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the health experience of workers in the petroleum manufacturing and distribution industry

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ABSTRACT

A review over one hundred papers on the health effects of workers engaged in the manufacture and distribution of gasoline revealed inconsistent results. This may, in part, be due to the variable quality of the epidemiological studies. There is, however, the consistent finding of a deficit for "all causes mortality" and for "all cancers mortality", thus implying that a widespread serious health effect of gasoline exposure seems remote. The evidence for a link between occupation and health effects is weak; however, the possibility exists that occupational aetiological factors may play a part in the pathogenesis of brain cancer and renal disease. Further work of better quality is necessary to investigate those diseases where there remains a suspicion of an occupational aetiology.

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1. INTRODUCTION

As part of its continuing assessments of health aspects related to European petroleum industry activities, CONCAWE's Health Management Group considered that, in view of growing interest in the possible health effects of exposure to gasoline, it would be valuable to review published epidemiological studies on the health experience of workers involved in the manufacture and distribution of gasoline. 105 published papers which appeared to be relevant were identified and have been reviewed by an independent epidemiologist, Professor J.M. Harrington of the Institute of Occupational Health, University of Birmingham, U.K. Many of the papers covered workers involved in manufacture and distribution of other petroleum products in addition to gasoline. Therefore, Professor Harrington's review, which is presented in this report, is entitled "The Health Experience of Workers in the Petroleum Manufacturing and Distribution Industry: A Review of Published Epidemiological Studies".

2. SCOPE AND PURPOSE OF THE REVIEW

During the past half century, industrialised societies have come to depend heavily on petroleum and petroleum products. This fossil-based resource is not only of crucial importance as the fuel for the internal combustion engine, but also as the starting point for the manufacture of an enormous range of organic chemicals considered essential to modern life. Many national economies depend upon petroleum or its products for survival either as a crucial export commodity or as an essential import to maintain technological progress or both.

The industrial processes of extracting, refining, "cracking" and distributing this fossil fuel are thus common activities in some combination or other for many countries. The numbers of workers who may have occupational exposure to petroleum or petroleum products is thus extremely large. It follows, therefore, that any serious health effects resulting from such exposures would have considerable economic as well as medical implications.

The purpose of this report is to review the human health effects of exposure to gasoline, one of the most important materials in the petroleum industry. Whilst the acute effects of gasoline exposure - such as mucous membrane irritation, dermatitis and central nervous system depression - have been known for many years, the more chronic effects of occupational exposure have only been addressed in recent years. Indeed, it was possible in 1977 for the US National Institute of Occupational Safety and Health (NIOSH) to state the "existence of chronic poisoning (from gasoline) has not been established" (1).

A similar statement could not be made today, though neither could the opposite. What has happened in the intervening years is that there has been a spate of publications about the health hazards of working in petroleum refining plants with a lesser emphasis on distributing and retailing the product. Claim and counterclaim regarding these health effects have followed such that today there is considerable confusion not only over the issues of the existence of the health effects but also over the methods used to establish these effects. Most of the studies have been epidemiological to some extent or other, and many contradict each other.

This review has limited its scope to human health effects and, in the main, to studies of populations of exposed workers. The starting point for the exercise was to obtain a comprehensive line listing of all publications in the clinical, toxicological and epidemiological literature where the health effects of occupational exposure to gasoline were apparently addressed. Using this list, a medical subgroup of CONCAWE, in consultation with the author, drew up a list of over 100 references which seemed, a priori, to fulfil the criteria for inclusion in the review. Special emphasis was placed on papers describing the mortality and morbidity experience

of workers in the petrochemical/refinery/distribution areas, whilst another group of particular relevance were those papers which implicated gasoline through population-based case referent studies identifying "at risk" occupations. All but a handful of papers were traced and, where the original language was not English, full translation of the paper was obtained.

One hundred and five papers constituted the final batch for review, not counting other references of a more general nature. Virtually all the papers cited were published in the last ten years and most of these since 1980. The review contains papers published and available to the author up to and including February, 1986.

The review is divided into several sections. After an initial discussion of previous reviews, all of a more limited scope that the present one, a short account is given of the inherent limitations of the epidemiological method. This is followed by an assessment of the studies which addressed malignant and non-malignant disease effects of occupational exposure to gasoline. The report ends with some conclusions.

3. PREVIOUS REVIEWS

The literature search did not reveal any reviews with a similar brief to the present one. The broadest one extant is a World Health Organisation publication in the Environmental Health Criteria series (2). Selected petroleum products were assessed though the account is marred by the lack of any serious attempt to review critically the papers cited. Furthermore, the report concentrates on general population effects rather than occupational exposures. The conclusion is that the health risks to humans from petroleum products is low. Skin cancer from crude oils and bitumen products are noted as well as the risks of neuropathy and leukaemia from n-hexane and benzene respectively. Oil mist is cited as a possible lung carcinogen and the possibility of reproductive disorders from "petroleum solvents" is mentioned.

The most extensive review of cancer risks to oil refinery workers is that of Savitz and Moure (3). They reviewed eight industry based and six general population surveys, all but one of which were North American. Whilst recognising that the amount of epidemiological information on these populations has burgeoned in recent years, there had been relatively little increase in the firm conclusions that could be drawn from the literature up to 1983. They concluded that methodological shortcomings may be responsible for some of the contradictions in the results published, but felt that overall, refinery populations did not seem to experience any "substantial elevations" in cancer risks. What remained unresolved was whether smaller sections of the workforce experienced elevations in certain cancers - particularly melanoma, brain, stomach, kidney and pancreas.

In the same year, 1984, Enterline and Viren specifically addressed the epidemiological evidence for an association between gasoline and kidney cancer (4). They concluded that there was little support for an aetiological link in the 12 cohort, 3 case referent and 3 ecological studies included in their review. The weakest evidence was from the ecological surveys, but even the cohort studies were not consistent enough in either results or statistical power to enable them to propose an arguable case for linking gasoline exposure to kidney cancer.

Similar conclusions had been reached at a workshop devoted to the renal effects of gasoline a year earlier (5, 6). Cigarette smoking did seem to be aetiologically linked to kidney cancer, but occupational factors were not established. At the same workshop, evidence was cited for the ability of hydrocarbons to cause toxic nephropathy - particularly in animals (7) - but the evidence for human glomerulonephritis being caused by hydrocarbon exposure was conflicting (8). In large measure this conclusion may arise from the methodological shortcomings in the human studies preventing any rational consensus on the published material (9). The whole question of the non malignant renal effects of gasoline is discussed further in Section 5.2.5.

The only other review of potential relevance was a general account of the shale oil industry in the United States (10). Apart from citing the longstanding link between such oil and skin cancer, the study noted that a cohort of shale oil workers was to be followed prospectively. No follow up reports of this proposal have been traced since the initial account in 1979.

In summary, no attempt appears to have been made to review the full range of potential human health effects from occupational exposure to gasoline. The cancer risks to refinery workers were well reviewed up to 1983, but otherwise the literature contains few review references of note other than those restricted to the questions of renal disease.

4. THE LIMITATIONS OF THE EPIDEMIOLOGICAL METHOD

Before assessing the epidemiological literature relevant to the gasoline exposed workforce, it is perhaps germane to consider the epidemiological method itself. For many occupational health specialists, epidemiology is viewed either as a complex science, the secrets of which are known only to a few academic cogniscenti, or it is seen as common sense made complicated. Neither of these extreme views can be justified, but the epidemiological method does have its shortcomings, and these must be understood if any review of the literature using this method is to make sense.

Epidemiology has three primary objectives:

- to describe disease patterns in human populations
- to identify aetiological factors leading to those diseases and
- to provide information necessary for the treatment, control and ultimately the prevention of the disease under study (11).

The diseases studied are usually defined reasonably well : the simplest and least controversial end point being the diagnosis at death. Such studies are clearly restricted to fatal diseases, but for most occupational cancers, this is satisfactory. Morbidity raises additional problems of diagnostic accuracy, but broadens the scope of diseases that can be investigated. Much more problematic are the details of occupational exposure. This half of the exposure-effect equation is inadequate in most retrospective studies and that includes most of the studies cited in this review. Much as one would value having accurate job exposure records, these do not exist for inclusion in the analysis of historically based workforce groupings.

So far as types of studies are concerned, two dominate the epidemiological scene:

- the cohort (or follow up) study and
- the case referent (or case control) study.

In the cohort study, a group of individuals is identified through available job histories, either from plant records or union records, and this cohort is followed to an identifiable outcome - frequently death. Comparisons can then be made of health outcome with exposure category. In a case referent study, cases of the disease of interest are identified (usually from a general population base) and details are then sought of past occupational exposures. These exposures are compared with similar information gleaned from a comparative enquiry of referents who, though not suffering from the disease of interest, do have comparable characteristics to the cases for such items as age, sex, ethnic origin, socio-economic status and residence.

Mortality studies dominate the cohort type of investigation and are prominent, but not pre-eminent, in the case referent type of study. Some countries such as the United Kingdom, the United States and those in Scandinavia have excellent vital statistical records with ready access for the bona fide researcher. Thus mortality studies using national statistical data can be undertaken relatively easily. Such national statistics have been of considerable importance in occupational epidemiology (12). Nevertheless, occupational mortality studies do have limitations. In particular, the commonly used index, the Standardised Mortality Ratio (SMR) has statistical limitations when comparisons to the general population reveal the so called "healthy worker effect". This is, in fact, evidence of a comparison bias as the national population is not strictly comparable to the inherently healthier working population. Furthermore cause of death is not always as accurately recorded as one might wish whilst the occupation cited on the death certificate is usually the last one and, therefore not necessarily the longest one nor the one of greatest relevance to the study (13).

Another approach to occupational epidemiology is to use registers of workers such as professional groupings, industry records, cancer registries, census data and exposure registers. Such register-based studies form an important and growing resource for the investigations of work-related diseases. The quality of national data is increasing but the denominator/numerator mismatch continues to act as an important bar to validity. The validity question is particularly important as far as exposure data are concerned (14).

Indeed, it is exposure data which are particularly deficient in the studies reviewed here. Such shortcomings may be recognised by the authors or may be highlighted in correspondence provoked by the results and the conclusions put on those results by the researchers (2, 6, 15). In addition, the populations selected for study may not always allow any real assessment to be made of exposures, for example, the use of union records rather than employment records. Even with the latter, however, detailed accurate job histories are often lacking.

The failure to establish a population at risk precludes the use of the SMR. Thus, researchers resort to some form of proportionate mortality assessment which is much less accurate, as no assessment can be made of absolute risk (16, 17, 18, 19). Competing risks may need to be considered in SMR studies too, but this is a new concept, not only not accepted as standard practice, but also not applied in most of the studies referred to in this review (20).

Additional methodological flaws include the accuracy of the diagnoses used in the study - a special problem at some sites such as the brain (21), the control of factors which can influence both the exposure and the health outcome - so called "confounders" (3, 15, 19, 22) and the eligibility for inclusion in the study in the first place. Here allusion has already been made to validity of

membership of the group (union, factory record, etc) but an additional problem is the length of exposure before inclusion in the study population and the length of follow up from the first exposure. Table 1 for example, illustrates this variation from "ever employed" through to one year minimum with follow up periods varying from 1 year to 40 years. The shorter the accepted exposure time and the shorter the follow up period, the more likely it is that the exposure will be less hazardous or those exposures will have less time to produce their effects. All this combines to produce a dilution of any real health effect that might be present, thus diminishing the chance of demonstrating that effect. This, in turn, means that the power of the study is limited.

One further aspect of the epidemiological method is work noting. Epidemiology can never prove causation. It can, and does strengthen the belief that an association could be causative. The factors of particular importance in making that assertion of causation are the strength of the effect described, the corroborative evidence of several studies (preferably using different methods or population bases), the specificity of the disease to the exposure, and any evidence of a dose-outcome relationship. Other factors may be included depending on the exposure-effect characteristics of interest, but those cited above are of fundamental importance (23).

5. HEALTH EFFECTS

As outlined in Section 2, it is really only in the past decade that attention has been focussed on the chronic health effects of gasoline exposure. The acute effects were well known in earlier times, but apart from a few cohort studies in the late 1970s, it was the emergence of a possible brain cancer or leukaemia risk in oil refinery workers in the early 1980s that produced the stimulus for the current interest in the subject.

Gasoline is an organic solvent and thus might be expected, a priori, to exert any toxicological effects on target organs such as the liver, kidney, as well as central and peripheral nervous systems. Particular interest has focussed on the possibility of chronic non-malignant brain damage from organic solvents (24, 25), but such effects do not figure prominently in a review of occupationally exposed groups where epidemiological evidence rests heavily on a fatal outcome or on large scale population studies.

In this context, most of the literature for review concerns malignant disease and most of this comes from cohort studies. Assessing evidence of carcinogenicity from such a data base is acceptable as the International Agency for Research on Cancer (IARC) rates highly such analytical studies as cohort and case referent studies in their evaluations (26). Lesser credence is given to descriptive (ecological) studies where the incidence of cancer in human populations is found to vary spatially or temporally with exposure to the agent in question. Case reports and non-human in vivo and in vitro studies are given even less weight. These latter publications do not figure in the present review.

The rest of Section 5 is divided into malignant and non-malignant health effects with the former effects being considered under epidemiological study types.

5.1 MALIGNANT DISEASES

5.1.1 Cohort Studies

Twenty-five publications are considered under this heading (22, 27-50), though these studies do not relate to 25 different populations (Table 1). There are series of papers from groups of authors reporting studies. with updates, based on the same populations. For example, there are series of papers from Thomas, Waxweiler and co-workers on the cohort of Oil, Chemical and Atomic Workers Union members (OCAW) (38, 39, 40, 42, 47); as well as the Gulf Oil studies of Wen, Tsai and co-workers (30, 32, 43, 45); and the British studies of Rushton and Alderson on oil refinery workers (39, 44). Other studies are included of refineries in the United

States and Canada for which only one or two reports have been published. There is also an early report from a newly established cohort of Australian petro-chemical workers (31). Oil refinery worker studies predominate throughout.

The size of the study populations varied markedly from 454 (33) to 55,007 (46). A more appropriate index of power is, however, the person years at risk, ranging from 5,900 (33) to 575,982 (39). This reflects the great range of observation time 4 years (31) to 49 years (49) and of latency-induction from 1 year to 49 years. Not surprisingly, the number of deaths analysed in the studies also varies greatly from 33 (31) to 4406 (44). All the studies except that of Schottenfeld and Warshauer (46) relied on death certificate diagnoses with all the problems of diagnostic inaccuracy that can arise depending on age at death, site of tumour, type of tumour and place of death certification.

Most of the studies used national mortality rates for their comparison, but a few attempted to diminish such inherent bias by using local death rates (22), county death rates (40) or provincial rates (49). The incidence study cited above (46) used S.E.E.R. (Surveillance, Epidemiology and End Results Program) data for comparison whilst the Hanis study of Imperial Oil (Canada) was the only one to use internal oil company comparisons (48).

The statistical measures used were the SMR or the SIR (Standard Incidence Ratio) with the exception of the series of papers on OCAW members. The authors of these union based group of studies were forced to use the less accurate proportionate mortality ratio (PMR) though they attempted to refine this cruder index with some internal standardisation when considering specific cancers vis-a-vis all cancers. Nevertheless, the inherent weaknesses of the PMR must be borne in mind when considering the statistical significant excesses for a number of cancer sites found in the OCAW series.

More seriously, many investigators ignored the latency-induction period when analysing their data - a biological nonsense when many of the study population members had been followed for less than 20 years. This flaw is compounded by the almost total lack of consideration given to confounding factors and effect modifiers in assessing the likely cause of any excess cancer risk found. To present no data on smoking history, nor any exposure information on other potential cancer risk factors makes it difficult to assert that any association found between occupation and cancer excess can only be due to the occupation. Moreover, it is rare in the studies cited to show more than the vaguest attempt to define what is meant by "exposure". In most studies, the exposed workers will have faced many chemical and physical hazards in the course of their working life. Such lack of detailed exposure information precludes any rational statement regarding cancer causation and gasoline exposure.

The study populations are, by and large, white, male and North American. Some authors attempt to distinguish between hourly paid and salaried employees, but most rely on job histories usually as defined in the payroll records. The inclusion or otherwise of retirees can markedly alter the ascertainment rates and effect and outcome. The exclusion (or loss to follow up) of the workers who left the industry will be likely to diminish the cancer risk whilst the inclusion of everyone under the rubric "all workers" will dilute the truly exposed worker with those with little or no exposure. Nevertheless, some large studies had ascertainment rates of 99.8% (39) whilst others had more than half of the study population followed for at least 25 years (22).

When all these shortcomings are considered, some studies still stand out as being relatively powerful in statistical terms. Of particular note are the studies of Wen and his co-workers on the Gulf Oil Refinery populations and those of Rushton and Alderson on the refinery workers in the United Kingdom. Similar good study design applies to the study by Nelson (22) though the number of deaths is relatively small. The OCAW studies are most difficult to evaluate not only because of their population base but also because these studies are the ones with the greatest reported cancer excesses.

5.1.1.1 All causes

Turning to the result of the studies, the first point that can be made is that there is a consistent all causes mortality deficit ranging from an SMR of 0.43 (45) for a small cohort followed for less than 25 years to a ratio of 1.04 for the "terminated" workers in the Gulf Oil cohort (30). The comparison bias of the healthy worker effect is clearly a factor of note here.

5.1.1.2 All cancers

For the grouping of "all cancers", again the most commonly reported result is a cancer deficit - as low as 0.58 in the small, short follow up investigation of Schottenfeld and Warshauer (46). Statistically significant excesses of 1.19 and 1.17 are found in the OCAW cohort (42, 47) but in only one study employing the SMR method - that of Hanis et al in Canada (48) with an SMR of 1.29. It is particularly noteworthy that the Hanis study was the only one to employ the preferred comparison method of using internal controls. Nevertheless even if a consistent excess of "all cancers" had been found, such a result would be of limited aetiological value, given the heterogeneity of the exposures and the outcomes.

5.1.1.3 Specific cancer sites

Statistically significant cancer excesses are found in some studies. There is one study with such an excess for lung with 1.25 for white employees and 1.40 for blacks (47), one for stomach of 1.52 (42), one for colon of 1.97 (48), one for pancreas of 1.42 (42), one for prostate of 1.38 (42), one for bone of 2.28 (32), two for leukaemia of 2.13 (28) and 1.83 (42), three for brain of 2.28 (40), 2.21 (42) and 6.52 (49) - two from the same population bases; and four for skin cancer of 2.01 (22), 7.88 (38), 2.16 (39) and 1.18 (42). SMRs of 1.27 for non-Hodgkins lymphoma (27), 4.0 for myeloma (28) and 2.24 for nasal cancer (39) are also noted.

In general these excesses are based on relatively small numbers (less than 25 deaths) and are isolated excesses in all the studies except those of Hanis et al (48) with two site excesses and the multiple excesses in the OCAW cohort. If non-statistically significant excesses are also considered, the most noteworthy cancer sites are brain, kidney, leukaemia, Hodgkins disease, pancreas, prostate and colon.

Some studies do attempt to include some assessment of exposure in an effort to address the dose effect relationship. Wong et al (27) found an increasing trend for an excess of lymphohaemopoetic malignancy with increasing length of employment, though the exposure details were merely first and last job at the refinery. McCraw, Joiner and Cole's study (28) of one refinery in Illinois found an excess of acute myloid leukaemia of 8 observed, 2 expected, though the most likely aetiological agent in an ill defined exposure analysis is benzene. One of Wen's papers specifically addressed benzene exposure with some actual environmental measures. The study only had 34 deaths and no cases of leukaemia. The one cancer incidence study (46) analysed 307 cancers in 118,566 person years of risk. Acute and chronic lymphocytic leukaemia (SIR 274), multiple myeloma (SIR 552) and cutaneous melanoma (SIR 278) were all statistically significantly elevated. The leukaemia excesses were in refinery workers, but comprised only 7 cases. The authors cautioned, however, that the study period was short and the number of older workers was few. More noteworthy, perhaps, is the fact that only retired workers with annuities were included from the total group who had left employment.

Nelson (22) reports the only study with some smoking history data with, at one refinery, some evidence of a dose response relationship for gastro-intestinal cancer and exposure to "light aromatics". The study has, however, only 9.1% of the population classified as dead at the end of the study period, though the power of the study is deemed satisfactory to detect a two-fold excess if present.

The brain tumour excess noted in the OCAW studies in Texas refineries is not seen in the Wen et al studies of the Gulf Oil Texas refineries. The Wen study is large and powerful and apart

from the bone cancer excess is unremarkable so far as cancer risks are concerned. In a review of their results compared with the OCAW studies, Wen et al (51) denied a dilution of their exposed population by white collar workers. An analysis of their brain cancer cases revealed no latency effect and no real difference in SMR when all cancers are compared with brain cancer (There is, however, an SMR for 1.44 non-white brain cancers based on five cases). The power of the study is, however, relatively high and should be capable of detecting an SMR of 1.75.

Rushton and Alderson's studies of oil distribution centres (35), oil refineries (39) and bus garages (34) provide large scale, well designed non-American investigations. The authors, however, caution against reading too much into a few statistically significant results given the multiple comparisons analysed and the small number of deaths in most cells. They also felt that the follow up was too short and the exposure information inadequate. They looked specifically at their 36 brain cancer deaths, but found no evidence of an occupationally related excess.

Austin and Schnatter (36) did find a trend of exposure with brain cancer excess in the Union Carbide population, but they rightly point out that this excess was the stimulus for the study. The authors are thus aware of the potential pitfalls in using hypothesis generating data as part of an hypothesis testing exercise.

Whilst there is no doubt that benzene is a human carcinogen, other aetiological factors for other malignancies are not obviously forthcoming in the refinery environment. Similarly, known skin carcinogens could be present in the oil workers skin contact experience. For the other tumours, often inconsistently cited, only genito-urinary and brain cancers were worth noting further. The former is discussed in greater detail in Section 5.1.3, but for brain cancer there does seem to be some suggestion from the cohort studies of a link with refinery exposure. Unfortunately, the greatest excesses come from the methodologically weakest studies.

5.1.2 Case Referent Studies

Seventeen case referent studies are considered in this section (52-56, 59-69, 71), but three other studies could be mentioned. Two of them (57. 58) are not listed in Table 2 because reference 57 is identical to reference 56 in its data base and data analysis, whilst 58 is an earlier incomplete report. Reference 70 is an earlier account of the data base described in reference 69.

The population bases are, again, mainly from the United States and include populations such as the OCAW membership in Texas (55), the Union Carbide plant in Texas City (60), and the 8 U.K. refineries 64) described in the Section 5.1.1. Other studies gleaned their cases from cities, States and even a country (Denmark), so the distinction between this type of study and the ecological investigations described in Section 5.1.3 is somewhat arbitrary.

The number of cases varied markedly from 21 cases of brain cancer (60) to 3578 cancer deaths in 20 Louisiana parishes (65). Most studies settled on a 1:1 case referent comparison, though 1:2 and 1:3 ratios were not uncommon. Ten of the papers addressed incidence rather than mortality. That is, the cases were diagnosed in life and where possible, interviewed. Mortality studies rely on less accurate diagnostic criteria and if a history of occupational exposure is taken, this has to come by definition from a relative or close friend.

The referent groups were mainly hospital based or population based. The latter is theoretically more satisfactory so far as bias is concerned, but such referents are more difficult to obtain. The matching characteristics varied somewhat, but tended to include age, sex, race, residence and date of death.

Researchers attempted to assess exposure by various manoeuvres - date of first membership of the union (55), payroll status and length of employment (60). Some expended considerable effort in obtaining full occupational and environmental histories from the cases and referents (53, 54, 56, 59, 61, 63, 66, 67, 71), whilst others relied upon the inadequate (for this purpose) occupational data on the death certificate (52, 65, 68, 69).

All studies used the risk ratio (RR) or Odds Ratio (OR) to define comparisons and all except the Thomas et al paper of OCAW workers reported on one cancer site only.

5.1.2.1 Brain cancer

Given the interest focussed on brain cancer in the cohort reports, it is perhaps surprising that so few case referent studies have addressed petro-chemical exposures and cancer at this site. The OCAW study (55) reiterates the report of an excess noted in the cohort analysis though the use of this technique here is superior to the PMR analyses of the cohort. Complete work histories were obtained from the oil companies and 31 brain cancers were matched to 93 dead referents, age, sex, race and refinery matched. Eleven exposure groups were arbitrarily defined. The RR for brain ranged from 0.6 to 2.8 - the latter statistically significant. No consistent work patterns or lengths of exposure could be found to account for the ratios. Diethylsulphate and vinylchloride monomer exposure were suggested as possible aetiological agents in an earlier study of 18 cases (72).

Austin & Schnatter (60) analysed 21 brain cancer deaths which were included in reference 40. Exposures were assessed for five known or suspect human carcinogens from company records, but no biological or statistical significance ensued from the analysis. The numbers are, however, small and the exposure records were poor for most subjects.

Overall, therefore, these case referent studies add little to the information gained from the cohort studies.

5.1.2.2 Stomach cancer

Three cohort studies showed an excess of stomach cancer (27, 35, 39) though the excesses barely exceeded an SMR of 1.0 (22). The one case referent study (55) showed the highest RR for maintenance and lubricating oil processors. Furthermore the ratio increased with length of employment. However, in view of the absence of other important variables such as socio-economic status, this finding alone adds little to a dubious association.

5.1.2.3 Leukaemia

The leukaemia excess in the above reference (55) is not statistically significant and same is true of Rushton's and Alderson's review of 36 cases in relation to benzene exposure in UK oil refiners (64). The benzene exposure data are poor and death certificates are probably an inadequate way to assess leukaemia and its sub-types. There was no evidence of a link between the disease and length of service.

5.1.2.4 Bladder cancer

Five case referent studies considered bladder cancer (52, 56, 63, 67, 71). Baxter and McDowell's study (52) had 1080 cases selected from London Boroughs with a high district mortality compared with the UK population base. The comparison with adequately selected controls showed statistically significant results for drivers of trucks and vans. This excess barely reached an RR of 2.0 and did not account for the boroughs' excess. A higher level of RR (2.7) was found in a review of 212 bladder cases in rural Denmark (53). Although a small attributable risk was found for smoking (a known associated factor), the link with "oil/gasoline" exposure allows little progress to be made on the aetiology of bladder cancer.

Seventy-five New Jersey cases lead to an RR of 2.5 for petroleum exposure (67). Double this excess was noted in 632 cases of bladder cancer from three Canadian provinces (67) though a careful study by Cole et al (71) in Eastern Massachusetts noted an RR of 1.0 for petroleum products.

Overall, the case against gasoline - or even the petroleum industry - as a bladder carcinogen is not proven.

5.1.2.5 Kidney cancer

The studies by McLaughlin (54, 59, 62) dominate this cancer site. 506 incident cases of renal cancer were carefully matched with 714 population based referents. The cases and referents were interviewed blind and the only statistically significant association was for cigarette smoking. The chemical-petroleum industry odds ratio was 1.4 on 9 cases (62) and 1.0 on 37 cases (54), though a trend for length of employment was found. A similar non-positive result was found in a study of 92 incident cases in Buffalo, New York (53).

The subject of kidney cancer and gasoline exposure was extensively reviewed in 1983 at a workshop (5, 6, 73). The chairman, in his summing up noted that most studies (case referent and cohort) showed a "null effect" (15) but the problems of crude exposure indices, study objectives different from this possibly chance finding, multiple comparisons, and the absence of any control for confounding all militated against a firm conclusion. Raabe (6) went further and used Hill's criteria for association-causation (23). None stood such rigorous testing. Similar conclusions were noted by Enterline and Viren (4).

5.1.2.6 Liver cancer

Two hundred and sixty-five biopsy proven decedent and incident cases from New Jersey were compared with 530 referents for job history (61). A relative risk of 4.2 was found for gasoline service station staff. Nevertheless, the high proportion of deaths among the cases, the small number of biopsy proven cases (compared with the initial planned sample of 959), the exposure criteria of six months or more, response bias and non-blind interviews leave much to be desired methodologically. At present, this report of an excess stands alone in the literature.

5.1.2.7 Pancreatic cancer

Two studies looked at pancreatic cancer. One was of 876 cases in 19 Louisiana parishes (68), the other of 109 cases from 115 hospitals across the United States (66). The former relied on occupation on the death certificate for exposure data, the latter on interviews. An odds ratio of 2.11 on 15 cases was found in the Louisiana study for oil refinery work, whereas in the multi-centre study, the RR ranged from 1.69 for less than 2 years work to 5.70 for more than 10 years work with "gasoline or dry cleaning industries".

Neither study advances knowledge on any aetiological hypotheses for gasoline exposure and pancreatic cancer.

5.1.2.8 Lung cancer

Three studies by Gottlieb and his co-workers (65, 79, 70) in Louisiana suggest a twofold excess of lung cancer in oil field workers or welders or petroleum industry employees. Such a result is difficult to equate with the results from the cohort studies which show an overwhelming majority of well planned studies with a lung cancer deficit. Indeed, the deficit is usually statistically significantly low. One positive case referent study cannot be equated with such a large weight of opinion in the opposite direction from what is, arguably, the preferred epidemiology method.

Overall, the results of cancer studies using the case referent approach are not striking; neither do they show particularly consistent results nor do they necessarily have a trend in the same direction as the cohort studies. Case referent studies are notoriously prone to bias of one kind or another (74) whether it be the selection of the cases, the controls, the interviews, the recall bias or the statistical power. Most of the studies reviewed here suffered from some, or even all, of these flaws.

5.1.3 Ecological studies

Ecological studies are the weakest of the epidemiological studies in methodological terms and thus in their power to test hypotheses. Hypotheses may be generated but little else. Such studies use groups as the unit for analysis. Such groupings can be people living in the same time or space or by characteristics such as race or creed. Several studies in the present review could be thus classified (50, 75-79). The 1967 study of cancer mortality near one large oil refinery is not, by modern standards, worth considering further. Two studies in the San Francisco Bay area contradict each other (77, 79). The study by Heary et al used Kaiser Permanente data on cancer incidence in the Delta area with boundaries which ignored the state county lines. No association with residence was found. Kaldor et al (79) did find an association between proximity to petrochemical installations and in males, cancer of the buccal cavity, pharynx, stomach, respiratory tract, prostate, genito-urinary tract and "all sites". For females, excesses were found for buccal and pharyngeal cancers. It is difficult to decide which is the more reliable study. Both have flaws relating to the authors' differing perceptions of what constitutes a reasonable boundary between different arbitrary levels of pollution, or indeed, even what constitutes a suitable study population. In the presence of more accurate epidemiological studies, perhaps the merits and demerits of these studies matter less.

Certainly the Kaldor study bears a closer resemblance to the cancer mapping undertaken in the 1960s by the US National Cancer Institute. The data used to generate the maps have also served as a starting point to look for associations between cancer incidence rates by county (or state economic area) and industrial

concentrations. For example, comparing the US counties with 0.1-1% and more than 1% of the employees working in the petroleum industry (76), lung cancer excesses are associated with the higher concentration of employees (0.98 to 1.32). In a later study, 39 counties were selected where at least 100 persons were employed in petroleum manufacturing and where these employees constituted more than 1% of the county population (75). Comparison was made with 117 counties of similar geographic region, population size, percentage urban, and other personal demographic features such as educational status and ethnic mix. Twenty-three cancer sites were compared. Statistically significant excesses were found for all cancers (1.06), nasal cancer (1.48), lung (1.15), skin (1.10), testes (1.10), stomach (1.09) and rectum (1.07).

A similar study of multiple myeloma suggested an excess in the West and North Central US (not the highest concentration of oil refineries) with a trend for the petroleum industry groups of 0.055 (for 0.1-1.0% employed) to 0.38 for more than 1% employed (78).

At the time most of these ecological studies were undertaken little information was available on petroleum industry employees. In the absence of any such data they can serve as hypothesis generation exercises. In the presence of succeeding better studies, their results must be considered with considerable circumspection.

5.1.4 Conclusions

The number of epidemiological studies which have investigated the risks of malignant disease in association with the petroleum industry have burgeoned in the past few years. This mass of data has not led to any firm conclusions. However, certain statements can be made with some degree of confidence.

There does not appear to be any evidence that working in the petroleum industry - particularly refining processes - leads to any dramatic excess of cancers in general and most cancer sites in particular. There is some corroborative evidence from the studies cited here that known carcinogens such as benzene and the polynuclear aromatics have resulted in some excess of leukaemia and skin cancer in limited numbers of petroleum industry workers, but these findings are not consistent across even the best designed studies. This may be due to relatively low level exposure in the past. Of the remaining cancer sites where excesses have been reported in one or more studies, the evidence of a link with kidney cancer remains weak with few cohort studies exhibiting an excess and with the best case referent study showing no excess. Interestingly, some studies show a reversal of the normal bladder/kidney dominance for genito-urinary cancers.

For brain cancer, the highest excesses occurred in the studies weakest on methodology. Nevertheless, modest excesses are found in some well planned studies and corroborative evidence linking solvent exposure with brain cancer exists elsewhere in the literature. The excess risk for pancreatic cancer is rarely statistically significant but cannot be easily ignored with 10 cohort studies showing SMRs ranging from 1.08 to 1.38. Such relatively low excesses must be viewed in the light of low SMRs for "all causes" and "all cancers".

However, the pre-eminent message to be drawn from a reading of the epidemiological literature on malignancy and petroleum industries is the methodological flaws. The main concerns must be with the almost uniform poor exposure information, the widespread practice of ignoring latency, the failure to control for confounding, and the relatively low power of many studies. If such shortcomings persist in future publications, it is unlikely that further progress will be made regarding aetiology. Further work, more carefully designed, and larger populations are needed to evaluate the significance, if any, of leukaemia and melanoma, as well as cancers of the renal tract, the brain and the pancreas. The oil refinery and distribution industries cannot be given clean bill of health on these cancer sites at present.

5.2 NON-MALIGNANT DISEASES

It is clearly important to distinguish possible life threatening work-related diseases but the literature sometimes seems to imply that concern is restricted to malignancies. Emotive though cancer may be, attention must also be paid to non-malignant disease patterns. In this section of the review, mortality studies dominate the picture. All the mortality studies of relevance have been cited in the malignancy section, but the patterns for non-malignant disease are summarised in Table 3.

Morbidity studies of recent origin are largely restricted to the Russian literature. These data, with a few exceptions, are inadequate in method and/or reporting to enable any firm conclusions to be drawn.

In order to force some pattern on a pot pourri of papers, the section will be sub-divided by organ systems and in each case mortality and morbidity studies will be discussed under the organ system heading.

As a preamble to this, some space will be devoted to studies undertaken to investigate general sickness absence patterns in the industry.

5.2.1 Sickness Absence and Shift Working

Three Russian papers attempted to describe sickness absence patterns in petrochemical plants in different locations (80-82). A review of 6 years records of "primary disability" in the Omsk petrochemical complex revealed that injuries (24.3%) were proportionately the most important cause. Cardiovascular disease (19.0%) came second. At the Kuibyshev refinery, morbidity was related to workload rather than any toxicological influences (81), whilst in the Ukraine, the absence rates had fallen by 25% in the period 1975 to 1981 (82). The fall was largely attributed to decreases in the incidence of tuberculosis, "rheumatism" and enteric infections. The highest rates were for acute respiratory disease and to a lesser extent from "neuralgia" and "neuritis".

In Singapore, the absence rates at a refinery were lower than in Western Europe, but equivalent to those in the local shipyards. Shift workers experienced the greater morbidity (83). A similar adverse health effect of shift work was noted in an Austrian refinery where the ageing shift workers fared worst of all (84). The dominant causes of absence were psychoneurosis, skin disorders as well as diseases of the gastro-intestinal and cardiovascular systems.

However, none of these recent studies has a superior design nor epidemiological value compared with the virtually unique series of studies from Taylor and his co-workers in the 1970s (85, 86). Taylor's work originated as a study of an oil refinery population in the UK where he postulated thirty possible factors related to absenteeism of which only one related to working conditions and one to medical conditions (86). Not only do none of the papers included in this review cite such studies, they also fail to take these now well established aetiological factors into account when assessing absence form work. Furthermore, few papers address the influence of shift work on morbidity. Taylor's papers reported a relatively high SMR for ex-shift workers of 118.9 compared with 101.5 for current shift workers. In view of the healthy worker effect, Taylor fails to find this comparison bias effect in his studies, suggesting that shift workers might be at higher risk of death than day workers. Overall, however, shift workers morbidity is rather unremarkable except for some excess of gastro-intestinal morbidity. They are a self-selected population and do experience considerable circadian rhythm disruption, but there is little evidence in the world literature of significantly elevated mortality or morbidity in those that can tolerate the privations involved.

5.2.2 Cardiovascular Disease

Cardiovascular disease remains the most important cause of death in Western society. However, the relative importance of these diseases

to petrochemical populations is less than the overall experience for the national population. Table 3 shows that, apart from the PMR studies of OCAW members where a modest excess was noted, all but one of the other studies show deficits (many of them statistically significantly lowered) ranging from 0.54 in one Texas refinery (33) to 1.01 in the Exxon plant in Louisiana (41). Allowing for comparison bias, the most rational conclusion is that refinery workers show no evidence of excess cardiovascular mortality. Where the more specific rubric is ischaemic heart disease is reviewed, a similar mortality deficit is noted - the exception being an SMR of 1.22 in one of the OCAW reports (47).

Four studies in this review address the issue of cardiovascular morbidity (87-90). One study of the Standard Oil plant in Indiana reviewed periodic health examination data on 9,955 white male workers (87). Forty-two per cent of the workers had an excess weight (on the Quetelet index), 15% undertook inadequate exercise, 16.5% were hypertensive (diastolic blood pressure above 90 mm Hg) and 20.3% were current smokers. The authors do not relate this to cardiovascular morbidity nor mortality at the plant. Indeed there is little evidence to suggest that their findings are in any major way different from those that might be found in any working population.

Results from the three Russian studies are hard to interpret. In one, evidence is presented of a rising blood pressure and pulse towards the end of the shift (88). In another, 60% of the worforce are deemed to be "hypertonic" (89) whilst in a review of the Perm City complex, Lebedeva and co-workers found a blood pressure elevation in 14.3% of the 353 workers (90). Such a prevalence of hypertension is in line with the U.S. study but evidence for increased heart size and electrocardiographic changes are difficult to interpret in the absence of any comparison group.

In short, cardiovascular disease mortality and morbidity does not seem to be in excess in workers exposed to gasoline.

5.2.3 Respiratory Disease

Respiratory disease mortality is not as important a cause of death as cardiovascular diseases but disorders of the respiratory tract are one of the commonest causes of morbidity. In the occupational context, the lung is the target organ par excellence as toxic materials in the workplace usually gain entry to the body via an airborne route. Nevertheless, the petrochemical industry is not a predominant cause of occupational lung disorders though the chronic effects of gasoline on the lung are not well documented. One study has been found for the present review which investigates this subject (91). Forty non-smoking subjects were divided into two groups and given gaseous mixtures to inhale for three-hour periods in a cross-over design. The mixtures were air with 50 ppm of carbon monoxide and air with petrol exhaust gas diluted to 50 ppm

of carbon monoxide, but also including 1% of nitrogen oxide and various hydrocarbons. No difference was noted in the respiratory function of the groups dependent upon which mixtures they breathed.

Mortality studies of respiratory disease are remarkable for consistently low SMRs for all respiratory disease as well as the more specific grouping of chronic bronchitis/emphysema (Table 3). The mortality deficits are some of the lowest noted for any disease and the suggested reason is the limited opportunities for smoking that exist on a refinery site. Most studies failed to acquire smoking history data though one study reports this alone (92). The prevalence of smokers seems to between 32.5 and 39.6% for refinery workers which is below the national average.

This limited evidence along with the generally low mortality rates for both malignant and non-malignant respiratory disease suggests that refinery workers smoke less than the average and that this is the major determinant of their favourable respiratory disease outcome rather than any direct beneficial effect of refinery work.

5.2.4 Gastrointestinal Disease

The cancer mortality studies suggested that a possible excess of cancers of the stomach, pancreas and colon might be related in some way to work in petrochemical establishments. The evidence for an occupational link with non-malignant disease is lacking (Table 3). The grouping of all gastro-intestinal disease, as well as peptic ulcer as a specific subgroup shows consistent patterns of mortality deficit.

The large number of organic solvents which exist in the petrochemical complexes, however, raised the possibility of an hepatic effect given the toxicological evidence of liver damage from a large number of hydrocarbons and the citation that "petroleum refiners" are an example of an occupational group with exposure to hepatotoxic chemicals (93).

Although no morbidity studies could be found which investigated this area of occupational hepatotoxicity in refinery workers, there is no evidence for excess mortality from cirrhosis of the liver.

In short, despite the environmental evidence that workers in the oil industry are theoretically exposed to a number of chemicals capable of damaging the liver, no published evidence exists to support these views.

5.2.5 Genito Urinary Disease

Unlike some of the other organ systems described in this section, the genito-urinary system has been the subject of intense interest

in the past few years, with regard to the possibility of gasoline exposures being nephrotoxic. A workshop was convened in 1983 to discuss this issue and allusion was made to this in Section 5.1.2.5. The workshop also reviewed non-malignant renal disease (7, 8). There seems to be some evidence to suggest that certain rodent species - particularly the ageing male rat - is prone to renal disease which can be exacerbated by exposure to organic solvents. Of the mortality studies, Rushton and Alderson's study of 8490 workers at 71 bus garages did have an SMR of 1.57 for "nephritis". The results are based on 6 deaths and the authors do not discuss this finding. The workshop, however, looks more broadly at solvents in general, but Phillips (8) concluded that although 5 of the 6 case control studies found a positive association between solvent exposure and renal disease (defined in many ways), all but one of the studies suffered from serious methodological shortcomings. This view was reiterated by Churchill in his review in the same year (9). More recently, Lauwerys et al (94) have reviewed the literature. They state that while short term exposure to certain solvents such as halogenated hydrocarbons and petroleum distillates may cause tubular necrosis, the epidemiological evidence for repeated exposures leading to chronic glomerulonephritis is not adequately proven. They do, however, feel that the link is "suggestive" but the risk, if it exists, is "not very high".

The present position thus seems to be that the case for linking solvent exposure to renal desease - particularly glomerulonephritis - is not proven. All the extant studies are flawed, many of them seriously. No evidence to support such an aetiological link comes from the mortality studies, and no papers exist in the literature which look specifically at gasoline and kidney disease. A question mark thus hangs over this issue which will not be removed unless the methodological quality of relevant studies is improved.

5.2.6 Neuropsychiatric Disorders

The well recognised acute narcotic effect of organic solvents has recently led various researchers to suggest that a chronic neurasthenic syndrome can follow repeated low doses. Some workers, mainly in Scandinavia, postulate that organic psychoses can ensue from such exposures (24, 25). Population based studies have concentrated on painters, but any corroboration of the Scandinavian studies is not yet forthcoming from the United Kingdom or the United States. One of the problems concerns the diagnostic criteria for a case. This is an issue that has produced conflicting symptoms/sign groupings at two recent international fora (95) and even the diagnostic tests suitable for making these diagnoses are not universally established (96).

So far as populations of oil industry workers are concerned, six papers are relevant here (97-102). The three Russian reports are difficult to interpret largely through the absence of comparison groups and through the failure of the authors to define their

terminology. Of 610 persons examined at one plant, 18% were said to exhibit the "neurasthenic" syndrome - apparently 2-4 times more likely in workers with more than 5 years exposure (97). In another study, the incidence of "chronic poisoning" at a petroleum processing plant had declined overall whilst the syndromes themselves had changed from a "cerebrasthenic" variety to "vegetovascular dystonia" (99). Central nervous system effects of airborne pollutants at another Russian refinery were apparently the cause of 32% of the morbidity (98).

Three Danish studies investigated the specific effects of occupational exposure to jet fuel (100-102). The exposed group of 30 was selected by a committee and matched for age, education, job duration and union activity with a non-exposed group of 30 workers. Reaction times, memory recall, dexterity and perceptual speed tests were all marginally (though statistically significantly) worse in the exposed group (100). This group also had higher ratings for dizziness, headache, nausea, palpitations and fatigue - the neurasthenic syndrome (101). Fourteen of the exposed group were re-examined recently and 7 were pronounced to have "mild organic brain damage" (102).

These studies demonstrate the problems of diagnostic tests and diagnostic labels which still bedevil this area of epidemiological research. Until these matters are resolved, it is unlikely that any firm conclusions can be drawn on whether organic solvents in general, and petroleum derivatives in particular, cause organic brain damage. Certainly suicide does not seem to be a sequela of such central nervous damage if it exists. Only one mortality study showed an excess for suicide (27). This excess was greatest (2.06, not statistically significant) for the laboratory populations at the two refineries, most noticeable in the 10-19 years latency period (1.49 - statistically significant) and after 15 years employment (1.33 - not statistically significant). It is difficult to draw conclusions from this isolated report.

5.2.7 Chromosomal Aberrations

The induction of cancer is thought to proceed in a series of steps. The first step - initiation - is thought to involve DNA damage resulting in heritable modifications in, or rearrangements of, genetic information. Various short term tests have been devised to investigate this phenomenon and one of these is to examine human bone marrow cells for evidence of chromosomal abnormalities. Such tests cannot, in the present state of knowledge, be considered to predict accurately the carcinogenic potential of a given exposure, neither do such tests, if positive, reliably predict the degree of carcinogenic potential (26).

Ideally, the exposure should be assessed by means of a battery of such short term tests. This literature review has identified four papers which looked at chromosomal abnormalities in bone marrow

cells of tank cleaners (103, 104), gasoline tanker drivers (105) and petroleum refinery workers (106). Six out of 15 tank cleaners had chromosomal breaks on chromosomes number 9 (which is apparently a chromosome preferentially engaged in various pre-malignant and malignant disorders) (103). These fifteen cleaners plus an additional cleaner were compared for chromosomal and micronuclei aberrations with 16 controls (6 paper factory workers and 10 bus drivers) (104). Chromosomal aberrations were higher in the cleaners than the controls at 3.5% versus 2.3%, though the authors are unclear about whether to assign this difference to exposure to petrochemicals or heavy metals.

In a study of gasoline tanker drivers, a second group of milk tanker drivers was used as a control to test the hypothesis that benzene not gasoline was the putative causative agent. No statistically significant difference between the two groups was found (105).

Only one study looked at oil refinery workers (106). Eighteen non-exposed workers were compared with cancer patients and 22 petroleum refinery workers for sister chromatid exchange rates (SCE). The frequency of SCE in the cancer patients was high (8 out of 10) in those on treatment but nil in those not on treatment with cytotoxic agents. Ten of the 22 refinery workers had an elevated SCE frequency which was more than two standard deviations greater than the non-exposed group.

Data of this type, with no other corroborative in vitro tests carried out on small groups of workers exposed to a variety of chemicals, matched in some ill defined way to referent groups, cannot be taken as incontrovertible evidence of a mutagenic effect. Further work would certainly be justified on the basis of these papers, but no conclusions can be drawn thus far.

5.2.8 Reproductive Disorders

The number of studies on the epidemiology of reproductive outcome has increased markedly in recent years. Such work stems from observations of reproductive toxicity in animal testing as well as some well publicised occupational studies such as those associated with dibromochloropropane, and possibly 2, 3, 7, 8 tetrachlorodibenzo-para-dioxin. Nevertheless, despite this interest, the methodological problems of investigating pregnancy outcome are formidable. The definition of a terminated pregnancy, the ascertainment of early pregnancy, as well as selection bias, ascertainment bias and confounding make clear-cut well designed studies extremely difficult to execute (107).

The world literature does, however, contain a number of references relating "solvent exposure" to abnormal pregnancy outcome (108). Such citation without a critical assessment of the value of the observation does little to further knowledge but much to fuel fear.

So far as refinery workers are concerned, there is little substantive evidence in the literature. One study reported recently analysed sperm counts and sperm morphology in a cross sectional study of 42 employees in the waste water section of the refinery and 74 working elsewhere (109). No significant differences were noted between the two groups. The original stimulus to the study was the complaint of a 17% spontaneous abortion rate in the wives of waste water plant employees between 1976-81 compared with 8% for the period when their husbands worked elsewhere (1934-1976). Clearly, recall bias and the small number of events studied could influence the validity of such an assertion, but such reports are typical of the current literature.

Population based data from the UK Office of Population, Censuses and Surveys has recently been published (110). The author is at pains to point out the many statistical and epidemiological shortcomings of a national reporting system of abnormal pregnancy outcome. Nevertheless, occupational unit 182 (chemical, gas and petroleum process plant operators) does show evidence of a statistically significant elevation in abnormal outcomes - ratios of 152 on 274 cases of "all malformations", 186 on 20 cases of spina bifida/anencephaly, 446 on 6 cases of tracheo-oesophageal fistula, 177 on 24 cases of hypospadias and 161 on 49 cases of talipes. In addition, occupational unit 182 showed elevated perinatal and infant mortality ratios (135 and 147 respectively). Reporting of such a broad range of conditions in such a diverse group collected at national level does little more than encourage the need for detailed studies to test these hypotheses. Generic guidelines for reproductive surveillance studies were developed for the American Petroleum Institute (111).

What remains of the literature search are six papers from Russia (112-117). None has a design that stands close epidemiological scrutiny. The clinical categories are often vague, the comparison groups are often inadequate, ill described or absent. They are cited here for completeness, but little can be gleaned from them to even generate hypotheses. Neshkov (112) investigated 66 males attending a sexological clinic; their prime complaint was diminished potency. Sperm counts were "normal" in only 22 with lowered 17 keto steroids in 16. Removal from exposure to tetraethyl lead resulted in recovery. Mukhametova and Vozovaya (113) examined female workers exposed to "benzene" and chlorinated hydrocarbons where 40% of the air test values exceeded the MAC for the USSR. Spontaneous abortion rates were 17.2% compared with 4.9% in an ill defined comparison group. Similar one and a half to two-fold elevations were found for "complicated" pregnancies "late toxicosis", "placental abnormalities" and "foetal asphyxia". Perinantal mortality was elevated three-fold (6.3% vs 1.8%).

A two-fold excess of menstrual abnormalities (27.7% vs 10.9%) was found in another study of female refinery workers (114). The excess rate of such abnormalities was three-fold (12.1% to 4.0%) when 894 women at the Koraev refinery were compared with 500 women at the Lenin machine building works (115). These refinery workers also had

an excess of inflammatory gynaecological disorders (14.9% vs 10%). The ratio for this condition at the Vladimir Il'ich Novo-bakinsk refinery was 16.2% vs 8.6% (116). "Ovarian disturbances" predominated in a study of 184 female gluers and 134 other factory workers (21.7% vs 10.4%). The cause of the excess is considered by the authors to be exposure to gasoline vapours at concentrations of 250-350 mg/m^3 (117).

The present state of knowledge on reproductive outcome and the methods required to undertake a valid epidemiological study leaves little room for any conclusions. There does appear to be an association between spontaneous abortion rates and occupational exposure to a number of organic solvents. No study of refinery workers is available to support or refute this assertion. Clearly, it is important to undertake better, more detailed studies though the epidemiological difficulties are uniquely formidable.

5.2.9 Skin Diseases

Skin cancer has long been associated with the industries producing or using shale oil, mineral oil, tar pitch and creosote (118). Oil acne and hyperkeratosis can be precursors of such cancers though the relatively benign nature of the lesion and its obvious visual occurrence usually prevents it being a significant cause of mortality these days. However, the evidence for an excess SMR for melanoma in some of the cohort mortality studies (22, 32, 38, 39, 42, 46) implies that our knowledge of the aetiological agents may be incomplete for this variety of skin cancer which appears to be truly increasing in fequency.

Studies of hyperkeratosis from the USSR (119, 120) suggest that in the Apsheron and Mangyshlak fields at least, the prevalence varies from 5.46 to 35.8% per 100 workers examined.

In addition, the irritative and skin degreasing effects of petroleum products are well known. Perhaps it is the commonality of the conditions that precludes any recent publications; or perhaps the conditions are so well recognised that preventive measures have obviated the incidence of the disorders. It would be interesting to know what is the current position in Western countries.

6. CONCLUSIONS

The health effects of gasoline on occupationally exposed workers have received considerable attention in the medical literature in recent years. Most of the emphasis has been on the chronic sequelae of employment in petrochemical plants and the vast majority of papers have focussed on the mortality experience of oil refinery employees in the United States of America. Despite this concentrated epidemiological effort, it is difficult to find a consensus view from the somewhat conflicting results of the various studies.

The purpose of this review was to evaluate critically the methods and results of over 100 relevant papers, most of them published within the past decade. No previous review of this kind is extant, though there are recent good reviews of cancer risks among refinery workers and of the renal effects of gasoline.

Epidemiological studies predominate in this area of human health effects, but in many cases, there were serious methodological shortcomings in the execution of the studies which most probably contributed to the conflicting results found by the researchers. The main flaws were the lack of reliable exposure data, the small numbers of cases (deaths) in each cell, the relatively short follow up period, dubious diagnostic accuracy, an inability to control for confounding factors and a widespread failure by many authors to consider any latency-induction period. Moreover the size and scope of the investigations varied markedly.

Nevertheless, some authors were aware of these epidemiological pitfalls and some good studies have been published. Notable among the cohort groups are the series of papers by Wen et al, Nelson, and Rushton and Alderson. Among the case referent groups, the McLaughlin et al studies have produced well executed analyses. The studies of Thomas, Waxweiler and others on the union based records have achieved considerable methodological success given the inferior data base from which they started and within the limitations of the PMR approach.

Several general points of consensus do emerge from the assembled literature. There is the consistent finding of a deficit of "all causes mortality" and for "all cancers mortality", thus implying that a widespread serious health effect of gasoline exposure seems remote. So far as specific cancers are concerned, there remains a doubt as to whether oil refinery workers in particular experience an excess risk for malignancies of the bone marrow (leukaemia), the brain, skin, kidney and pancreas. Such excesses that exist must also be viewed in the context of competing risks, given a low "all cancers" risk. In particular, further attention must be focussed on cancer sites such as the brain and kidney where the epidemiological evidence, though not convincing, is nevertheless suggestive of an aetiological link with occupation. The leukaemia and skin cancer risks may be related to high past exposure to benzene and various mineral oils. Exposures such as these should be much lower nowadays.

Non-malignant health effects are of less concern. Low rates for the main causes of death and disease are almost uniformly reported. Nevertheless, a question mark hangs over the possibility of occupational factors being active in the pathogenesis of glomerulonephritis and chronic neuropsychiatric syndromes, although most of the published data relates to organic solvent exposure in general rather than gasoline in particular. The evidence for these conditions being occupationally caused or exacerbated is not persuasive whilst the evidence for abnormal pregnancy outcome and chromosomal aberrations is weaker still.

Thus, despite a generally favourable health experience of gasoline exposed workers, and notwithstanding the epidemiological flaws noted in the published literature, there remains some concern over a number of specific malignant, pre-malignant and non-malignant diseases.

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Table 1 Cohort studies - malignant diseases

REF. NO.	YEAR	AUTHOR(S)	LOCATION	POPN.	PYR	N (DEATHS)	OBSERVATION PERIOD	STATS.	REFERENT POPULATION	ELIGIBILITY CRITERIA	DURATION OF EMPLOYMENT	LATENCY (yr)	ASCER-TAINMENT (%)	EXPOSURES	ALL CAUSES
27	1986	Wong, Morgan et al	2 Chevron ref. California	14179	?	2292	1950-1980	SMR	U.S. ♂	1 day +	1 yr by 1980 (14 yr. av.)	40% >35 yr	95.0	1st and last job	0.72
28	1985	McCraw, Joyner et al	1 ref. Illinois	3976	?	640	1973-1983	SMR	U.S. ♂	1 day + (actives) Alive 1973 (retirees)		50% >25 yr	92.0	job histories	0.76
22	1985	Nelson	10 Amoco refineries	9187	92540	921	1970-1982	SMR	U.S. (nat.) U.S. (loc.)	1 day +	6/12 +	50% >25 yr	97.9	job titles + int. comp.	0.73
29	1985	Divine, Barron et al	Texaco plants	19077	358029	4024	1947-1977	SMR	U.S. ♂	1 day +	5 years (min.)	50% >20 yr	97.7	job codes	0.75
30	1984	Wen, Tsai, Gibson et al	Gulf Oil	12526	313188	3441	1937-1978	SMR	U.S. ♂	1 year +	1 year +	41% >20 yr	94.2	Active Terminated Retired	0.68 1.04 0.89
31	1984	Christie, Robinson et al	Australian Pet. Ind.	11596	?	33	1981-1983	SMR	Aust. popn	5 years +	5 years +	30% >20 yr	92.0	Petroleum industry	0.61
32	1983	Wen, Tsai, McClellan et al	Gulf Oil	15095	372505	4269	1937-1978	SMR	U.S. ♂	1 year +	1 year +	41% >20 yr	93.6	Hourly salaried	0.84
33	1983	Tsai, Wen, Weiss et al	1 Texas refinery	454	5900	34	1952-1978	SMR	U.S. ♂	Ever employed	8 years (av.)	13 yr (av.)	99.3	Benzene (measured)	0.58
34	1983	Rushton, Alderson et al	71 bus garages (UK)	8490	50008	705	1967-1975	SMR	E & W ♂	1 year +	?	5.9 yr (av.)	98.8	20 job codes	0.84
35	1983	Rushton, Alderson	3 refin. + distrib. UK	8470	397569	3926	1950-1975	SMR	E & W ♂	1 year +	?	17.1 yr (av.)	99.8	11 job codes	0.85
36	1983	Austin, Schnatter et al	1 Union Carbide plant	6588	137745	765	1946-1977	SMR	U.S. ♂	1 day +	80% 6/12 +	10 yr 20 yr	97.2	job titles	0.83
37	1983	Waxweiler Alexander et al	U.C.C. Texas City	7595	?	812	1947-1977	SMR	U.S. ♂	-	15 years +		96.7		0.80
38	1982	Reeve, Thomas et al	OCAW local Texas City	?	n/a	264	1948-	PMR	U.S. ♂	OCAW membership	?	?	?	2 refineries	n/a
39	1982	Alderson, Rushton	8 U.K. refineries	34781	575982	4406	1950-1975	SMR	E & W ♂	1 year +	1 year +	?	99.8	job groups	0.84
40	1982	Thomas, Waxweiler et al	OCAW 3 refineries	-	-	2132	1943-1978	-	U.S. ♂ + County	OCAW membership	-	-	92.0 (death cert.)	-	n/a
41	1982	Hanis, Holmes et al	Exxon L.A.	8666	52791	1199	1970-1977	SMR	U.S. ♂	1/12 +	1/12 +	61% >15 yr	90.4	Work summaries	0.92
42	1982	Thomas, Waxweiler et al	OCAW 3 refineries	?	-	2059	1945-1979	PMR	U.S. ♂	OCAW membership	?	?	92% death cert.	3 refineries	n/a
43	1982	Wen, Tsai et al	Gulf Oil	17521	408073	4766	1935-1979	SMR	U.S. ♂	1 day +	1 day +	40% >20 yr	90	job titles	0.92(W) 0.81(B)
44	1981	Rushton, Alderson	8 U.K. refineries	34781	575982	4406	1950-1975	SMR	E & W ♂	1 year +	1 year +	?	99.8	job groups	0.84
45	1981	Wen, Tsai	Gulf Oil	443	?	?	1952-1976	SMR	U.S. ♂	?	?	?	?	?	0.43
46	1981*	Schottenfeld Warshauer et al	19 U.S. chem	55007 14729	122607	502	1977-1979	SMR	U.S. ♂	1 day +	?	41% >20 yr		job hist./ exp.	0.56 0.56
46	1981**	Schottenfeld Warshauer et al	19 U.S. chem.		118566	307		SIR	S.E.E.R.						
47	1980	Thomas Decoufle et al	OCAW 3 refineries			3105	1947-1977	PMR	U.S ♂	OCAW membership			90% death cert.	OCAW	n/a
48	1979	Hanis, Stavraky et al	Imperial Oil Canada	17244	696158	1601	1964-1973	RR	Internal oil co. referents	Cancer matched		80% >10 yr	98.4 death cert.	Pet. products	-
49	1979	Theriault Goulet	Shell ref. Canada	1015	17546	100	1928-1976	SMR	Quebec ♂	5 years +	5 years +	60% >20 yr	84	4 job categories	0.78
50	1967	Baird	Humble Oil Texas			377 Canc.	1935-1963		Gen. rates c 1945						

* Mortality
** Cancer Incidence

SMR(PMR) / N(OBS.) (SMR) = STAT SIGN. 5% LEVEL

ALL CANCER	LUNG	STOM.	COLON	PANC.	PROST.	BLAD.	KIDNEY	HODG.	LEUK	MYEL.	BRAIN	SKIN/MEL.	BONE	ADDITIONAL NOTES
0.76 / 462	0.67 / 124	0.76 / 26	0.71 / 40	0.59 / 80	0.78 / 34	0.62 / 12	0.88 / 13	0.52 / 4	0.88 / 22		1.26 / 22	0.43 / 10		(127) / Non-Hodg. 17 lymph.
0.41 / 161								2.00 / 2	(2.13) / 14					(4.0) / Acute Myel. 8 leuk.
0.84 / 259	0.63 / 75	1.48 / 17	1.13 / 30	1.10 / 18	0.86 / 13	1.09 / 8	0.99 / 8	0.47 / 1	0.43 / 4		0.76 / 7	(2.01) / 11		
0.75 / 767	0.59 / 182	0.70 / 45	0.68 / 64	1.07 / 62	0.85 / 62	0.56 / 19	0.96 / 24	1.08 / 13	1.18 / 48		1.11 / 31	0.84 / 14		
0.85	0.67	0.93		1.46	0.70	0.18	1.42	0.90	1.55		0.88			
0.98	1.15	0.59		1.13	1.30	0.62	0.44	1.60	0.51		0.88			
1.05	1.18	0.84		0.95	1.14	0.48	1.32	1.37	1.58		1.17			
0.96 / 839	0.99 / 239	0.97 / 68	0.84 / 65	1.09 / 53	1.08 / 78	0.46 / 13	1.12 / 22	1.45 / 16	1.14 / 28		0.99 / 30	1.22 / 16	(2.28) / 9	
0.87 / 10	0.52 / 2	3.23 / 2							NIL		4.26 / 2			Between 2.8% and 12.7% above 5ppm benzene
0.95 / 216	1.01 / 102	1.02 / 26	0.76 / 10	0.92 / 9	1.23 / 11	1.39 / 12			1.51 / 7		1.21 / 7			
0.87 / 1002	0.80 / 384	0.85 / 123	0.79 / 57	0.83 / 39	1.09 / 53	0.75 / 32	1.21 / 23	1.39 / 17	1.04 / 28	1.17 / 11	1.07 / 39	0.59 / 5		
0.86 / 150	0.85 / 48		0.78 / 11	1.08 / 10	0.32 / 2	0.51 / 2	1.07 / 5		1.16 / 9		1.62 / 12			Trend for brain and exposure time
0.80 / 160	0.78 / 50	0.60 / 7	0.81 / 13	0.83 / 9		0.64 / 3	1.22 / 6	0.30 / 1	1.36 / 11		1.81 / 13			
1.18 / 37	0.94 / 10					2.2 / 2					2.2 / 3	(7.88) / 15		
0.89 / 1147	0.78 / 416	1.04 / 167	1.07 / 84	0.97 / 50	1.02 / 47	0.77 / 34	1.00 / 22		0.94 / 30		0.80 / 36	(2.16) / 14		Nasal sinus 2.24 / 7
											(2.20) / 27			1.47 / 27 for county rates
0.92 / 249	0.91 / 78	0.80 / 11	0.96 / 24	1.52 / 23	0.66 / 19	0.98 / 9	1.55 / 9	0.97 / 9			1.02 / 9			1.25 / 4 lympho-retic
(1.19) / 553	1.14 / 157	(1.52) / 48	1.08 / 44	(1.42) / 37	(1.38) / 46	0.14 / 2	1.37 / 15	1.32 / 20	(1.83) / 33		(2.21) / 28	(1.81) / 13		
0.99 / 721											0.85			
1.01 / 173											1.5			
as for 1982 reference above														
									NIL					
0.75	0.24	1.00	0.71	1.22	0.94	0.91		0.23	0.69	0.91	1.24			Refinery
0.58	0.54		1.24											Pet./Chem.
0.86	0.81	0.58	1.15		0.85	0.57	0.94	1.10	1.45		1.29	1.31		Refinery
0.87	0.94		1.40		1.28	0.96	1.37	1.06				0.91		Pet./Chem.
(1.17) / 541(M)	(1.25)	← - - -	1.07	- - - - →	← - - -	1.04	- - - - →	← - - -	1.11	- - - →	1 death			
1.27 / 101(B)	(1.40)													
(1.29) / 164	1.18	1.22	(1.97)		1.27	← 1.19	- - - →	← - - -	0.46	- - - →				
0.89 / 25	0.35 / 3	← - - -	1.17 / 12	- - - →	← - - -	1.17 / 3	- - - →	← - - -	1.27 / 3	- - - →	3.89 / 3			Brain (6.52/3 <20 yr
														No difference of note

Table 2 Case referent studies - malignant diseases

REF. NO.	YEAR	AUTHOR(S)	LOCATION	SOURCES AND NUMBER OF		EXPOSURES	STATS.	MATCHING CHARACTERISTICS	BRAIN
				CASES	REFERENTS				
52	1986	Baxter, McDowall	6 London Boroughs	1080	all causes & other cancers	occn. on death certificate	RR	age, year of death, Borough	
53	1985	Dominiano, Vena, Swanson	Buffalo N.Y.	92	1588 hospital non cancer	occupation histories	RR	age groups, date of admission	
54	1985	McLaughlin, Blot et al	Minneapolis - St. Paul	506	714 popn. base	occupation histories	OR	age, sex, residence	
55	1984	Thomas, Waxweiler et al	OCAW Texas	2132 deceased members (1:3)		11 work categories	MAX. LIK. EST.	age, date of death, sex race, date of first membership	0.6 (2.8)
56	1984	Mommsen, Aagard	Denmark	212	259 popn. base	occupation histories	RR	age, sex, residence	
59	1984	McLaughlin, Mandel et al	Minneapolis - St. Paul	495	697 popn. base	occupation histories	OR	age, sex, residence	
60	1983	Austin, Schnatcer	U.C.C. Texas City	21	40 cancer VO non cancer	U.C.C. employees job histories	RR	year of hire, age, sex latency, payroll status	no. stat. sign.diff.
61	1983	Sremhagen, Slade et al	New Jersey	265	530	job histories	RR	age, sex, race residence, admiasion date	
62	1983	McLaughlin	Minneapolis - St. Paul	495	697 popn. bases	as ref. 59 —— above			
63	1982	Najem, Louria et al	New Jersey	75	150 patients	occupation hiatories	RR	age, sex, birthplace, smoking	
64	1982	Rushton, Alderson	8 U.K. refineries	36	2 sets of 3 refinery controls	job records	MAX. LIK. EST.	ref. and year of birth and as above plus service years	
65	1982	Gottlieb, Shear et al	20 LA parishes	3518	3518	death cert. information	RR	parish, age, sex, race, year of death	
66	1981	Lin, Kessler	115 U.S. hospitals	109	non cancer patients	occupation histories	X^2	age, sex, race, date of admission	
67	1980	Howe,Burch et al	3 provinces Canada	632	632 neighbourhood	occupation histories	RR	age, sex, neighbourhood	
68	1980	Pickle, Gottlieb	19 LA parishes	876	876 non-cancer	death cert. information	RR	parish, age, sex, race year of death	
69	1980	Gottlieb	19 LA parishes	200 petrol.	-	death cert. information	OR	employed in petroleum industry	
71	1972	Cole, Hoover et al	E. Mass.	461	485 popn. base	occupation histories	RR	sex, year of birth, residence	

CANCER — RELATIVE RISK (RR) OR ODDS RATIO (OR) — (RR) = SIAI. SIGN. AT 5% LEVEL								
STOMACH	LEUKAEMIA	BLADDER	RENAL	LIVER	PANCREAS	LUNG	MULTIPLE	NOTES
		1.7 drivers 1.9 lorry/van						Mortality
			0.59					Incidence
			1.0 for petrol. exp.					Incidence
0.4-(4.5)	0.4-1.6							Mortality & length of employment
		1.82 industrial 3.11 kerosene 2.71 oil/gasoline						Incidence
			1.6 petrol/ tar/pitch (4.6 for ♂)					Incidence
								Mortality
				(4.20) gasoline service stations				Mortality & Incidence
								Incidence
		(2.5) petroleum (3.4) plastics						Incidence
	1.1 lymph 0.8 myelo							Mortality
						ca. 1.0 petrol industry trend for exposure		Mortality
					(5.1) gasoline dry cleaning (10 yr.+)			Incidence
		(7.5) chemical) (5.3) petroleum) industries						Incidence
					1.16 chemical) 2.11 oil refin.) W ♂			Mortality
						2.33 oilfield/welder 1.19 all workers		Mortality
		1.00 petroleum (1.57) rubber						Incidence

Table 3 Cohort studies - non malignant diseases

REF. NO.	YEAR	AUTHORS	LOCATION	POPN.	NO. CASES	STATS.	SMR (PMR) ALL CIRCUL.	ISCHAEMIC HEART	ALL RESPIR.	BRONC. EMPH.	ALL GASTRO.IN	PEPTIC ULCER
27	1986	Wong, Morgan et al	2 Chevron ref. California	14179	2292	SMR	0.74	0.79	0.56	0.54	0.64	-
28	1985	McGraw, Joyner et al	1 refinery Illinois	3976	640	SMR	0.77	0.44	-	-	0.49	-
22	1985	Nelson	10 Amoco refineries	9187	921	SMR	0.75	0.78	0.50	0.23	0.60	-
29	1985	Divine, Barron et al	Texaco plants	19077	4024	SMR	0.79	0.81	0.52	0.60	0.56	-
30	1984	Wen, Tsai, Gibbson et al	Gulf Oil	12526	3441	SMR	0.73 0.80 0.85	0.88 0.81 0.86	0.45 0.90 0.68	0.44 1.38 0.68	0.46 0.46 0.75	0.28 0.68 0.39
32	1983	Wen, Tsai McClellan et al	Gulf Oil	15095	4269	SMR	0.79	0.85	0.68	0.82	-	0.40
33	1983	Tsai, Wen, Weiss et al	1 Texas refinery	454	34	SMR	0.54	0.46	0.32	-	0.30	-
34	1983	Rushton, Alderson	71 bus garages UK	8490	705	SMR	-	0.88	-	0.77	-	0.83
35	1983	Rushton, Alderson	3 UK ref. + distr.	8470	3926	SMR	-	0.99	-	0.67	-	0.79
36	1983	Austin, Schnatter et al	1 Union Carbide plant	6588	765	SMR	0.82	-	0.58	-	0.39	-
37	1983	Waxweiler, Alexander et al	U.C.C. Texas city	7595	688	SMR	0.77	-	0.58	-	-	-
38	1982	Reeve, Thomas et al	OCAW local Texas	?	264	PMR	0.93	-	0.62	-	-	-
39	1982	Alderson, Rushton	8 UK refineries	34787	4406	SMR	-	0.90	-	0.64	-	0.92
41	1982	Hanis, Holmes et al	EXXON L.A.	8666	1199	SMR	1.01	-	0.71	-	0.71	-
40	1982	Thomas, Waxweiler et al	OCAW 3 refineries	?	2059	PMR	(1.04)	-	0.57	-	-	-
44	1981	Rushton, Anderson	8 UK refineries	34781	4406	SMR	← see reference above					
46	1981	Schottenfeld, Warschauer et al	19 US petr. chem. plants	69736	502	SMR	-	0.55	-	-	-	-
47	1980	Thomss, Decoufle et al	OCAW 3 refineries	?	3105	PMR	(1.06)	(1.22)	0.41	-	0.59	-
49	1979	Theriault, Govlet	1 Shell ref. Cansda	1015	108	SMR	0.84	-	0.51	-	1.06	-

(SMR) = SMR

SIAI SIGN 5% LEVEL

CIRRHOSIS	ALL GENITO-URINARY	NEPHRITIS	SUICIDE	NOTES
0.79	0.50	-	1.28	mainly W ♂
-	-	-	-	W ♂
0.70	0.38	-	0.64	All ♂
0.47	0.53	-	-	W ♂
0.35	0.36	-	0.56	active
0.34	1.19	-	0.89	terminated W ♂
0.61	0.65	-	0.75	retired
0.40	0.59	-	0.73	All ♂
-	-	-	-	All ♂
-	-	1.57	-	All ♂
-	-	0.46	0.57	All ♂
-	-	-	-	W ♂
-	-	-	-	All ♂ (hourly)
-	-	-	-	White ♂
-	-	0.85	0.70	All ♂
-	1.26	-	-	All (85% W ♂)
-	-	-	-	All ♂
-	-	-	0.46	
-	-	-	0.96	White ♂
-	NIL	-		