health risks from working in petroleum refining and from gasoline - a critique and recommendations in response to IARC monograph volume 45

Prepared by the CONCAWE Health Management Group's Special Task Force No. 20 (HMG/STF-20)

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ABSTRACT

IARC drafted Volume 45 of their Monograph series in March 1988. Volume 45, published in 1989, concerns occupational exposures in petroleum refining; crude oil and major petroleum fuels.

This CONCAWE report analyses the literature on refining and gasoline which IARC reviewed and comments on their conclusions. It concludes that the IARC findings:

1) do not establish a current occupational cancer risk at petroleum refineries, and
2) do not establish a health risk from the production and normal use of gasoline.

The report also provides advice for action by CONCAWE member companies.

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SUMMARY

The International Agency for Research on Cancer (IARC), an independently financed organization within the framework of the World Health Organization, states in its Monograph Volume 45, that "occupational exposures in petroleum refining are probably carcinogenic to humans", and that "gasoline is possibly carcinogenic to humans". This CONCAWE report outlines the procedure used by IARC to classify substances and occupations regarding carcinogenicity, and reviews in detail the human and animal studies on which IARC based its conclusions. For petroleum refining, the data come primarily from surveys which show increased rates of leukaemia and malignant melanoma in industry employees. For gasoline, IARC did not identify increased rates of any specific cancers, but considered that the total of the human and animal evidence indicated a possible cancer hazard.

CONCAWE's comments on the findings include:

- most studies of industry employees do not show cancer excesses;
- the data reviewed by IARC mainly relate to exposures many years ago, and over recent years the industry has expended considerable effort in controlling employee exposures;
- there are scientific flaws in some of the studies, so interpretation of them is difficult;
- information on death certificates is often inaccurate;
- other independent scientific reviews have failed to identify a significant hazard from gasoline;
- the alleged exposures to gasoline have not been properly measured in almost all epidemiology studies;
- the animal studies used are of doubtful relevance.

CONCAWE recommendations for industry action include:

- further control of exposures;
- further collection of health and exposures data;
- support for epidemiological studies;
- support for relevant animal studies.

1. INTRODUCTION

As part of their programme to evaluate the carcinogenic risks of chemicals to humans, the International Agency for Research on Cancer (IARC) drafted Volume 45 of their monograph series during 1-8 March 1988. The volume comprises six monographs: one on occupational exposures in petroleum refining, one on crude oil and four on commercially available petroleum fuels (gasoline, jet fuel, diesel fuel and fuel oils).

The purpose of this briefing document is to provide CONCAWE member companies with a detailed analysis of the IARC evaluations of work in refineries and gasoline, to place these into current perspective and to provide a basis for further action.

The objective of the IARC Working Groups is to review, summarize and evaluate human carcinogenic risk from a wide range of agents and certain occupations and to publish each review in a monograph. In considering the implications of IARC evaluations it is important to note qualifying statements which are made in the IARC preamble to their monographs, which states:

"The *Monographs* represent the first step in carcinogenic risk assessment, which involves examination of all relevant information in order to assess the strength of the available evidence that, under certain conditions of exposure, an agent could alter the incidence of cancer in humans. The second step is quantitative risk estimation, which is not usually attempted in the *Monographs*. Detailed, quantitative evaluations of epidemiological data may be made in the *Monographs*, but without extrapolation beyond the range of the data available. Quantitative extrapolation from experimental data to the human situation is not undertaken.

These *Monographs* may assist national and international authorities in making risk assessments and in formulating decisions concerning any necessary preventive measures. ..."

These qualifications by the IARC on the use of their evaluations clearly imply that an agent which is probably or possibly inherently carcinogenic to humans does not in reality necessarily present risk. Further assessment of possible exposure is needed to evaluate any actual risk.

The procedure adopted by the IARC Working Group initially involves judging the strength of evidence for the carcinogenicity of agents in animals and humans and classification of that evidence as either "sufficient", "limited" or "inadequate", according to criteria described in the preamble to each of the IARC monographs (see Appendix).

Finally, using these individual evaluations of strength of evidence for animals and humans, the Working Group arrives at an overall evaluation of carcinogenic risk to humans and places the agent into one of the following groups:

GROUP 1 : The agent is carcinogenic to humans.
GROUP 2A: The agent is probably carcinogenic to humans.
GROUP 2B: The agent is possibly carcinogenic to humans.
GROUP 3 : The agent is not classifiable as to its carcinogenicity to humans.
GROUP 4 : The agent is probably not carcinogenic to humans.

The Working Group then considers any supporting evidence which is available and upgrades the overall evaluation when this is considered justified. The criteria used by the Working Group for the overall evaluation are described in the preamble to each monograph and are reproduced in Table 1.

Table 1: Criteria used by IARC to make an overall classification

Strength of evidence (a)		Overall evaluation (b)
Animals	Humans	
S	S	Group 1
S	L	Group 2A
<S	L	Group 2B
S	<L	Group 2B
<S	<L	Group 3
Exceptions requiring supporting data		
-	L	Group 2A
S	<L	Group 2A
L	<L	Group 2B

Notes:

a) S = Sufficient
L = Limited

b) Group 1 - the agent is carcinogenic to humans
Group 2A - the agent is probably carcinogenic to humans
Group 2B - the agent is possibly carcinogenic to humans
Group 3 - the agent is not classifiable as to its carcinogenicity to humans

The results of the evaluations made by the IARC Working Group were:

- occupational exposures in petroleum refining - Group 2A, probably carcinogenic to humans;
- crude oil - Group 3, not classifiable as to its carcinogenicity to humans;
- gasoline - Group 2B, possibly carcinogenic to humans;
- jet fuel- Group 3, not classifiable as to its carcinogenicity to humans;
- marine diesel fuel - Group 2B, possibly carcinogenic to humans;
- distillate (light) diesel fuel oil - Group 3, not classifiable as to its carcinogenicity to humans;
- residual (heavy) fuel oil - Group 2B, possibly carcinogenic to humans;
- distillate (light) fuel oil - Group 3, not classifiable as to its carcinogenicity to humans.

This report only addresses the conclusions reached by the IARC on occupational exposures in petroleum refining and on gasoline.

2. OCCUPATIONAL EXPOSURES IN OIL REFINING

The IARC concluded that occupational exposures in petroleum refining are probably carcinogenic to humans (Group 2A). This was based on the limited human epidemiological data relating to skin cancer and leukaemia, the strength of which was considered weak. This weakness is due not only to the quality of the studies, but also for example, to the nature of the skin cancer evidence associated with process and related exposures largely discontinued during the 1950s. For all other types of cancer on which information was available the human evidence was considered inadequate. Because of the weakness of the human data, the IARC Working Group then considered supporting data. These were provided by the presence in refineries of materials for which there is sufficient evidence of carcinogenicity to humans (benzene, untreated mineral oils and mildly treated mineral oils) and to animals (light vacuum distillates, heavy vacuum distillates, light cat-cracked distillates and heavy cat-cracked distillates). The Working Group concluded the supporting data justified an overall evaluation of Group 2A for occupational exposures in petroleum refining. No other cancers were identified as having increased incidence in this occupational group.

2.1 HUMAN DATA

The limited epidemiological evidence comes from an examination of ten cohorts from the US, two from Canada, one from the UK together with a case control study from the UK.

2.1.1 Epidemiological evidence on skin cancer

Statistically significant excess mortality from skin cancer (squamous cell carcinoma and malignant melanoma) was reported among only three of the thirteen refinery cohorts.

In the first cohort an excess of squamous-cell carcinoma was reported among wax pressmen who had skin contact with crude paraffin wax saturated with aromatic oils, during the period 1937 to 1956. Based on 11 cases, there was an increased rate of scrotal cancer of 806/100 000 compared with 0.15/100 000 expected. The overall incidence for all types of cancer in men who had worked in wax manufacturing for ten or more years was more than four times that of US men. (1,2).

In a second cohort, the overall excess was due to an elevated incidence of malignant melanoma and this is from the Alderson and Rushton UK study (3) of about 35,000 employed in one of

eight oil refineries for at least one year between 1950 and 1975. The authors commented that the increased risk could not be attributed to occupational exposure.

In the third cohort, excess malignant melanoma was again reported (4). This study of 10 763 Amoco employees in the US who had worked at any of ten refineries between 1970 and 1980 and followed until 1982, showed an excess of skin cancer, almost exclusively in men who had worked in maintenance jobs. Ten of the 11 skin cancer cases were melanoma. In this study, exposures were classified both by job title, and by a classification system. All employees were placed into one of three occupational groups involving exposure to (a) other refinery processes, (b) light aromatics or (c) heavy oils. Within these groups, exposure potential was classified as none, occasional, routine or unknown. Statistically significant elevated skin cancer mortality rates were seen in maintenance workers, and in those routinely exposed to heavy oils, light aromatics and to other refinery processes. Skin cancer Standardized Mortality Ratios (SMRs) for both light aromatic and heavy oil increased with increasing exposure (4).

A case control study among men employed in the coal and petroleum products industry showed significantly elevated risk for malignant melanoma with a cluster of four cases among those employed in petroleum refineries (5). The study period was 1959-1979. The occupations of the four were: process worker/blender, engineer, security officer, and clerk of works. The study was restricted to men of age 18 to 54. The authors report shortcomings of the study as being:

1) incompleteness of occupational data from the death certificates, since only the most recent full-time job is recorded and

2) no alcohol or smoking history was available.

2.1.2 CONCAWE Comment on skin cancer evidence

1. Technology

Some of the evidence used dates back several decades, and since then, exposure conditions and process technology have changed substantially. The manual slack wax pressing process referred to in the first cohort was largely phased out during the 1950s.

2. Latent interval

The mean latent interval for oil-induced scrotal cancer is around 35 years (6), but may vary from a few to 50

years, consequently published findings in all probability relate to exposure conditions many years earlier.

3. Reduction of exposures

Following an industry symposium in 1951 (7), safer operating procedures, more effective use of personal protective clothing and improved personal hygiene were widely introduced. Since then, significant effort has been expended by industry to ensure that practices have improved further. This action has resulted in much less skin contact with substances found in the industry.

4. Malignant melanoma

Apart from squamous cell carcinomas related to the redundant slack wax process, the excess of skin cancer relates to the incidence of malignant melanoma. In follow-up investigations of some of the studies described, occupational health professionals have attempted to link these findings to exposure to aetiological agents in the workplace, but without success.

There are numerous examples in the literature of the finding of an excess incidence of malignant melanoma in studies of occupational cohorts in a variety of industries and countries. These include: Norwegian asbestos workers, Swedish rubber workers, Swedish telecommunication workers, Swedish electrical engineers, English semi-conductor workers, and American physics researchers. In all of these cohort studies, no specific agent has been implicated as the cause of malignant melanoma and so it seems that this finding can arise in a study as a pure coincidence.

The rate of increase in the incidence of melanoma in the general population is one of the highest among all types of cancers, being comparable to that of cervical cancer (8). There is no doubt that solar radiation is a causal factor in the development of malignant melanoma, with infrequent but intense exposure to sunlight being more important than continual exposure (9).

Although not reported by IARC, CONCAWE is aware of two published experimental animal studies associating skin exposure to a specific Polycyclic Aromatic Hydrocarbon (PCAH) with malignant melanoma. The first (10) involved a straightforward skin painting study; the second (11) a skin painting study combined with ultraviolet light exposure. The development of malignant melanoma in man is known to be different to that observed in these animal experiments, so

given the increase in community rates of malignant melanoma, it is difficult to evaluate the relevance of these findings to refining operations without further investigation.

Conclusion:

Although there undoubtedly have been a small number of cases of oil-induced skin and particularly scrotal cancer in the industry, the data probably reflect operating procedures, processes and exposures of some decades past. Indeed, the offending conditions were essentially discontinued or subject to major control efforts during the 1950s and 1960s. In CONCAWE's view the IARC evaluation does not, therefore, reflect risks associated with recent or prevailing exposures in the oil refining industry. The bulk of the evidence cited by the IARC relates to malignant melanoma which, except for occupations involving considerable exposure of the skin to sunlight, is not generally regarded as an occupationally related disease.

2.1.3 Epidemiological Evidence on Leukaemia

In the thirteen cohorts studied, although there were increases in specific lympho-poietic cancer classifications, mortality from overall "leukaemia" was significantly elevated in only two.

The Wong and Raabe 1988 (12) study reports previously unpublished data from three Mobil refineries in the period 1945 to 1978. At the Beaumont refinery, leukaemia mortality increased with duration of employment and with time since first employment. The overall Standardized Mortality Ratio (SMR) for leukaemia was 1.72 (23 deaths), but for those with more than 30 years employment the SMR was 2.35. In males the SMR was 2.14 with a latency period (time since first exposure) of 20-39 years.

In the second study, workers in a Shell refinery showed a leukaemia SMR of 2.13 (13). The authors reported that none of the men who died from leukaemia had been subjected to high benzene exposure and a case-control study did not demonstrate any clustering in particular jobs or work areas.

IARC noted that there were also increased rates of overall leukaemia in two other cohorts, but these were not statistically significant.

A subset of the British study (3) reported no excess of leukaemia overall, but did find elevated mortality from unspecified lymphatic leukaemia, unspecified myeloid leukaemia and acute monocytic leukaemia. An analysis suggested a link between increased leukaemia risk and benzene exposure, but this was not statistically significant.

In a large cohort study including many refineries in the US a significantly elevated incidence of lymphocytic leukaemia but not overall leukaemia was noted (14).

Five refinery cohorts reported non-statistically significant excess mortality from "cancer of other lymphatic tissues" (multiple myeloma, polycythaemia vera and non-Hodgkin's lymphoma excluding lymphosarcoma and reticulum sarcoma).

There is one report of significant excess mortality from leukaemia and "cancer of other lymphatic tissue" combined.

Although not referenced in the IARC study, incidence data from an Australian industry-wide study show an increased leukaemia risk for those employed before 1970, compared with those employed after 1970, suggesting that although a risk may have existed some decades ago, it seems to have now disappeared (15).

In making its final evaluation that occupational exposures in petroleum refining are probably carcinogenic to humans (Group 2A), IARC took into account:

- Benzene and untreated and mildly treated mineral oils are carcinogenic to humans.

- There is sufficient evidence from animal studies for the carcinogenicity of several process streams containing polycyclic aromatic hydrocarbons (light and heavy vacuum distillates, light and heavy cat-cracked distillates).

2.1.4 CONCAWE comments on leukaemia evidence

1. Findings

Most methodologically-acceptable cohort studies do not show a statistically significant excess of deaths from leukaemia. Only 2 of the 13 cohort studies reviewed by IARC and 3 of the 19 studies considered by Wong and Raabe showed an excess (12). The findings are thus regarded as being very inconsistent.

2. Hydrocarbon exposure

In recent years, hydrocarbon vapour exposure has decreased due to improved engineering controls over fugitive emissions, greater automation of refinery operations, including sampling and analysis of streams, and more emphasis on the observation of safe working practices (16). Even in the few studies which

demonstrate leukaemia there is some evidence that leukaemia incidence has reduced over recent years which correlates with reductions in hydrocarbon exposures which have been effected by the industry (15).

3. Benzene

The chemical most likely to be implicated as causing leukaemia is benzene. However, few leukaemia cases have been found in workers actually working on benzene units. It is also notable that benzene is linked primarily with only one particular type of leukaemia - acute myeloid (International Classification of Diseases ICD code 205.0). However, most of the studies reporting an excess of leukaemia have combined several different pathological types of the disease in the database used for the evaluation. For example, the Wong and Raabe review defined leukaemia as ICD 204-207, thus including many types which have no established link with benzene. Only one study (13) showed a statistically significant excess of acute myeloid leukaemia in petroleum refinery workers, but this could not be linked to benzene exposure.

These points indicate that there is no strong evidence in the data reviewed by IARC implicating benzene as a major causative agent, and that the term "leukaemia" as used by IARC is really a group of several different diseases, none of which taken separately is clearly present in excess in refinery workers.

The long-term potential hazard of benzene exposure has nevertheless been recognized and addressed by the petroleum industry. Exposures to benzene have been tightly controlled to well within accepted exposure limits for many years.

4. Chance (Clusters)

Some of the references quoted by IARC involve clusters of leukaemias though few or none of those concerned had jobs with a potential for exposure to benzene or other chemicals. While clusters can be associated with occupational carcinogens, they are more frequently related to random occurrence (chance), genetic or possibly environmental factors such as smoking or lifestyle.

5. Smoking

Recently published data indicate that smoking may be related to the development of leukaemia (17). This is a

recent finding and, if validated, will have implications for all studies, including many reviewed by IARC, which do not take smoking into account.

6. Diagnosis

In the past, the death certificate data for lymphatic and haemopoietic diseases has often been inexact due to inadequate diagnostic technology and lack of knowledge of pathological mechanisms. Doubtful diagnostic accuracy is in fact one of the major interpretive problems in occupational epidemiology, and is particularly important in areas such as haemopoietic diseases.

7. Real risk

It was pointed out in the introduction that the IARC does not assess the actual risk to workers currently employed. Its reports are restricted to the identification of hazards, and do not take into account risk control measures such as engineering controls, safe operating procedures and personal protective equipment. This means that even though the IARC may correctly identify a substance as a potential cancer-causing agent, in practice there is minimal real risk to the health of the workers.

8. Weakness of data

CONCAWE believes IARC's initial assessment of the direct evidence would have resulted in a classification of Group 2B (possibly carcinogenic to humans).

The IARC Working Group clearly highlighted the weakness of the available data, since no clearly defined hazard could be identified. The classification as Group 2A emerged only after the consideration of supporting data. The supporting data was a knowledge of the presence in refineries of benzene, process streams and some base oils which have been previously classified as carcinogenic by IARC.

CONCAWE believes that a classification of 2B (possibly carcinogenic to humans) is an appropriate conclusion based on relevant data and the upgrading to 2A based purely on "association" cannot be justified scientifically.

Conclusion:

CONCAWE agrees with the IARC evaluation that elevated total leukaemia rates have been found historically at a few refineries, but believes that the findings are inconsistent and a current occupational hazard has not been identified. Any historical risk will have been markedly reduced by the improved controls which have been implemented so with the result that exposures are now lower than they may have been many years ago.

3. GASOLINE

IARC concluded that there was inadequate evidence of carcinogenicity in humans and limited evidence in experimental animals from gasoline. This would have given an overall evaluation for gasoline of Group 3 (not classifiable as to its carcinogenicity to humans). However, in reaching the final overall classification that gasoline is possibly carcinogenic to humans (Group 2B), IARC took into account the following:

- wholly vaporized unleaded gasoline induces some change in genetic material (as indicated by unscheduled DNA synthesis) in animal liver cells;
- there is limited evidence for animal carcinogenicity of light straight-run naphtha and light catalytically-cracked naphtha;
- benzene is carcinogenic to humans;
- for 1,3-butadiene (a trace constituent of contaminant in some gasolines and refinery streams) there is inadequate evidence of carcinogenicity in humans and sufficient evidence in animals.

IARC did not associate any particular type(s) of cancer with gasoline in its final assessment.

3.1 HUMAN DATA

IARC noted that the epidemiology studies available to it did not include any useful gasoline exposure data, so it was only able to review occupations where gasoline exposure may occur. These included gasoline station attendants and automobile mechanics. In addition, it was noted that there was no opportunity to separate the effects of combustion products from those of gasoline itself.

IARC reviewed the following studies and commented:

Cohort studies

- In the UK (18) information was studied on over 23 000 men employed for at least one year between 1950 and 1975 at oil distribution centres with the largest group of workers being drivers. Exposure data were not available. A significantly lower total cancer mortality (SMR 0.85) was observed, and this was consistent for all malignancies. Slightly elevated deaths for haemopoietic and lymphatic cancers were not statistically significant, except for myelofibrosis.

- A Swedish study investigated pancreatic cancer in different occupations by comparing cancer registry and census data (19). Information on about 2 million males of employment age was examined and an SMR of 1.6 was calculated for gasoline station workers (confidence interval 1.1-2.3). IARC noted the lack of exposure data and the absence of any control of confounding factors in this study.

- Two US proportionate mortality ratio (PMR) studies were noted. The first study (20), involving over 400 000 men in Washington State, compared occupation and cause of death from death certificates. IARC examined the data for occupational groups where exposure to benzene may occur (gasoline station attendants, fuel dealers and automobile mechanics). The results were as follows:

  Mechanics - increased PMRs for cancer of the oesophagus, bronchus/lung and non-Hodgkins lymphoma;
  - increased PMR for lymphatic leukaemia for the period 1960-69 (8 cases - PMR 2.8);

  Attendants - increased PMR for bladder cancer for 1950-59 (9 cases PMR 2.2) and for 1960-69 (11 cases PMR 1.8).

  The second study (21) analyzed information from death certificates of all white males in the state of New Hampshire from 1975 to 1985, and 453 deaths of automobile mechanics were recorded. As the numbers of deaths for gasoline service station attendants was too low for meaningful analysis, the authors analyzed the 134 deaths in the gasoline service station industry. Due to lack of occupational history, analysis by duration of employment and latency was not possible. IARC noted that exposure data were not available, and that there was a lack of control of confounding variables. The results were as follows:

  Mechanics - no statistically significant elevated PMR for malignancies, but a (non significant) slight increase for leukaemias (PMR 1.8, 6 deaths);

  Attendants - with 3 deaths, a statistically significant increase (PMR 3.3) for leukaemia and aleukaemia.

Case-control studies

IARC noted that each of the case-control studies had (a) no details of exposure to gasoline, (b) no details of other exposures, (c) minimal attempts at the identification and control of confounding variables.

- A US case-control study of 506 cases of kidney cancer in the period 1974-79 (22) found an odds ratio of 1.7 (95% confidence interval 1-2.9) for occupational exposure to petroleum, tar and pitch products. In a more detailed analysis (23) there was no link with either petroleum-related occupations or working as gasoline attendant. Although IARC noted some evidence of an increasing rate with duration of employment as a service station attendant, this was not statistically significant.

- Another US study of kidney cancer cases from a New York hospital in the period 1957-65 showed decreased risk for gasoline exposure (based on four cases), but increased risk for smokers employed in service stations (odds ratio 1.6 [0.5-5.3]).

- A Canadian case-control study of 3726 men aged 35-70 with cancer diagnosed between 1979 and 1985 included attempts at exposure assessment by occupational hygienists. For exposures to aviation gasoline, there was increased kidney cancer risk (odds ratio 2.6 90% CI 1.2-5.8). Indications of dose-response were seen in the substantial exposure group (3.1, [1.7-6.5]).

- Several case-control studies of lower urinary tract cancer with no consistent results, were considered. No exposure data were used, and the occupational classifications are not comparable between studies. It is most likely that many of the cases described had no significant exposure to gasoline at all. (see Table 2).

Summary of case-control studies of lower urinary tract cancer

Table 2

	Odds ratio (% confidence interval)	Occupation/exposure	Comments
1.	1.0 (95% 0.75-1.3)	Exposure to petroleum products suspected	No gasoline information (24)
2.	2.7 (95% 1.2-6.1)	"oil or gasoline exposure"	No adjustment for confounders (25,26)
3.	2.4 (95% 0.9-6.1)	"petroleum tar & pitch products"	No further occupational detail given (27)
4.	1.2 (95% 0.6-2.4)	gasoline service attendants	(28)
	1.0 (0.6-1.4)	mechanics	
5.	2.4 (95% 1.5-3.8)	garage/gas station workers	(29)
	1.3 (0.87-1.8)	mechanics	
	1.1 (0.9-1.4)	petroleum materials	
	0.76(0.6-1.0)	organic solvents	
6.	1.3 (95% 0.77-2.3)	mechanics (non-smokers)	200 cases, 313 controls. (30)
	1.2 (95% 0.9-1.6)	mechanics (smokers)	

- Other studies showed isolated results of increased risk for acute non-lymphatic leukaemia, testicular cancer, pancreatic cancer, liver cancer and stomach cancer.

- Nine case-control studies with data on risks of childhood cancer from paternal exposure to hydrocarbons showed no consistent pattern.

- One study of maternal work exposure to hydrocarbons during pregnancy suggested an increased risk for leukaemia in their children (31).

3.2 CONCAWE COMMENTS ON HUMAN DATA:

1. Findings

In his review of the literature, Harrington (32) concluded that the possibility of "a widespread serious health effect of gasoline exposure seems remote", and CONCAWE agrees with this assessment.

2. Exposure data

IARC noted that none of the epidemiological studies available to it included any usable exposure data. In fact the occupations considered, where gasoline exposure is assumed to have occurred, probably involved multiple exposures to numerous hydrocarbons, usually as a mixture, or perhaps no significant exposure to gasoline at all. In addition, the possible contribution of combustion products was not taken into account, although this is unlikely to have been a significant factor. These factors suggest that meaningful interpretation of the data is exceedingly difficult, and perhaps impossible.

3. Types of cancers

There is no consistent finding of excess of any specific cancer. Although some papers report statistically significant excesses for several different cancers, IARC describes many other papers of equal or better quality which do not confirm such findings.

4. Relevance of studies

The human evidence quoted by IARC arises from two cohort studies, two proportionate mortality studies and several case-control studies.

PMR (proportional mortality ratio) studies suffer from several methodological flaws which mean they always overestimate cancer risk. They are used when the age distribution of the study population is not known, so only the deceased population is analysed with respect to age and cause of death. A deficit for any cause is then distributed amongst other causes, leading to the overestimation of rates. The inherent limitations of PMR studies means they must be interpreted with caution, especially with regard to the demonstration of cause and effect.

Many of the references are to large case-control studies of particular cancers, for example the US national bladder cancer study. In the manipulation of such study data, the occasional excess for occupations vaguely associated with gasoline has sporadically been identified. There are many general population studies of this type, and as IARC states, most of the published reports refer to positive findings ("publication bias"). It is likely that most of the occupational data from such studies are unreported when their findings are essentially negative. Therefore, these findings are likely to have arisen by chance (33).

It is CONCAWE's view that the case-control studies reviewed have such methodological flaws and are so unrepresentative that they are of little relevance to an evaluation of human carcinogenic risk from gasoline.

5. Historical perspective

For at least three decades, the petroleum industry has expended great efforts to improve health and hygiene in the workplace - both within the industry and also in advice to customers. During this period industry has changed many of its refining processes, improved its control technology, created a much higher standard of awareness of possible hazards, reduced exposure, promoted good work practices and personal hygiene, automated more plant operations and significantly reduced the numbers exposed. For example, there has been a significant decrease in exposure to gasoline liquid and vapour due to the possibility of skin damage (dermatitis) and concerns over potential exposures to benzene. Skin contact with oils has been subject to major control efforts through adoption of safer working practices and improved personal hygiene since the 1950s when oil induced skin cancer in refineries was identified as a real problem.

As most of the studies reported involve exposures dating back many decades, in some instances to the early part of the 20th century, their relevance to the modern workplace is limited.

6. Weakness of data

In its initial assessment of the direct evidence, IARC would have evaluated gasoline as Group 3 (not classifiable as to its carcinogenicity to humans) thereby fully recognizing the weakness of the epidemiological data. However, because of evidence from animal studies (see below), and the presence of benzene and 1,3- butadiene a trace constituent of some gasolines, in the mixture, the classification was modified to 2B (possibly carcinogenic to humans). CONCAWE exposure data (34) demonstrate that the presence of benzene and possibly 1,3-butadiene in gasoline are unlikely to constitute a significant health hazard in most routine activities.

The exposure levels reported by CONCAWE are generally only a fraction of prevailing exposure limits in Europe, and in any event are substantially below the levels thought by industry health professionals to be representative of a significant health risk.

7. Community evidence

Given the ubiquity of gasoline in the community, it should be noted that there is no evidence of any increased health risk to the general population from its normal use. Studies in various countries have demonstrated that there has been no increase in the incidence of leukaemia despite the enormous increase in the use of gasoline since the early 1940s (35).

8. Real risk

Again it should be noted that IARC does not assess the actual risk to currently employed workers. Its reports are restricted to the identification and classification of potential cancer hazards. They do not take into account current occupational health measures which minimize exposures. The result is that although IARC may from historical data correctly identify a substance as a cancer-causing agent, under current conditions there may be minimal or no real risk to the health of the workers.

3.3 ANIMAL STUDIES

The IARC reviewed the results of two experiments which had been carried out for the American Petroleum Institute (API). Mice and rats had been exposed for two years to a range of concentrations of wholly vaporized unleaded EPA reference gasoline. A dose-related increase in adenomas and carcinomas of the kidney was observed at the end of the study in the male rats only. No renal tumours were observed in either the female or control rats or in any of the mice. In the mice a statistically significant increase in adenomas and carcinomas of the liver had occurred in the highest dose-group females only. Although the IARC considered these results to provide limited evidence of carcinogenicity in animals, the API has interpreted the data differently.

3.4 CONCAWE COMMENTS ON ANIMAL EVIDENCE

CONCAWE agrees with the API interpretation that the occurrence of kidney tumours in male rats is a sex and species specific effect resulting from a metabolic peculiarity and has no relevance for man. The increased liver tumour incidence in the high dose female mice is also considered to be of dubious relevance for man, especially when seen against a high spontaneous incidence of such tumours in mice. Furthermore, the experimental data were generated using exposures to wholly vaporized gasoline, in contrast to exposure from normal production and use where the exposures are to only the very volatile light hydrocarbon fraction, of which only benzene has been identified by IARC as a carcinogen. The studies cannot therefore be easily interpreted in terms of a real cancer risk to workers handling gasolines.

4. RECOMMENDATIONS FOR INDUSTRY ACTION

4.1. CONTROL OF EXPOSURES

The IARC review does not indicate the presence of any previously unrecognized cancer hazards in petroleum operations. The oil industry awareness of these hazards and the resulting action to minimize exposure and hence risk, should obviously be continued and periodically reviewed. In preparation for a response to concerns arising from the Monograph, it is recommended that CONCAWE member companies have a current assessment of the risks to employees from, in particular, benzene and 1,3-butadiene exposures and skin contact with the higher risk streams and products. The assessment should include a summary of prevailing exposure data and an evaluation of the effectiveness of engineering controls and work practices. This information should be readily available to employees.

CONCAWE reports (16,34,36) may be useful in informing or responding to questions from employees, customers and the media.

4.2 COLLECTION OF EXPOSURE DATA

It is recommended that there is regular collection of exposure data such that a high level of confidence exists that it is statistically representative for exposed employee groups. The pooling of these data would be valuable to the industry overall through the updating of CONCAWE reports (3/86 and 4/87). The availability of pertinent exposure data on an historical basis will be of great benefit in the evaluation of any future epidemiological work.

4.3 MONITORING OF HUMAN HEALTH DATA

It is recommended that individual and group records of worker health experience are maintained and reviewed on a regular basis. Particular attention should be paid to skin and haemopoietic conditions.

4.4 EPIDEMIOLOGY

The epidemiology data used by IARC arose from industry work mainly in the US It is recommended that CONCAWE member companies support the updating and further analysis of

epidemiological studies, in particular the work of Alderson and Rushton (3,18) in the UK, which is the only European study. It is recognized and must be emphasized that, currently, participation in epidemiology studies is restricted in some European countries because of data protection legislation. This unfortunately restricts effective epidemiology to a very limited number of countries, and it is recommended that CONCAWE take any opportunity to highlight this difficulty with both national and EC legislators.

Since malignant melanoma has been implicated in several epidemiological studies, consideration should be given to a properly controlled skin cancer refinery worker or cohort study. This is particularly important because current cohorts do not adequately examine skin cancer outcomes nor have adequate controls.

4.5 ANIMAL STUDIES

It is recommended that CONCAWE completes its programme to evaluate the potential carcinogenicity of middle distillates. These results will allow a more adequate assessment of the carcinogenic risk of these materials.

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APPENDIX IARC: DEGREES OF EVIDENCE FOR CARCINOGENICITY

(i) HUMAN CARCINOGENICITY DATA

The evidence relevant to carcinogenicity from studies in humans is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between exposure to the agent and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of doses to which human beings are known to be exposed, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the cancer sites, circumstances and doses of exposure and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence for the carcinogenicity of the agent for specific organs or tissues.

(ii) EXPERIMENTAL CARCINOGENICITY DATA

The evidence relevant to carcinogenicity in experimental animals is classified into one of the following categories:

Sufficient evidence of carcinogenicity: The Working Group considers that a causal relationship has been established between the agent and an increased incidence of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in (a) two or more species of animals or (b) in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols.

Exceptionally, a single study in one species might be considered to provide sufficient evidence of carcinogenicity when malignant neoplasms occur to an unusual degree with regard to incidence, site, type of tumour or age at onset.

In the absence of adequate data on humans, it is biologically plausible and prudent to regard agents for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans.

Limited evidence of carcinogenicity: The data suggest a carcinogenic effect but are limited for making a definitive evaluation because, e.g. (a) the evidence of carcinogenicity is restricted to a single experiment; or (b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the study; or (c) the agent increases the incidence only of benign neoplasms or lesions of uncertain neoplastic potential, or of certain neoplasms which may occur spontaneously in high incidences in certain strains.

Inadequate evidence of carcinogenicity: The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect because of major qualitative or quantitative limitations.

Evidence suggesting lack of carcinogenicity: Adequate studies involving at least two species are available which show that, within the limits of the tests used, the agent is not carcinogenic. A conclusion of evidence suggesting lack of carcinogenicity is inevitably limited to the species, tumour sites and doses of exposure studied.