procure reference values from a control group.

The results of the psychological tests were not related to the painters' age or to the CT scans. They should also have been related to exact figures for the exposure to organic solvents; these were, however, unknown. All considered, it may be concluded that the scientific content of the results is so minimal that if affords no foundation for the existence of a chronic painters' syndrome.

The second paper on which the thesis of Arlien-Søborg is based [18] deals with vestibular dysfunction in chronic solvent exposure. From a study of the vestibular function, the authors concluded that about 55% of the painters examined had vestibular dysfunction, primarily in the form of reduced-temperature-stimulated vestibular function. However, it is necessary to point out considerable deficiencies in their data from test subjects and control subjects in the analysis of the results. No attempt was made to elucidate the nature and history of the painters complaints of vertigo; although their subjective complaint of vertigo was mentioned, there was no analysis of individual cases. Nevertheless, the authors report, in the section on results and discussion, that there was no statistically significant difference in vestibular function between painters with and without vertigo, a finding which does not help in the understanding of Fig. 2 of their paper.

Finally, it must be pointed out that this paper again failed to present factual information about the painters' exposure to organic solvents, the nature of such exposure, its magnitude, duration, working conditions, and protective measures. In the section on materials and methods no mention was made of control subjects. Nevertheless, they appear in Fig. 1 in the section on results, which lists 141 normal subjects and the total duration of nystagmus. It is not apparent from the paper whether these normal data were derived from the authors' own studies or procured from other sources. However, by reading two of the papers referenced in the article

it was established that the authors had not worked out the normal data by themselves, but founded the normal data on two sets of data derived from the two references. One set was published in an article by K.A. Thomsen in 1953 comprising 48 persons, of whom only 16 were more than 30 years old. The other set was from an article by Hallpike et al. from 1951, comprising 93 completely fit R.A.F. cadets aged from 18 to 22 years. From these individuals the normal data of 141 persons was derived. However, this was not distributed in a scientifically acceptable way in relation to the experimental group. It is scientifically deplorable that the authors did not work out their own control group when using the caloric test. Further, it is scientifically unacceptable to use control material which was 28—30 years old when the article was published. Further a control group should ideally be identical, in all respects but one, to the experimental group, the difference in this case being the exposure to organic solvents. Apparently, the authors did not try to meet this demand.

Moreover, in the article a vestibular hyporeactivity to <350 s and a hyperreactivity to >550 s is established arbitrarily without any scientific argumentation. Neither on the basis of the control data, which on the grounds mentioned cannot be used, nor other information provided in the article, is there a scientific basis for the given time factors for vestibular hypo- and hyper-reactivity. However, by studying the original article of Hallpike and co-workers and that of Thomsen, it is possible to calculate a vestibular hyporeactivity to less than 310 s and a hyperreactivity to more than 530 s using a statistical method stipulating that 95% of the normal material is within $\pm 2 \times$ the standard deviation. With this background information there is no scientific basis to fix a vestibular hyporeactivity to less than 350 s as the authors have done, and it follows that there is no scientific basis to quote that 43 painters had a vestibular hyporeactivity. This may be one of the reasons why the authors had difficulty in finding a correlation between vestibular dysfunction and the duration of exposure to organic solvents or the duration of the interval without exposure. This also applies to the lack of correlation between the degree of intellectual dysfunction, cerebral atrophy, and vestibular dysfunction, and the lack of a statistically significant difference in vestibular dysfunction between painters with and without complaints of chronic vertigo. The degree of reproducibility of the method used for measuring the duration of nystagmus was not mentioned, and this further weakens the results reported. It is stated that the subjects had not taken more than 60 g of alcohol a day for several years, but there was no information about the alcohol intake of the control subjects, in particular whether it was identical to that of the painters. The duration of nystagmus in the 113 painters presented in Fig. 2 of the paper is summary only and does not permit further analysis. It is misleading to give the total duration of nystagmus after four irrigations of the auditory canal, as in Fig. 2 of the paper. To be of scientific value the results for each individual subject must be accessible, therefore the authors should have reported the individual results of irrigating the right and left ear with water at 30

and 44°C. Like the authors, the readers must wonder why there was no correlation between vestibular dysfunction and the duration of exposure to organic solvents (unknown, but assumed by the authors), as well as between vestibular dysfunction and the occurrence of cerebral atrophy and reduced intellectual function. In addition, why some of the painters exhibited unilateral dysfunction and others bilateral is inexplicable.

A statistical analysis of the results in Figs. 1 and 2 of the paper [18], performed by the present authors, revealed that the painters differ significantly from the control group with respect to the duration of nystagmus. The reason for this difference between the two groups cannot be deduced from information given in the paper. Therefore, it cannot be maintained that the difference in vestibular function between the painters and the controls is due to the painters' exposure to organic solvents. This is indeed stressed by the authors who state: "The changes in vestibular function did not correlate with the duration of exposure or with the length of the interval without exposure". In a truly scientific analysis of the experimental results, to examine a possible correlation among the painters between the duration of nystagmus and the degree of exposure to organic solvents, these data should have been related to each other, i.e. the duration of individual painter's nystagmus (not reported in the paper) should have been related to the duration of their individual exposure to organic solvents. In the paper, the exposure time is only given in terms of the mean exposure time for the whole group and the minimum and maximum exposure times. The duration of exposure might perhaps be assumed to be equal to the length of time of occupation as a painter, but the latter is an inexact measure of the exposure to organic solvents. The object of collating such data would be the possibility of constructing regression lines for painters and controls, respectively, but this was not possible as the necessary data were not available to us. Such a statistical analysis has been performed on the results of cerebral blood flow (CBF) in painters and controls. This showed that it was not possible to conclude that exposure to organic solvents was the cause of the lowered CBF measured in the painters. This will be discussed in more detail in the review of the fourth paper.

A similar conclusion could be expected in relation to the possible vestibular dysfunction in painters, if such a calculation had been possible. This view is supported by the authors' unsubstantiated claim, already mentioned, that they were unable to demonstrate a correlation between changes in vestibular function and the duration of exposure to organic solvents. On this basis also, it seems inexplicable why the authors believe that an investigation of vestibular function might be helpful in disclosing early changes in people exposed to organic solvents.

Lastly, it should be mentioned that according to a statistical analysis (χ^2 test) of the distribution of the normal data, the distribution was so near to ideal that, from a statistical point of view, the group must be assumed to have been selectively chosen.

It must be concluded from the above that the control and experimental

data were scientifically so deficient that is must be doubted whether exposure to organic solvents can have been the cause of the vestibular dysfunction demonstrated in the painters. Before venturing to conclude that vestibular dysfunction can be considered an early sign of chronic poisoning by organic solvents, more detailed and adequately performed research must be demanded.

In 1981, Arlien-Søborg was a co-author of a paper on the prognosis of chronic toxic encephalopathy [19]. This was the third of the papers on which his thesis was based. This study was a follow-up examination of the 50 painters included in the first paper [17]. However, the authors felt that not all 50 could be used in the follow-up, which seems incomprehensible. Thus, 12 painters were excluded from the follow-up examination because their PEG had previously shown cerebral atrophy, and for ethical reasons the authors did not feel that this physically exacting examination could be repeated. Since the authors consider psychological tests of extreme importance in diagnosing presenile dementia, these tests could have been applied to the 12 painters, especially as the authors do not anywhere try to correlate the presence of cerebral atrophy to the results of psychological tests. Another five painters were omitted from the follow-up examination, evidently because they had not exhibited cerebral atrophy and/or intellectual dysfunction. This would suggest that these five painters were normal with respect to CT scanning and psychological tests. This ground for exclusion from follow-up examination is unacceptable, as there was a possibility that these previously normal painters could have shown divergences from the original results. Yet another seven painters were excluded from the original group of 50. However, only three of these seven should have been excluded: two who refused to take part in further examinations and one who did not respond to the request to attend. Two painters who had undergone various psychological tests elsewhere (which might have been repeated at Rigshospitalet, if needed), and two whose follow-up period exceeded 3 years should have been included. It is quite unacceptable that at the follow-up examination the group of painters comprised only 23 persons; it should have been 47.

This arbitrary reduction of the original group of patients appreciably reduces the scientific value of the study. Moreover, just as in the first paper, there was a lack of information about the conditions of exposure to organic solvents. Likewise, the assumption that the premorbid intelligence level had been normal is contentious, as is further elaborated in the discussion. Finally, the paper also lacks any details concerning the painters' alcohol intake.

The authors felt able to conclude that in the course of the follow-up period of 2 years, during which the painters had not been exposed to organic solvents, they had not exhibited a statistically significant alteration in intellectual dysfunction or cerebral atrophy. It must be mentioned that in this paper also, there were no controls matching the painters with respect to psychological testing. Also, it would have been of value if the results of

psychological testing and CT scanning from the initial examination had been stated for each person, as well as the results from the follow-up examination. Again, it must be emphasized that no attempt was made to correlate the results of CT scanning with those of the psychological tests.

It is surprising that the authors attribute such decisive value to the results of psychological tests in diagnosing presenile dementia. They have graded the presenile dementia into vaguely defined groups, and in the thesis itself ([16], p. 84) Arlien-Søborg states that the neuropsychological studies are encumbered with certain methodological difficulties: the evaluation of the premorbid level of mental function, the test–retest effect and the role of the patient's motivation and collaboration. It is also surprising that the method used for assessing psychological functional level does not, unlike other scientific methods, have any indices of reproducibility and sensitivity; the specificity of the psychological tests is considered, by the authors, to be very low, since they give no indication of the cause of presenile dementia. In the authors' opinion, presenile dementia of the Alzheimer type can be ruled out, because they feel that the condition had remained stationary during the 2-year follow-up period. However, this period must be said to be too short.

All considered, the paper has such scientific deficiencies that it cannot provide convincing evidence regarding the occurrence of the chronic painters' syndrome.

The fourth of the five papers upon which the thesis is based had been accepted for publication but had not been published when the thesis was approved. It has since been published [20]. With regard to experimental subjects, the authors have not stated specifically that persons with cerebrovascular diseases of a different aetiology and pathogenesis were excluded. It is reported that the painters' alcohol consumption did not exceed 60 g daily, but individual painter's alcohol intake is not given. No mention at all is made of the alcohol intake of control subjects. If their daily alcohol intake was low, this alone might explain a possible difference in CBF between the painters and the controls. The CBF in the painters was said to be significantly lower than that in the controls. This is interpreted by the authors as incipient presenile dementia.

A statistician who has examined the results assessed them as being insufficiently analyzed. The authors should have evaluated the results for controls and painters by the aid of regression lines. When regression lines were constructed for the controls and painters, they were parallel (identical slopes), indicating that the CBF decreased identically in the two groups with advancing age. The location of the lines differed significantly, indicating that the CBF in the painters was lower than that in the controls. This might induce the uncritical reader to draw the conclusion that the reduced CBF in the painters was caused by exposure to organic solvents. However, that conclusion cannot be upheld, due to the very fact that the two regression lines were parallel. Parallelism between the two regression lines could only occur if a very brief period of exposure to organic solvents

had produced a maximum effect upon cerebral metabolism and CBF. This would mean that the relationship between exposure to organic solvents and brain damage would not follow the usual dose—effect relationship, and this seems unlikely. In other words, the parallelism of the two regression lines suggests that factors other than the exposure to organic solvents are the cause of the reduced CBF in the painters.

It must further be questioned why the authors did not correlate the CBF with the results of the psychological tests of the painters, even though they were included in their data ([20], Table 2). Whether psychological tests were performed on the control persons is not apparent from the paper; this would be expected in a good scientific study.

A final conclusion is that this study does not support the hypothesis that chronic exposure to organic solvents reduces the cerebral oxidative metabolism and CBF, and thus does not support the title of the thesis "Chronic Toxic Encephalopathy in House Painters".

DISCUSSION

This critical review demonstrates that no *single* study provides proof, or even an indication, that the painters' symptoms and signs are related to their occupational exposure to organic solvents. Nor do all studies together support the existence of a painters' syndrome, more correctly designated the psycho-organic syndrome (p.o.s.), manifesting itself in presenile dementia caused by chronic encephalopathy. The reason for this conclusion is that the studies reviewed are vitiated by important defects in scientific planning, reporting and analysis of the tests performed and their results. For example, a major defect in most cases is the absence of control data, and controls, when present, were deficient. Exposure conditions, which were not defined at all in the studies reviewed, are a fundamental necessity if a conclusion is to be made that abnormal mental function is the result of exposure to organic solvents. It must also be mentioned that none of the studies reviewed gave information about the hygienic conditions of the workplaces or the painters' use of protective measures relative to publication No. 21 of the Labour Inspection of 1968, "Painting, Instructions and Precautions Against Health Hazards in House Painting". These instructions were developed on the basis of the work carried out by a committee consisting of representatives from the National Association of Danish Master Painters, the Painters' Union in Denmark, the Association of Denmark's Lacquer and Dyestuff Industry and the Directorate of Labour Inspection. In 1973, this instruction was replaced with a new publication, No. 41, in which regard was paid to criticisms made by the painters' union. In the preface to this publication, S. Drachmann, then Head of the Labour Inspectorate, wrote that "the measures comprise the personal protection to be used to guard against health hazards connected with this work. The section at the end of the publication gives more detailed specifications for

working methods, workplaces, and personal protection. Furthermore, a more detailed account is given of the guidelines for labelling products for solvents and other unhealthy constituents. The Labour Inspectorate considers that regulations of the law on workers' protection have been fulfilled if the instructions are complied with or if measures have been taken which, in the opinion of the Labour Inspectorate, afford the workers equal safety". Of the 20 painters questioned in the painter report from Aarhus [2], none knew of the instruction in force at that time, i.e. No. 21/1968.

If the guidelines and instructions on working conditions and on performance of the work have not been complied with by the painter, the complaints or damage caused are considered self-inflicted and cannot be designated as occupational injury, provided the employer has observed his part of the rules and instructions in force.

Any substance or product to which the human body is exposed may produce effects or health hazards if present knowledge and instructions concerning the use of the substance or product are not observed. For these reasons, the various authors should have focussed directly on the problem of whether the health regulations relating to the work, general as well as personal, had been observed.

It is a common feature of the papers reviewed that a large percentage of the painters included in the studies exhibited impaired mental function in a varying number of the psychological tests employed. The authors of the papers state that the painters' premorbid intellectual function must be assumed to have been normal, as they had completed an average of 7 years elementary school and thereafter a normal apprenticeship as painters.

In this connection it should be mentioned that Erik Høgh, Reader to the University Institute of Longitudinal Studies, gave the following information on the basis of "Project Metropolit" [21]. This was a longitudinal study of boys born in 1953 in the metropolitan area of Copenhagen. A total of 11352 boys were studied and 7868 of them intelligence tested in 1965.

In 1971 it was recorded that 71 of the 7868 boys had chosen the painter's trade. The IQ test is Swedish; it has been used by the Danish Institute of Social Research and also in a similar Swedish study of a Swedish birth cohort of boys since 1953. Intelligence Quotient is scored on a scale from 1 to 120, 120 being the maximum score. The median IQ value is 68 and this divides the population in half.

It is apparent from Table 1 that 28.2% of the painters were from the group with the lowest IQ and none of them were from the highest. Of the painters, 77.4% had an IQ below the median. It must be borne in mind that the IQ was tested before the subjects became painters. These data show that the painters' IQ was not normally distributed. This perhaps explains some of the abnormalities in the results of psychological tests on painters exposed to organic solvents.

All the papers reviewed also failed to pay sufficient regard to the great importance of alcohol intake in presenile dementia. It has been reported by Lee et al. [22] that "alcohol abuse must be considered the most common cause of this condition". None of the reports dealt in detail with the consumption of alcohol, either qualitatively or quantitatively, by the persons included in the various studies. Incidentally, it is very difficult to derive exact information about people's alcohol habits [23]. Nevertheless, it is of prime importance to the present problem of presenile dementia to procure information about alcohol intake and to ensure that such information is correct.

Arlien-Søborg [16] states that he excluded persons who consumed more than 61 g of pure ethanol a day, without further indicating why he decided on this quantity, said to correspond to five drinks a day, each drink containing about 12 g of 100% ethanol.

In relation to the total consumption of alcoholic beverages by the Danish population, it should be pointed out that in 1970 each person aged over 14 years consumed a total of 6.5 litres of alcohol and, in 1980, 11.63 litres, i.e. 33 ml day^{-1}, corresponding to two drinks [22]. An ordinary drink, e.g. a bottle of lager, contains 4.7 vol. % (3.7 g%) alcohol; the normal volume (337 ml) contains 12.5 g (15.8 ml) of pure alcohol. Five drinks contain 62.5 g, corresponding approximately to Arlien-Søborg's limit of 61 g.

In Hans Kristenson's thesis of 1981 [24] it is stated that the daily intake of more than 40 g of pure alcohol, i.e. three drinks, can be defined as heavy drinking. It is also stated that between 35 and 60 g of alcohol a day leads to an increase in alcohol-related morbidity, and that an intake of 48 g (60 ml) a day is sufficient to cause habituation.

Lee et al. [22], describing brain and liver damage in 37 young men (aged 21—35 years), who consumed large quantities of alcohol daily (from 100 to 400 g, mainly as beer), felt able to conclude that intellectual dysfunction could arise at an early stage of alcoholism. In another publication [25], Lee, reporting on the occurrence of alcohol dementia and organic dementia due to other causes, concluded that the results of her study support the claim that alcoholism may be the most common cause of presenile dementia. In correspondence Lee has pointed out that in fact little is known about the dose, time factor, or age in connection with the development of alcoholic dementia. It has gradually been discovered that alcoholic dementia may occur at a relatively early stage of alcoholism, far more frequently than alcoholic hepatic cirrhosis, and in fairly young people.

Hollstedt and Rydberg [26] have posed the questions: What is the threshold daily dose of alcohol that can be taken without risk, and how is early alcohol damage detected? They state that when using the normal toxicological safety factor, which in the case of alcohol is about 10 in relation to the acceptable daily dose, an adult should not take more than ~0.1 g of alcohol per kilogramme body weight. In that case, an adult person weighing 70 kg can only consume ~7 g of alcohol a day, if organic damage is

TABLE 1
A BIRTH COHORT OF BOYS (1953, Project Metropolit) DISTRIBUTED BY CHOICE OF OCCUPATION IN 1976 AND IQ IN 1965

Choice of occupation 1976	IQ 1965 (%) 1—44	45—55	56—68	69—80	81—90	91—120	Total	*N*
Painter's trade	28.2	26.7	22.5	16.9	5.7	0.0	100.0	71
Others	10.4	14.3	24.8	24.6	15.8	10.0	99.9	7797
Total	10.6	14.4	24.9	24.5	15.7	9.9	100.0	7868

to be avoided. Such organic damage is, according to Lee, primarily encephalopathy. In other words, the safe intake of beer is little more than half a bottle a day.

Hollstedt and Rydberg gave a graphic presentation of the risk involved at various levels of alcohol intake (Fig. 1). In this figure the quantity of alcohol is stated as grammes of alcohol consumed *weekly*.

Group I covers an intake of up to 50 g (about four bottles of lager) of pure alcohol per week, which should not incur a health hazard to a healthy person.

Group II covers an intake of up to 110 g (about nine bottles of lager) of pure alcohol per week, at which there is hardly any risk of habituation or other detrimental effects in the long term.

Group III covers an intake of up to 250 g (about 20 bottles of lager) of pure alcohol per week. This leads to the risk zone, especially at the right-hand end of the curve.

Group IV covers an intake of up to 400 g (about 32 bottles of lager) of pure alcohol per week. At this level there is a major risk of habituation and of damage to the nervous system and other organs. In this connection it should be borne in mind that Arlien-Søborg fixed his limit for alcohol damage at 61 g day^{-1}, a total of 427 g $week^{-1}$, and this is clearly in conflict with the information in Fig. 1 and with what is stated below.

Hollstedt and Rydberg quoted a French study in which the safe limit was fixed at 40 g day^{-1} for men and 20 g day^{-1} for women with respect to the more severe diseases, such as oesophageal cancer, hepatic cirrhosis and delirium tremens.

In a report in the Danish Medical Journal (*Ugeskrift for Læger*) [27] on an international symposium on biological research on alcohol, it is mentioned that Noble (Los Angeles) submitted studies indicating an affect on intellectual function (especially abstract thought and concept formation) at an average intake of one or very few drinks daily.

This account of part of the available literature on the health hazards

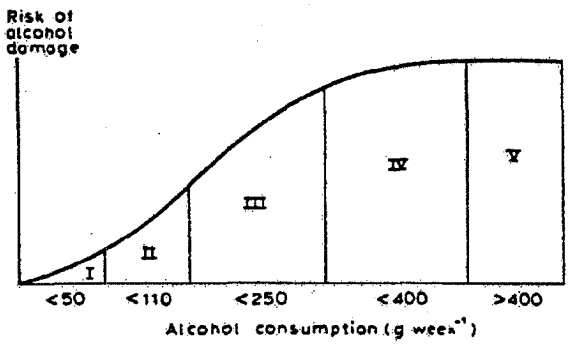

Fig. 1. Risk of alcohol damage as a function of weekly alcohol intake.

associated with alcohol intake clearly demonstrates a problem to which no regard has been paid in the studies reviewed. This discloses a fundamental weakness in these studies. Moreover, it should be pointed out that alcohol has clearly been emphasized as a disturbing (confounding) factor in the Joint Nordic Report of 1975 [28] on response-recording in exposure to solvents.

Another differential diagnostic problem to which sufficient regard does not seem to have been paid is cerebrovascular disease [29]. Every year at least 5000 Danes experience one or more episodes of transient cerebral ischaemia (TCI), episodes defined as having no sequelae more than 24 h after the acute onset of symptoms. On the other hand, investigations comprising CT scanning and neuropsychological testing appear to show that many patients with TCI do have brain damage, manifesting itself as cerebral atrophy and reduced mental capacity. This state has presumably been preceded by many, neurologically "silent" TCI episodes. After apparent complete recovery, the episodes prove to have had serious sequelae, and do pose a differential diagnostic problem in relation to "painters' syndrome".

The problem of dementias, which may occur before the age of 65 (presenile dementias), has also not been satisfactorily clarified. Dementia of the Alzheimer type may appear as early as 45 years of age, as may vascular or multiinfarct dementia, both of which are progressive; this is in contrast to presenile dementia related to organic solvents, which is not believed to progress after cessation of exposure [30]. However, the follow-up period in the study, which suggested the disease was non-progressive, was only about 2 years, which must be considered too brief.

With regard to the two most important objective examinations for dementia, psychological tests and CT scanning, it should be recognized that psychological testing is considered the quickest aid in diagnosing dementia, but it can never be used for differential diagnostic purposes.

psychological testing

In addition, it is markedly affected by the attitude of the examiner as well as of the subject, the extent to which each is aware of the problem concerned, and the examiner's technique and experience. Therefore, it must be a condition in studies attempting to elucidate a possible relationship between exposure to organic solvents and presenile dementia that the examiner performs the psychological tests blindly on subjects as well as controls.

Computer tomography scanning also, cannot be used for differential diagnostic purposes. In fact, its value in judging the degree of loss of intellectual function is in doubt in the presence of alcoholic damage to cerebral function [22]. In those studies reviewed, in which CT scanning had been used, the authors did not elucidate its value in the diagnosis of intellectual deficiencies. The assessment of CT scanning results should also be performed blindly on subjects as well as controls.

A number of the studies reviewed were retrospective epidemiological investigations based upon questionnaires. The questionnaires were designed on the pattern of the so-called "Örebro form", worked out at a Scandinavian joint meeting in 1975 [28]. The questions are extremely vague so that they can be answered in the affirmative both by unaffected persons and by those suffering from various diseases or those having been exposed to substances other than organic solvents. Diagnostic importance was attached to an excess of positive answers in the study groups compared with the control groups. This must be criticized, since there could have been a great degree of bias due to the pre-existing knowledge among painters of the possible hazardous effects of organic solvents, arising from the wide public discussion about the poisonous effect of solvents.

A particularly marked defect of the questionnaire studies was the failure to supplement them with a history and physical examination. In the only study in which this is claimed to have been done, no data were supplied concerning the history and objective findings of each individual subject [15]. On epidemiological studies in general, it is evident that they can never prove a causal relationship, and that most statistical correlations have proved to be incidental.

The statistical analyses in two of the papers were sent to a statistical expert for further evaluation (see appendices). One of the analyses [8] was, despite the quality of the statistical method, not sufficiently profound to be of any value in clarifying the problem of occupationally induced encephalopathy resulting from exposure to organic solvents. To this must be added the deficiencies of this study mentioned previously.

The analysis in the other study [13] was to a great extent incorrect and unacceptable from the statistical point of view.

In studies which did use psychological tests as well as neuroradiological methods to examine subjects, and in which age and presumed duration of exposure were stated, no information was provided about the mutual correlation of the findings. Information on the degree of correlation would

have contributed considerably to the examination of the hypothesis concerning the role of organic solvents in chronic encephalopathy.

If quantitative aspects of the relationship between exposure to organic solvents and induction of chronic encephalopathy are to be examined further investigations are essential. In such prospective studies there must be sound knowledge of the nature of the exposure, the concentration and the period of exposure to the organic solvents concerned, the hygienic conditions and the extent to which personal protective measures were used. The subjects' health status must be accurately known, including their habits, especially as regards alcohol. In addition, a considerable effort must be made to examine the possible differential diagnoses of the cerebrovascular disorders.

It must be emphasized that the *widespread* occurrence of the painters' syndrome in the form of presenile dementia is subject to much doubt. There has been no proof of its existence, and the indications for it are very slender indeed. In future investigations a considerably higher scientific standard must be demanded, based upon:

(1) Relevant and well-defined control groups. Control and test subjects must be examined blind.

(2) The questionnaires must be clearly formulated to obtain unambiguous answers.

(3) Answers indicating disease or minor complaints of possible occupational origin must be supported by a medical history.

(4) The symptoms determined by items (2) and (3) must be confirmed by relevant investigations.

(5) All alternative, non-occupational causes of the symptoms and signs must be ruled out with certainty.

(6) The nature, concentration and duration of occupational exposure must be well authenticated.

(7) Rules and regulations for performing the work and the use of protective measures must have been observed.

(8) A professional statistician must be involved in planning the intended investigations and in the statistical analysis of the results.

Only if items (1)—(6) have been fulfilled, and if the worker has fulfilled his part of item (7), is it permissible to conclude that a person has developed an occupational disease through no fault of his own.

APPENDIX I

Svend Sabroe and Jørn Olsen: "Changes of Mental Function in Solvent-exposed Cabinet Makers" [8]

This study appears to be sound, and I have no criticism to make on the experimental design. The stratification by age seems to have succeeded quite well, even after drop-out. Indeed, the drop-out is small and will hardly give

rise to problems. With regard to questions in Table IV, it is necessary to pay attention to the problem that the subjects interviewed may have known or have been suspicious that they were participating in a study. It is striking:

(1) That the differences between the lacquer workers and non-lacquer workers are small in most respects. I have carried out calculations on the question "do you suffer from dizziness?". Here, the deviations are rather small (though systematic) considering the number of persons involved.

(2) All differences are "in the right direction", and it seems a bit suspicious that the tendency is so uniform. This may be due to a "participation" effect.

Questions of the type shown in Table IV can be analyzed in more detail by a so-called latent structural analysis, but this is a new technique, so perhaps it could be done later.

I am not particularly enthusiastic about the last section dealing with correlations. Correlations have a tendency to blur facts which would otherwise have easily been detected; and, incidentally, they are indeed small (none exceeding 0.15!). Also, there are more modern methods for dealing with the lacquer index and the symptom index.

Conclusion

All considered, a good study using relevant, but not quite up-to-date statistical methods. In my opinion, the major problem is that the questions may not have been answered on the basis of the actual circumstances, there may have been a lurking suspicion that questions were being asked because of having worked with lacquer.

APPENDIX II

Sigurd Mikkelsen: "Dementia and Organic Solvents" [13]

This study consists of two parts. Part I is an analysis of a cohort of painters and a cohort of bricklayers studied throughout the period 1971—1975. These two cohorts were compared with a group of men over 30 years of age in the municipalities of Copenhagen and Frederiksberg and in the County of Copenhagen. Any increase in the incidence of dementia was evaluated by calculating the relative risk of becoming disablement pensioners because of dementia for painters compared with bricklayers and men from the Copenhagen area. The fact that it is a cohort study is utilized by calculating the expected number in the two control groups on the basis of the same risk period as that applying to the painters. Thereby, the risk of becoming a disablement pensioner is correctly related to the number of painters working at any time. This method is relatively new, but yet, even now, a standard in socio-medical longitudinal studies.

In order to arrive at the risk calculations, Mikkelsen had to perform a large number of calculations of his data, evidently including a reclassification

of diagnoses. A number of these manipulations are poorly described in the text, and in several cases it is difficult to follow, let alone check, the data of the layouts. As there is no question of actually setting up a statistical model and testing, but rather a descriptive statistical study, in which the relative risk (RR_i) is used as a tool, this part of the paper gives an opportunity to comment only on the logistic regressions on p. 48 on which the age dependence of the RR_i is investigated. The analysis is badly described and the calculations cannot be checked. Thus, it is difficult to see against what the model

$$RR_i = RR_0 k^i$$

is being tested. However, a remark on p. 44 indicates that the testing is against the model

$$RR_i = RR$$

i.e. a situation without age influence. The conclusions of the four analyses are not very clearly formulated. In particular, there is no comment on the lack of statistical significance where the painters are compared with bricklayers, *without any statement of the cause*. In addition, it would seem that the enormous differences between the parameters *with* and *without* statement of cause might have called for a word or two.

Part II of the study is a case-control study carried out to evaluate whether other factors distinguish painters from bricklayers, to establish if the increased risk of disablement pension due to presenile dementia might possibly be attributable to these factors. The method used was to match 42 painters with 42 bricklayers and then let two teams of physicians evaluate whether two members of a pair differ with respect to variables ranging from total alcohol consumption to premorbid intelligence. The total material from this part of the study is presented in a large table on p. 73. Skimming the page, the conclusion is immediately seen:

(1) Apart from the "degree of dementia" the two teams of referees were almost agreed.

(2) As to the majority of variables the two teams of referees were also agreed that no difference could be found.

(3) As to the "degree of dementia" the referees were very far from agreeing.

These evident features of the material are not apparent from Mikkelsen's comments.

The values are collected in a table (p. 74), showing only the marginal values for "painter more" or "control more". This table suffers from several errors. Among other things, the last two lines concerning referees A should be (16, 18) and (17, 14). In addition to which, the statistical tests based upon G^2 are used incorrectly. A mean cannot be formed in numerical tables, as is done for "alcohol" and "head trauma". Therefore, the correct, approximately χ^2-distributed magnitude becomes almost twice that shown. In view of these numerous errors, I have desisted from a more

detailed evaluation. However, after the corrections that I can arrive at on the basis of Table 3.6, it is apparent that the conclusion concerning "agreement A x B" is wrong, and that where there are differences between "painter more" and "control more" this difference concerns almost exclusively the variable "head trauma".

There is also a lack of a more detailed formulation of the hypothesis being tested, with reference to the way the figures are set up in Table 3.6. The way the analysis is performed, it is conditional on the number of cases in which A and B did *not* make the statement "no difference". But this statement does support the hypothesis, and therefore the values should not be excluded from the analysis.

In Section 3.3.3 of the paper, a logistic regression analysis is carried out to elucidate whether the "odds for being a painter" is related to five "confounding" variables. (One cannot but wonder whether this sort of language is comprehensible except to those closely initiated.) Again, I shall desist from a more detailed evaluation, because the text raises a number of questions concerning the data and methods used which cannot be clarified even by close reading. For example, it is not clear which values z_i has. On p. 75 one is given the impression that z_i is 1 or 0, but to what do 1 and 0 correspond? On p. 71 one receives the definite impression that z_i stands for the values -1.0 and $+1$. Furthermore, the statements on the two hypotheses at the bottom of p. 75 are pure nonsense. An alternative hypothesis cannot be tested *under* a null hypothesis, but a null hypothesis can be tested *against* an alternative hypothesis. The statement $k = \mathrm{MLE}(k)$ is also an estimation statement and not the definition of an alternative hypothesis. It applies, in general, to the use of statistical methods in the study, in that it employs statistical methods from epidemiology and social medicine, but without any kind of profound statistical insight. Items on which actual tests or adaptations to a model have been performed are badly described, without obtaining a satisfactory conclusion from the analyses. In the case of one item, where the calculations can be checked, there are quite a number of errors.

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