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Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP)

Phase I

Literature Review

Final Report
July 2003

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SYNOPSIS

The Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP) represents a retrospective cohort study of health differences between particular work groups of interest. Commissioned by the Department of Defence, the study aims to investigate the health of individuals involved in any of the F-111 aircraft fuel tank Deseal/Reseal programs (DSRS) conducted at RAAF Base Amberley from 1975 to 1999 to answer the questions –

> *Is there an association between adverse health status and an involvement in F-111 Deseal/Reseal activities?*
>
> *If so, what is the nature and strength of those associations?*

The study is to be conducted in three phases, the first phase of which included an extensive review of the scientific literature for evidence of adverse health affects from occupational exposure. This report summarises the literature review process and evidence found for associations between specific exposures relevant to SHOAMP and outcomes of interest.

A systematic and wide-ranging literature review was conducted to ensure that all appropriate outcomes and exposures, as well as important confounders and effect modifiers are considered and assessed. It also ensured that the most appropriate measures are used based on evidence for valid and reliable testing procedures and instruments.

The overall yield of occupational exposure and chemical literature was high. The bulk of the published literature consisted of toxicology summaries for specific chemical components, health hazard reports for individual organisations and small case study reports detailing symptoms where exposure intoxication had occurred, which could have been a reflection of the search style and database facilities utilised.

Ensuing search techniques concentrated on references quoted within published literature; search terms using specific authors; and known journals. Greater attention was directed towards identification of case-control and cohort studies that investigated associations between adverse health outcomes and exposure, which were more in line with the aims and hypotheses of the Study of Health Outcomes.

Based on the scientific literature reviewed for this report the following key recommendations were made for the Study of Health Outcomes in Aircraft Maintenance Personnel –

- Conduct a study of mortality and cancer incidence to further investigate the development of cancer by workers involved in the F-111 DSRS programs compared with appropriate comparison groups;
- As part of the General Health and Medical Study:
    - → Include screening items suitable for questionnaire or interview administration for identification of previous diagnoses particularly involving depression, dementia, cancer, multiple sclerosis, and motor neurone disease;
    - → Include screening items suitable for questionnaire or interview administration for identification of alcohol and smoking habits, and opportunity for occupational exposure to hazardous substances outside of the F-111 DSRS programs;
    - → Administrate a battery of tests to assess neuropsychological abilities for both exposed and comparison cohorts, giving consideration to brevity of tests and reducing repetition;
    - → Collect data on the reproductive health of female workers involved in the F-111 DSRS programs and also female partners of male workers; and
    - → Include tests for chromosomal aberrations and storage of blood samples for future analysis.

ACKNOWLEDGMENTS

We would like to take this opportunity to thank members of the Scientific Advisory Committee (SAC) and Consultative Forum, representatives from the Departments of Veterans' Affairs (DVA) and Defence for their contributions to this Report.

Also many thanks to Amanda Wilson for her writing and research skills, and to Rowena Brown for her tireless work searching and retrieving documents and proof reading.

BACKGROUND

Ordered from the United States in the early 1960s, the F-111 aircraft are an important part of Australia's defence. The advantage of these aircraft is that they can fly long distances at high speed. This requires the ability to carry a large quantity of fuel and the fuel tanks to be sealed in such as way as to avoid leakage under such extreme conditions. F-111s have numerous fuel tanks of varying size. At the time of manufacture sealant was put between the overlapping metal surfaces in the tanks. Over time the sealant used deteriorated and needed to be replaced. This involved removing the original sealant inside the fuel tanks (desealing) and replacing it with new sealant (resealing). Removal of the sealant required firstly the use of chemicals, then physical removal using water jets and then manual removal using hand tools. For the fuselage fuel tanks the process of desealing and resealing required physical entry to the tanks; while for wing tanks actual entry was not required.

There were four F-111 Deseal/Reseal programs conducted over the period 1975 to 1999, involving RAAF personnel and some contracted civilian workers, in addition to routine maintenance activities carried out in between programs as necessary. Methods used during each program varied over time; however there was evidence that neither respiratory protection nor skin protection requirements were complied with. Moreover, there may have been a multiplication effect on health when DSRS practices were combined with confined working space and high temperatures.

Some concerns have been reported regarding adverse health effects as a direct result of participation in the F-111 DSRS programs. These concerns have included neurological and psychological problems and possible increased rates of cancer and multiple sclerosis. In response to this, a Board of Inquiry (BOI) was conducted into the chemical exposure of F-111 DSRS workers to clarify exactly what happened.

Simultaneously, the (then) Chief of the Air Force also decided that an epidemiological study be conducted into the health of personnel involved in the F-111 DSRS programs compared with appropriate comparison personnel.

This study, known as the Study of Health Outcomes in Aircraft Maintenance Personnel (SHOAMP), is being undertaken by researchers from The University of Newcastle Research Associates (TUNRA Ltd) and the Hunter Medical Research Institute. The Study consists of three Phases:

a) Phase I involved a detailed literature review to explore evidence of relationships between exposures potentially encountered during F-111 DSRS activities and adverse health outcomes, a qualitative study to obtain in-depth information on activities and exposures of individuals involved in DSRS, finalisation of definitions of the exposed and comparison cohorts and development of a detailed protocol manual for the General Health and Medical Study.
b) Phase II is a Mortality and Cancer Incidence Study, based on record linkage with data from the National Death Index and all State and Territory Cancer Registries.
c) Phase III of SHOAMP is a General Health and Medical Study involving a detailed postal questionnaire and a series of health and neuropsychological examinations to assess exposure and outcomes for individuals involved in F-111 DSRS activities and comparisons.

The task faced by the SHOAMP is to determine if there is evidence to support anecdotal reports of adverse health problems in personnel involved in the F-111 DSRS programs. Because of the variety and complexity of the different exposures it was determined that a detailed literature review should be undertaken to obtain the most recent information on the relationship between exposures potentially encountered during DSRS activities and possible outcomes. This would then inform measures required for the General Health and Medical Study examinations to be undertaken as Phase III of SHOAMP.

STUDY ORGANISATION AND ADMINISTRATION

The Study of Health Outcomes in Aircraft Maintenance Personnel is a collaborative study conducted by researchers from The University of Newcastle Research Associates (TUNRA Ltd) and the Hunter Medical Research Institute. The study is administered by the Department of Veterans' Affairs on behalf of the Department of Defence.

The Scientific Advisory Committee (SAC) oversees the scientific aspects of the study. In terms of specific health tests to be administered as part of the General Health and Medical Study (Phase III), the SAC provided valuable recommendations and support for the research team. The SAC standing members are:

- Professor Judith Whitworth (SAC Chair), Director John Curtin School of Medical Research, Australian National University;
- Professor Michael Moore, Director National Research Centre for Environmental Toxicology;
- Dr David Roder, Anti Cancer Foundation of South Australia;
- Dr Deborah Glass, Department of Epidemiology and Preventative Medicine, Monash University; and
- Emeritus Professor Scott Henderson, AO, Centre for Mental Health Research, The Australian National University; Clinical Advisor in Mental Health, Commonwealth Department of Health and Ageing.

In addition to standing members, the SAC is also regularly attended by participants and observers representing a number of other organisations:

- Department of Veterans' Affairs
- TUNRA study team
- Defence Health Services Branch

- Defence Workplace Safety Project
- F-111 Advocate's Office
- Australian Institute of Health and Welfare
- Health Services Australia
- SHOAMP Consultative Forum

A Consultative Forum provides a link between the SAC and interested parties. Members receive regular briefings on proposals in relation to the conduct of the study and provide a forum for feedback from members on issues such as privacy, storage of information and selection of control groups. Organisations represented by the Consultative Forum include:

- Department of Veterans' Affairs
- TUNRA study team
- Defence Health Services Branch
- Defence Workplace Safety Project
- F-111 Advocate's Office
- SHOAMP SAC
- Warrant Officer of the Air Force
- Australian Veterans and Defence Services Council
- Armed Forces Federation of Australia
- Regular Defence Force Welfare Association
- Royal Australian Air Force Association
- Defence Community Organisation
- Returned and Services League of Australia Limited (RSL)
- SERCO Defence Services
- Repatriation Medical Authority
- Queensland Workcover
- Representatives from Deseal Reseal programs
- Health Services Australia

THE ISSUE OF OCCUPATIONAL EXPOSURE

Defined as contact that occurs during the performance of job duties, occupational exposure can potentially have both acute and chronic implications for poor health that is experienced by workers carrying out certain activities. In terms of the Study of Health Outcomes in Aircraft Maintenance Personnel, an occupational exposure that may place a worker at risk of developing adverse health outcomes was defined as having an involvement in any of the F-111 fuel tank DSRS programs or F-111 DSRS related activities.

Occupational exposure standards are concentrations of substances that are given as guidance in assessing the risk from exposure. In Australia, The National Occupational Health and Safety Commission (NOHSC) establishes the standards to be used as guides for control of hazardous substances. They are based on exposures to which most workers might be subjected to day after day during their working lives without suffering adverse consequences. The exposure limits are set by reviewing epidemiological and clinical studies of workers, over both short and long-term exposures to see if they indicate any adverse health effects. The long-term effects are particularly important for diseases with long latency periods (eg; cancer and dust diseases). Animal and in vitro studies have also been used, as have some human volunteer exposure experiments.

A large proportion of the literature investigating occupational exposure concerns the impact on the health of workers of exposure to organic solvents (eg; methyl-ethyl-ketone, toluene, xylene and benzene), organic chemicals that differ widely in structure (1). The topic of solvent toxicity is broad, and has been investigated by researchers seeking evidence of associations between exposure and outcomes.

Research areas have included central nervous system dysfunction (2, 3, 4), disorders of pregnancy, menstruation and paternal reproduction (5, 6, 7, 8, 9, 10), increased psychiatric symptomatology (11, 12), toxic encephalopathy (13, 14) and cancer (15, 16, 17).

There are a number of methodological issues that need to be considered when exploring the area of exposure and adverse health reactions, such as selection bias, matching of control subjects, acute versus chronic effects and the influence of confounders on test performance.

Recently, there has been a move towards “harmonisation of (investigative) methods” (18) employed for the purposes of assessing the effects of occupational exposure on body systems. Although not promoted as standardisation, the move towards harmonisation of approaches to risk assessment is envisaged to increase understanding of the methods used in order to increase confidence when using difference approaches. This includes planned efforts towards reproductive and developmental toxicity, carcinogenicity and neurotoxicity (19). The scope of the current literature review was to inform the decisions about which health outcomes to investigate during the General Health and Medical Study (Phase III).

In summary, chemicals have become an indispensable part of life. However, despite their benefits, there may be an association between some chemicals and adverse effects on human health, a suggestion supported within the epidemiological literature. Moreover, there have been a variety of techniques employed to assess exposure and to evaluate the effects of that exposure on health, which have important implications for the conduct of the SHOAMP General Health and Medical Study.

AIM OF THIS REPORT

The Final Report on the SHOAMP literature review has been prepared as per the Services Agreement between the Commonwealth Department of Veterans' Affairs and the Repatriation Commission and TUNRA Ltd.

The aim of the literature review was to provide a synthesis of the evidence of relationships between exposures and outcomes. Evidence of associations would provide a rationale for the conduct of the General Health and Medical Study by the identification of *a priori* areas for investigation.

It was not the purpose of this review to conduct a systematic appraisal of the evidence, nor conduct a meta-analysis. As such, this Report will not provide a detailed critique of issues such as quality assessment of studies, heterogeneity of effects and publication bias, which would normally be included as part of a systematic review. This review concentrated instead on bringing together the wide variety of information that exists regarding occupational exposure with particular emphasis on the needs and objectives of the Study of Health Outcomes.

With reference to the original aims and objectives of the SHOAMP literature review, the aims of this Report are to:

- Describe the processes used during the literature review;
- Provide details of search terms utilised for both exposure and outcomes of interest;
- Provide a full bibliography of all references and sources of information;
- Describe the yield of the search;
- Provide a summary of search results in terms of evidence for associations between exposure and health outcomes; and
- Provide a summary of search results in terms of measurement of exposure and outcomes.

The Results section of the Final Report is separated into two areas –

1) A description of the evidence for associations between exposure and SHOAMP specific outcomes, and
2) A description of the evidence for specific measurement techniques.

Given the different questions being addressed by this Report, the aims for each outcome-specific literature review differs across topics.

RESEARCH QUESTION AND HYPOTHESES

The General Health and Medical Study aims to answer the questions –

Is there an association between adverse health status and an involvement in F-111 Deseal/Reseal activities?

If so, what is the nature and strength of those associations?

The hypotheses of the study are that Australian Defence Force and contracted civilian personnel involved in any of the F-111 Deseal/Reseal programs, will have, relative to an appropriate comparison group –

- A higher rate of mortality;
- A higher rate of incidence of cancer;
- A higher prevalence of specific neurological disorders;
- A higher prevalence of neuropsychological impairment;
- A higher rate of reproductive outcomes;
- A higher rate of genetic damage; and
- Poorer general health and quality of life.

The literature review aimed to investigate and describe evidence of associations between occupational chemical exposure and adverse health outcomes. Specific health outcomes identified by the F-111 Deseal Reseal Interim Health Care Scheme were treated as priority areas during the literature search process. However, searches were not limited to these fields, and evidence for associations between exposure and other health conditions were also examined.

METHODS

Construction of search terms

Chemical search terms

A preliminary list of all F-111 Deseal/Reseal program activities was developed based on information provided within Volumes I and II of the Board of Inquiry Report. Against each activity type, according to program, were listed the main chemical substances used, where they were used and by whom.

Using the Board of Inquiry Volume I and II, other reports compiled by Defence as part of the Inquiry, toxicology web-sites and RAAF Material Safety Data Sheets for individual chemical types, the original list of chemicals was further expanded to include all chemical “brand” names, individual chemical components, synonyms and CAS (Chemcial Abstract Service) registry numbers (refer to Appendix A). Chemical substances not included within any of the F-111 Deseal/Reseal programs were not investigated further. The Chemical Spreadsheet then served as a tool for expert review, to enable the literature review to focus only on those substances most relevant to SHOAMP, and more likely to be related to adverse health outcomes in aircraft maintenance personnel assisting with Deseal/Reseal activities.

In order to rationalise the extensive list of chemical products and synonyms into a succinct list to crosscheck with other literature search terms, an expert review was conducted. Three experts were asked to review and justify the inclusion of specific chemical terms for use during the literature search, from the original list of chemicals reported to have been involved in the F-111 Deseal/Reseal programs.

The three experts who assisted with the review were –

- Professor Michael Moore – SAC standing member, Director of the National Research Centre for Environmental Toxicology and Queensland Health Scientific Services and Professor of Medicine at the University of Queensland;
- Dr Anthony Brown – Director of Population Health and Planning, Macquarie Area Health Service, Conjoint Associate Professor, Environmental and Occupational Health, The University of Newcastle; and
- Dr Diana Oakes – Postdoctoral Fellow in Reproductive Toxicology Laboratory, University of Sydney.

Each expert reviewed de-sealants and sealants, solvents and cleaners, adhesion promoters and primers, to exclude all unnecessary or incorrect terms and to highlight those terms that would facilitate an efficient and effective literature search. Appendix B provides a summary of all chemical search terms following expert review.

The word “solvent” had been excluded from the original search term list. The term had been thought too inclusive and would result in terminology artifact. However, it became apparent that searches limited by “title” would not identify many specific chemical terms. Therefore “solvent” was included in all database searches, and served to produce in particular, relevant papers for specific health symptoms/conditions (eg; corneal reflex, pulse rate).

Outcome search terms

The six main areas of interest were negotiated between members of the study team, representatives from the Department of Defence, Department of Veterans’ Affairs and members of the Scientific Advisory Committee. These included:

- Bio-markers
- Toxicology
- Neuropsychology

- Cancer
- Birth defects, and
- Multiple Sclerosis and Motor Neurone Disease

Each Study Investigator took responsibility for one of the review topics and generated a series of terms considered most representative of each health outcome of interest for SHOAMP. These terms were used to best capture relevant literature when cross-checked against each chemical term.

To assist the generation of search terms within each topic of interest, items were entered into The University of Newcastle's Medline search facility and checked against extended "tree" alternate search terms for the same topic (ie; search on "brain disease" also identified "encephalon diseases" and "intracranial CNS disorders"). Refer to Appendix C for the full list of outcome search terms.

Based on health symptoms reported by workers by the F-111 Deseal Reseal Interim Health Care Scheme, and health problems discussed during the Phase I qualitative interviews, several purposeful searches were conducted to explore the literature with regards to the following:

"pulse rate", "proprioception", "hypertension", "body fat", "caffeine", "olfactory nerve", "colon", "respiratory function", "neuropsychiatric", "neurobehavioural", "health condition", "mood", "neuropathy", "ischemic heart disease", "psoriasis", "nystagmus", "optic disk", "corneal reflex", "colour vision", "visual field disorder" and "neuropsychological".

This complementary search satisfied the need to explore scientific evidence for health complaints raised by individuals.

Identification of search facilities

Search facilities and resources utilised for SHOAMP included:

- Mainstream databases of peer-reviewed journals (ie; Medline, Cochrane Library, Toxline);
- General key-word searches using a variety of Internet search engines (ie; Google, AOL, Yahoo);
- Manual reviews of the reference lists of published papers;
- Local occupational health resources (ie; Environmental and Occupational Health, School of Health Sciences, The University of Newcastle); and
- Occupational Health and chemical-specific web-sites (ie; Environmental Protection Agency sites, National Toxicology Program).

The time frame employed for database search was 1970 to 2002. Initial search techniques included all studies, whether human or animal based. Secondary searches targeted “English” and “Human” publications only, especially during Toxline and Medline searches where the number of papers identified for each search regularly exceeded 1000. A list of resources used for identification of search terms and toxicology information in general is provided in Appendix D.

For the information of each investigator, “all fields” searches and “title only” limitations were conducted. The “title only” criterion was applied once the number of resulting papers and reports exceeded 1000 per single search (ie; “toluene” and “cancer”). In order to explore a wide variety of study types and review articles, an inclusive approach was taken, with each outcome search term matched against each chemical search term systematically.

Expert Review

A full list of all search result abstracts was presented to the Study Investigator or Consultant responsible for reviewing evidence of associations relevant to their area of expertise. Depending upon the health outcome of interest, different inclusion and exclusion criteria were applied by each investigator. However, across all areas of investigation, the following steps were applied:

- Agreement on the question being dealt with and the aim of the review;
- Identification of relevant works – each abstract had to include the search terms specific to the health topic of interest;
- Exclusion of abstracts which did hold relevant search terms but were not appropriate for the Study of Health Outcomes; and
- Priority ordering of remaining abstracts based on the type of literature (research paper versus hazard report), reliability of source (peer reviewed journal versus general web-site), type of study (single case study versus RCT etc), use of reliable and valid measures and methodology, and general overall quality of reporting.

In addition to these generalised steps the following issues were considered:

- Whether the study had been conducted using human populations: animal studies provided useful information but needed supplementation;
- Whether the exposures of interest had been identified within the paper: whether the appearance of the exposure preceded the health outcome; whether the study provided data on exposure;
- Whether the study specified *a priori* the hypotheses being tested; and
- Whether the study controlled for possible confounding factors.

The SHOAMP literature review aimed to explore the existing scientific evidence for associations between targeted adverse health outcomes and exposure to hazardous substances applicable to the issue of F-111 Deseal/Reseal maintenance. No meta-analyses were conducted, based on the aim of the review and the variety of published styles identified. A meta-analysis can only be done if the biases and confounding factors are adequately addressed in each study, and if the studies being reviewed measured the same exposures in the same way and compared risk between or among similar levels of exposure. No data combining was conducted as part of this review. Individual abstracts and reports were reviewed individually and summarised into table matrix format.

RESULTS

Yield of literature review

Table 1 provides summary information of the total number of papers identified using SHOAMP literature review procedures. Results are described according to each health outcome of interest, the total yield and the final number of papers and reports collected in full by the research team for further review.

A large number of toxicology reports and health hazard reports for individual organisations were identified during the search process. This may have been due to the nature of the chemical search terms used in combination with certain databases. Epidemiological studies published in peer reviewed journals did not necessarily specify the same level of detail in terms of exact chemical names and components, as toxicology reports, and therefore were not identified as readily.

Given the potential for toxicological artifact, articles identified using search facilities on the Toxnet web-site (20) were cross-checked against Medline and PubMed for completeness, to ensure that all relevant papers and reports were being found. This proved an invaluable step in the overall search process, given that Toxnet often reported zero papers, depending on the order of search terms entered. A rearrangement of the search terms was often necessary, which then yielded many relevant results.

Also included in the overall search results were articles identified by individual study Investigators/Consultants, based upon their own professional knowledge and access to on-line journal information. This adjunct to the initial inclusive search technique proved very successful in identifying more recent papers which contained exposure and measurement data relevant to SHOAMP.

Table 1 : Literature search results

Search Domain	Overall Search Result	Final Reviewed Papers
Bio-markers	723	58
Birth defects	57	10
Toxicology	751	59
Cancer	19,420	124
MS & MN Disease	152	69
Neuropsychology	321	166
Health and Aircraft Maintenance	60	24
	Total N = 21,484	***Total N = 510***

Literature search results for the “toxicology” terms served to validate findings within other domains of interest, and were incorporated accordingly into those reviews. Therefore “toxicology” is not presented in this Report as a separate area of review.

Associations between exposure and health outcomes

Cancer

The aim of the current review was to identify substances associated with F-111 Deseal/Reseal programs and assess their association to cancer. From an initial yield of 19,420 a more relevant 838 papers were reviewed, of which 124 were deemed to be relevant by the reviewers and full text versions were requested. There were two major sources of data on chemicals, which are carcinogenic or possibly carcinogenic. These were the International Agency for Research on Cancer (IARC) and US Environment Protection Authority (EPA).

There are some differences between the IARC and EPA in terms of their classifications of substances as to whether they were “known”, “probable” and “possible” carcinogens. In addition to presenting information on substances which have been classified, we also explored substances not identified by either organisation.

The International Agency for Research on Cancer (IARC) is part of the World Health Organisation. IARC conducts research on the causes of human cancer, the mechanisms of carcinogenesis, and the development of scientific strategies for cancer control. There is an ongoing evaluation of products and their carcinogenicity to humans and this information is published on the IARC Web-site. The last update for this IARC was 26 August 2002. The information in this list reflects the findings of current literature.

The US EPA has been working for more than 30 years with the mission to “protect human health and safeguard (the) community”. Part of the work of the EPA is the Integrated Risk Information System (IRIS) an electronic data base containing information on the possible effects of exposure to various chemicals on humans. Information contained in IRIS represents a consensus opinion of EPA health scientists. All new scientific data is reviewed and the IRIS files are revised as appropriate.

Published literature was reviewed independently in addition to IARC and EPA findings. Table 2 provides cancer classifications for those substances most relevant to SHOAMP. While the IARC and EPA reviews included results from numerous studies, some literature was not included. Table 3 provides a summary of studies involving cancer and exposure not included in IARC and EPA classifications. In addition, Appendices E and F report additional exposure articles.

There is good evidence that benzene, chromic trioxide, strontium chromate, zinc chromate (all of which contain the hexavalent form of chromium), ethylbenzene and crystalline silica are all carcinogenic to humans.

Benzene is known to cause acute and chronic nonlymphocytic leukaemia, chronic lymphocytic leukaemia and haematologic neoplasms. Hexavalent chromium is known to cause lung cancer.

White spirits, naphtha and Stoddard solvent are probable carcinogens and are associated with cancers of the lung and prostate as well as Hodgkin's lymphoma. Carbon black is possibly carcinogenic to humans and there is evidence that solvent extracts are carcinogenic to humans and can be linked to cancers of the lung and oesophagus. Lead chromate is also possibly carcinogenic in humans and is associated with cancers of the lung, stomach and kidney.

Acetone, chromic oxide (trivalent chromium – insoluble salts), manganese compounds (manganese dioxide), methyl ethyl ketone, toluene, isopropanol, bisphenyl A, 2-xylene and 3-xylene were not able to be classified as to their potential to cause cancer in humans.

Substances that have not been evaluated as to their cancer causing potential in humans include butoxyethanol ester, ethyl acetate, propylene glycol monomethyl ether and sodium hydroxide. The literature review did not identify any other substances that might be identified as carcinogenic.

To summarise, known carcinogens relevant to the SHOAMP, reported within the literature are benzene, strontium chromate, zinc chromate (hexavalent chromium) and silica. A number of case reports described associations between leukaemia and benzene, particularly myelogenous and lymphocytic.

Relevant to SHOAMP is the evidence for an association between exposure to benzene and the appearance of chromosomal aberrations following high levels of exposure. Strontium chromate, zinc chromate and silica have been related to pulmonary cancers, which may have implications for personnel involved in the F-111 spray seal program and the potential for inhalation effects.

Probable carcinogens include white spirit, naphtha and stoddard solvent. Possible carcinogens are carbon black and lead chromate. Not classifiable were acetone, ethyl benzene, isopropanol, manganese, methyl ethyl ketone, toluene, xylene and iron oxide. Not evaluated were bisphenyl A, butoxyethanol ester, ethyl acetate, propylene glycol monomethyl ether and sodium hydroxide.

Given that some of the exposures associated with the F-111 Deseal/Reseal programs and activities are known human carcinogens, the importance of undertaking the Mortality and Cancer Incidence Study was confirmed. A variety of cancers are likely to be associated with the DSRS exposures, although lung, other respiratory and hematopoietic cancers are commonly reported. It is recommended that participants taking part in the General Health and Medical Study examinations be asked to provide details of any cancers previously diagnosed. In addition, since breast and colon cancer have been linked to some exposures, and because of specific concerns regarding these outcomes, breast examination is suggested, and provision of a take home Faecal Occult Blood Test (FOBT) kit.

Table 2 : Summary of chemicals and cancer classifications

Substance	Program	IARC classification	EPA classification	Type of cancer	Comments
Acetone	Wing Program	--	D: Not classifiable as to human carcinogenicity	--	--
Bisphenyl A	Spray seal, Wing Program	3: Not classifiable as to carcinogenicity in humans	Has not undergone complete evaluation	--	See below
	Comments – No epidemiological data relevant to the carcinogenicity of bisphenol A diglycidyl ether were available. There is limited evidence in experimental animals for the carcinogenicity of bisphenol A diglycidyl ether.				
2, 4, 5-t Butoxyethanol Ester	--	--	Has not undergone complete evaluation	--	--
Benzene	Wing Program	1: Carcinogenic to humans	A: Known human carcinogen	Acute & Chronic nonlymphocytic leukaemia, Chronic lymphocytic leukaemia Haematoligc neoplasm	See below
	Comments – Workers and the general public are exposed to benzene as a result of a variety of activities in which it is processed, generated or used. Major contributors to benzene emissions into air include (1) gasoline production, storage, transport, vending and combustion; (2) production of other chemicals from benzene; and (3) indirect production of benzene (eg; in coke ovens). The last is the major source of benzene emissions into water. Chronic human exposure to benzene results in leucopenia, thrombocytopenia, anaemia or combinations of these. At early stages of such blood dyscrasias, these effects appear to be reversible. Exposure to high doses for longer periods of time may lead to pancytopenia, which results from aplasia of the bone marrow and is considered to be an irreversible stage of the disease. Benzene crosses the human placenta. There is a clear correlation between exposure to benzene and the appearance of chromosomal aberrations in the bone marrow and peripheral lymphocytes of individuals exposed to high levels of benzene (>100 ppm). Such levels of exposure usually lead to clinical symptoms of benzene-induced blood dyscrasias. These aberrations may persist for many years after exposure and after manifestations of haematotoxicity. The results are not so clear with lower levels (<100 ppm). Although aberrations have been reported following chronic exposures to as little as 10 ppm, this has not been a consistent finding. Environmental factors and exposure to other agents may have interacted with benzene in these studies of low exposure. Many case reports and case series have described the association of leukaemia with exposure to benzene, either alone or in combination with other chemicals. Most cases were acute myelogenous leukaemia, although some were monocytic, erythroblastic or lymphocytic; and some lymphomas have been noted. Two follow-up studies showed high incidences of leukaemia among individuals ascertained as cases of benzene haemopathy. A series of epidemiological studies, both cohort and case-control, showed statistically significant associations between leukaemia (predominantly myelogenous) and occupational exposure to benzene and benzene-containing solvents. These results were replicated in a number of countries and different industries. In the epidemiological studies of people exposed primarily to benzene, statistically significant excesses of leukaemia were observed.				

Table 2 continued…

Substance	Program	IARC classification	EPA classification	Type of cancer	Comments
Carbon Black	Program 1 Program 2 Spray seal Wing program	2B: Possibly carcinogenic to humans, sufficient evidence that solvent extracts carcinogenic to humans	--	Lung, oesophagus	See below
	Comments – Cohort studies of carbon black production workers have been conducted in the United States and in the United Kingdom. Interpretation of the study in the United States is hampered by problems of uncertainty in the completeness of the cohort and in the definition and completeness of follow-up. The study in the United Kingdom also had some problems in completeness of the cohort, but the follow-up was probably complete. In both cohorts, fewer observed than expected deaths due to all causes occurred and, in the study in the United States, this may in part have been attributable to under-ascertainment of deaths or to inflation of person-years of follow-up. The study in the United States found no excess mortality due to any type of cancer when compared to state vital statistics rates; in fact there were deficits for some types of cancer. The study in the United Kingdom found an excess of respiratory cancer deaths (standardised mortality ratio, 1.5, 95% confidence interval, 1.0-2.2). A nested case-control study within the United States cohort was hampered by small sample size and problems with interpretation. Most cases were of non-melanoma skin cancer. Neither for all cancers combined nor for skin cancers alone was there evidence that cases had higher cumulative exposure to carbon black than controls. A cohort study was carried out among workers in the United States to assess cancer risks due to exposure to formaldehyde. Ten participating plants were spread across several industries in which workers may have experienced exposure to formaldehyde. To control for confounding and modification of effect by other exposures, workers' exposures to various other chemicals, including carbon black, were assessed by industrial hygienists. For all assessed levels and duration of exposure to carbon black combined, there was a slight non-significant excess of lung cancer. There was no clear trend by duration of exposure. Carbon black-exposed workers in this cohort may also have been exposed to formaldehyde and other substances. In assessing all the available data, there is no evidence of an effect of carbon black for most cancer sites. For cancers of the urinary bladder, kidney and oesophagus, isolated results indicate excess risks, but these are not sufficient to support an evaluation of human carcinogenicity.				
Chromic Oxide	Program 1 Program 2 Spray seal Wing program	--	D: Not classifiable as to human carcinogenicity	--	Trivalent chromium (insoluble salts)
Chromic trioxide	Program 1 Program 2 Spray seal Wing program	1: Carcinogenic to humans	A: Known human carcinogen	Pulmonary / lung Nasal, pharyngeal, gastrointestinal, sinuses	Hexavalent chromium

Table 2 continued…

Substance	Program	IARC classification	EPA classification	Type of cancer	Comments
Ethyl Acetate	Program 1 Program 2	--	Has not undergone complete evaluation	--	--
Ethylbenzene	Program 1 Program 2 Wing program	2B: Possibly carcinogenic to humans. There is evidence that solvent extracts are carcinogenic to humans	D: Not classifiable as to human carcinogenicity	--	See below
	Comments – Two studies of workers potentially exposed to ethylbenzene in a production plant and a styrene polymerisation plant were available. In the first study, no excess of cancer incidence was found but the description of methods was insufficient to allow proper evaluation of this finding. In the second study, no cancer mortality excess was observed during the follow-up of 15 years.				
Iron Oxide	Wing	--	--	No evidence of association in one study in factory workers	See below
	Comments – On the basis of epidemiological evidence, exposure to haematite dust may be regarded as increasing the risk of lung cancer development in man. The risk is manifest in underground workers but not surface workers, and it is not known whether the excess risk is due to radioactivity in the air of mines, the inhalation of iron oxide or silica, or to a combination of these or other factors. There is no evidence that iron-ore dust (haematite) or iron oxide influences the incidence of cancers at sites other than the lungs.				
Isopropanol	Program 1 Program 2 Wing program	3: Not classifiable as to carcinogenicity in humans	--	--	See below
	Comments – An increased incidence of cancer of the paranasal sinuses and laryngeal cancer was observed in workers at factories where isopropanol was manufactured by the strong-acid process. One case–control study investigated the risk associated with occupational exposure to isopropanol, but for none of the investigated cancer sites was a significant increase in risk observed.				
Lead Chromate	--	2B: Possibly carcinogenic in humans	B2: Possible human carcinogen	Lung, stomach, kidney	A small study in the UK of workers producing lead chromate pigments showed no overall excess risk for lung cancer, but a nonsignificant excess risk for lung cancer was seen in a subgroup of workers with lead poisoning.

Table 2 continued…

Substance	Program	IARC classification	EPA classification	Type of cancer	Comments
Manganese compounds (Manganese dioxide)	Program 1 Program 2 Spray seal Wing program	--	D: Not classifiable as to human carcinogenicity	--	--
Methyl ethyl ketone	Program 1 Program 2 Spray seal Wing program	--	D: Not classifiable as to human carcinogenicity	--	Ketones generally unclassifiable by IARC
Propylene glycol monomethyl ether	Spray seal	--	Has not undergone complete evaluation	--	--
Crystalline Silicia	Spray seal	1: Carcinogenic to humans (crystalline silica)		Lung cancer	There is sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources. There is inadequate evidence in humans for the carcinogenicity of amorphous silica.
Sodium hydroxide	Program 1 Wing program	No data on carcinogenicity	--	--	--
Strontium chromate	Spray seal	1: Carcinogenic to humans	--	Pulmonary / lung Nasal, pharyngeal, gastrointestinal, sinuses	Hexavalent chromium

Table 2 continued…

Substance	Program	IARC classification	EPA classification	Type of cancer	Comments
Toluene	Program 1 Program 2 Spray seal Wing program	Toluene is not classifiable as to its carcinogenicity to humans (Group 3).	D: Not classifiable as to human carcinogenicity	--	See below
	Comments – Toluene was mentioned as an exposure in eight studies. Two were community-based case–control studies, one of which involved brain cancer and one involved several types of cancer. Of the six industry-based studies, three were analysed as cohort studies and three were configured as nested case–control studies of one or a few types of cancer. In two of the studies, that of shoe-manufacturing workers in the United States and particularly that of Swedish rotogravure printers, it was believed that toluene was the predominant exposure; in the other studies, there were probably concomitant exposures. Cancers of most sites were not significantly associated with toluene exposure in any study. Stomach cancer mortality was significantly elevated in the Swedish rotogravure printers' study, it was slightly, though not significantly, elevated in two other studies, and it was not associated at all in a fourth. Rates of lung cancer were significantly elevated in the cohort of shoe manufacturers and in the Swedish cohort of rotogravure printers, but was not associated at all in two other studies. Colorectal cancer was significantly elevated in the Swedish rotogravure printers' study and in the Canadian case–control study, and colon cancer was non-significantly elevated in the shoe manufacturer cohort. While results on leukaemia and lymphoma generally showed no association, these were based on small numbers. Considering the multiple exposure circumstances in most studies and the weak consistency of findings, these results are not strong enough to conclude that there is an association.				
Zinc chromate	Program 1 Program 2 Spray seal Wing program	1: Carcinogenic to humans	--	Pulmonary / lung Nasal, pharyngeal, gastrointestinal, sinuses	Hexavalent chromium
2-Xylene **3-Xylene**	Spray seal Wing program	3: Not classifiable	D: Not classifiable as to human carcinogenicity	--	No data were available to the Working Group.
White spirit, naphtha, Stoddard solvent	Program 1 Program 2 Wing Program	--	--	Lung, prostate Hodgkins lymphoma	In a single case-control study of cancer at many sites, potential long, high exposure to 'mineral spirits' was associated with increased risks for squamous-cell lung cancer and prostatic cancer. In two case-control studies, one of primary liver cancer and one of Hodgkin's disease, an association with organic solvents, including white spirits, was seen. The results of these studies could not be evaluated with regard to petroleum solvents themselves.

IARC: International Agency for Research on Cancer classifications -

1: Carcinogenic to humans based on: sufficient evidence in humans and sufficient evidence in animals

2A: Probably carcinogenic to humans

2B: Possible carcinogen to humans, limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals

3: Not classifiable

EPA classifications -

A: Human carcinogen

B: Probable human carcinogen

B1 Indicates limited human evidence

B2: Indicates sufficient evidence in animals and inadequate or no evidence in humans

C: Possible human carcinogen

D: Not classifiable as to human carcinogenicity

E: Evidence of non-carcinogenicity for humans

Table 3 : Summary of cancer studies not included in IARC and EPA classifications

Author / Year	Study type	No.	Population	Exposure	Site of Cancer	Results
Chen, 1996 (21)	Meta-analysis	55 published mortality studies	Organic solvent exposed workers	Solvents	All cancer mortality, Leukaemia, Liver cancer	Significant associations for: Leukaemia (SMR122.2; CI101.6-146.9) Liver & biliary passages (SMR119.7; CI104.4-137.2)
Ojarjarvi, 2000 (22)	Meta-analysis	92 studies	Studies with verified exposures	Substance exposure based on FINJEM job exposure matrix. Substances investigated included organic solvents.	Pancreatic Cancer	Increased meta-risk ratios include (RR, 95% CI): chlorinated hydrocarbon solvent, (1.0; 1.0-1.8) chromium & chromium compounds (1.4;0.9-2.3) polycyclic aromatic hydrocarbons (1.5;0.9-2.5) silica dust (1.4;0.9-2.0) aliphatic and alicyclic hydrocarbons (1.3;0.8-2.8)
Ojarjarvi, 2001 (23)	Meta-analysis	N/A	Studies which addressed occupational exposure directly	Chlorinated hydrocarbons	Pancreatic Cancer	Weak excesses were found for some substances however no statistically significant excesses were observed.
Hayes, 2001 (24)	Review article	106 papers	Various	Benzene exposure	Lymphohema-topoietic malignancies in humans	Association between benzene exposure and haematopoietic disorders including cancer.
Cocco, 1998 (25)	Population Based case-control	1219, (178 cases)	10% sample of all reported breast cancer mortality in US	Socio-economic status Occupational high temperatures PAH's and solvents Electro-magnetic fields	Breast cancer in males	Link with solvent exposure not significant, insufficient power. Low exposure (OR 0.8; CI 0.4-1.4) Medium exposure (OR 0.8; CI 0.5-1.5) High exposure (OR 0.7; CI 0.2-2.1)
Hansen, 1999 (26)	Matched case-control study	17,534	Danish women, 20-55 years, employed in industries with extensive use of organic solvents.	Investigated employment in industries with extensive use of organic solvents. Metal products, wood and furniture, printing, chemical, and textile and clothing industries.	Breast cancer	An association of breast cancer in women employed in these industries. Employed > 1 year (OR 1.43; CI 1.24-1.67) Employed > 10 years (OR 1.97; CI 1.39-2.79)

Table 3 continued…

Author / Year	Study type	No.	Population	Exposure	Site of Cancer	Results
Cocco, 1998 (27)	Population based case control	142,080	Deaths in 24 states of US, 84-92	Increased risk by industry & occupation	Central Nervous System	Elevated Odds Ratio for a number of occupations including Aircraft engine mechanics (OR 1.7; CI 1.1-2.6) Exposure to solvents (OR 1.0; CI 1.0-1.1)
Cocco, 1999 (28)	Population based case-control	142,080 (28,416 cases)	Deaths in 24 states of US 1984-1992 Women only	Increased risk by industry & occupation	Central Nervous System	Elevated Odds Ratio for solvent exposure (OR 1.1; CI 1.1-1.2) Chlorinated aliphatic hydrocarbons (OR 1.1; CI 1.1-1.2) Poly aromatic hydrocarbons (OR 1.1; CI 1.0-1.3) Nitrosamines (OR 1.1; CI 1.0-1.3) Benzene (OR 1.1; CI 1.0-1.2)
Gerin, 1998 (29)	Population based case-control	4263 (3730 cases)	Population-based ascertainment of cases with diagnosed cancer in Montreal	Benzene, toluene, xylene, styrene	Colon, rectum, prostate, oesophagus, lymphoma	Increased Odds Ratio between (at 95% CI): Oesophagus – toluene (OR 1.9; 0.9-4.2) Colon – xylene (OR 5.8;1.5-22.0) Rectum – benzene (OR 2.0; 1.1-3.6) Rectum – toluene (OR 3.2; 1.3-8.0) Rectum – xylene (OR 1.5; 1.0-2.3) Rectum – styrene (OR 5.1;-1.4-19.4)
Wong, 1999 (30)	Nested case-control study	18,000	Petroleum distribution workers exposed to gasoline containing 2-3% benzene	Gasoline, benzene	Leukaemia, multiple myeloma, kidney cancer	No increased Odds Ratio identified Leukaemia (OR 0.8; CI 0.56-1.07) Multiple myeloma (OR 0.79; CI 0.46-1.24) Kidney cancer (OR 0.73; CI 0.47-1.09)
Latendresse, 1995 (31)	Animal case-control study	640 rats, 340 hamsters	Rats & Hamsters	Hydrazine	Nasal	Duration of exposure is a more significant factor than concentration in hydrazine induced nasal tumorigenesis
Dosemeci, 1999 (32)	Case-control investigating gender difference	438 cases, 687 controls	Population based in Minnesota	Investigated association with organic solvents-combined, all chlorinated aliphatic hydrocarbons-combined, nine individual chlorinated aliphatic hydrocarbons.	Renal cell carcinoma	Significant association for women exposed to All organic solvents combined (OR 2.3; CI 1.3-4.2) chlorinated aliphatic hydrocarbons-combined (OR 2.1; CI 1.1-3.9) and trichlorethylene(OR 2.0; CI 1.0-4.0) No significant excess risk observed in men All organic solvents combined (OR 0.93; CI 0.7-1.3)

Table 3 continued…

Author / Year	Study type	No.	Population	Exposure	Site of Cancer	Results
McCredie, 1993 (33)	Population based case-control	1,159	Cases were all incident cases in 1989-90 of cancer or the kidney cancer	Occupational exposure to particular chemicals chosen because of suspected association with kidney cancer	Kidney cancer	Increased association observed for the following occupations: Dry cleaning industry (OR 4.68; 1.32-16.56) iron and steel industry (OR 2.13; 1.04-4.39)
Hu, (16)	Population based case-control	6,659	Cases were newly diagnosed, histologically confirmed renal cell carcinoma cases	Occupational exposure to 17 chemicals	Kidney cancer	Increased association observed with exposure to the following (at 95% CI): Benzene (OR 1.8; 1.2-2.6) Benzidine (OR 2.1; 1.3-3.6) Cadmium (OR 1.7;1.0-3.2) Isopropyl oil (OR 1.6; 1.0-2.6) vinyl chloride (OR 2.0; 1.2-3.3)
Siemiatycki, 1994 (34)	Population based case-control	2,363	Cases were pathologically confirmed cases of bladder cancer	Occupational exposure in 19 occupations, 11 industries, and 23 substances	Bladder cancer	Increased association observed in: Natural gas combustion products, aromatic amines, cadmium compounds, photographic products, acrylic fibres, polyethylene, titanium dioxide, and chlorine.
Hours, 1994 (35)	Hospital based case-control	348	Bladder cancer patients in Lyon, France	Occupational exposure a number of substances including inks	Bladder cancer	No increased risks observed.
Krstev, 1998 (36)	Case-control	60,878	Death in 24 states of US of prostate cancer	Usual occupation and industry	Prostate Cancer	The role of occupation was unclear. Authors suggested that classification of occupation by description on death certificate might be problematic.
Cordier,1993 (37)	Hospital based case-control	1,530	Patients presenting at urology departments of university hospitals in several regions of France where different industrial activities were represented.	Histologically verified bladder cancer	Bladder Cancer	Statistically increased risk for exposure to Chlorinated hydrocarbons (OR 1.86; CI 1.19-2.90) Industrial oils & greases (OR 1.44; CI 1.1-1.89) Metallic oxide dust (OR 2.99; CI 1.12-8.01)

Table 3 continued…

Author / Year	Study type	No.	Population	Exposure	Site of Cancer	Results
Dement, 1998 (38)	Proportionate mortality study	2,985	Oil refinery workers from 3 Texan facilities	Solvent exposure in petroleum refineries	Cancer mortality	Proportionate Mortality Ratios were significantly increased for: (CI not reported) Lip (384), Stomach (142), Liver (238), Pancreas (151), connective tissues (243), prostate (135), eye (407), brain (181), leukemia (175), benign & unspecified neoplasms (289)
Bulbulyan, 1999 (39)	Cohort	3,473	Russian women employed for minimum 2 years in printing industry	Solvent exposure in the printing industry is high. Substances include organic pigments, PAH's, benzene, toluene, xylene, ethylene glycol and carbon tetrachloride.	Cancer mortality	Significant increase in Relative Risk in: Oesophageal (RR 2.7; CI 1.1-5.4) Ovarian (RR 2.9; CI 1.5-5.0) Stomach (RR 2.2; CI 1.0-4.2)
Teta, 1992 (40)	Historical cohort	1031	Ethanol and isopropanol production workers	All cause mortality	All cancer mortality	The following increased risks were observed: Larynx, buccal cavity, and pharynx
Lundgerg, 1998 (41)	Cohort	411	Swedish paint industry workers with long-term exposure to organic solvents (particularly xylene)	Cancer Incidence	All cancers	Increased risks observed in the following: Prostatic cancer Lymphatic & haematopoietic cancers Multiple myeloma
Berlin, 1995 (42)	Cohort	5,791	Population were patients with suspected solvent-related disorders	Exposure to organic solvents	All cause cancer incidence & mortality	Increased risk of cancer Lymphohematopoietic system and uterine cervix
Garland, (38, 43)	Cohort	2,275,829 person years	All enlisted US Navy personnel 1974-79	A confirmed discharge diagnosis of testicular cancer	Testicular Cancer	Increased relative risk of cancer in the following job descriptions: Aviation support equipment technician (RR 6.2; CI 1.9-13.0) Engineman (RR2.6; CI 1.2-4.8) Automobile mechanic (RR3.4 ; CI 1.9-5.6)

Table 3 continued…

Author / Year	Study type	No.	Population	Exposure	Site of Cancer	Results
Ducatman, 1986 (44)	Cohort	153	Men engaged in the maintenance of exterior surfaces and electrical components of aircraft	A histologically verified testicular germ cell cancer following at least 3 years of working at an airframe maintenance facility	Germ cell tumours of the testicle	Statistically significant result. No point estimates provided.
Axtell, 1998 (45)	Cohort	1,384	Persons employed in chemical plant with exposure to benzidine (an aromatic amine)	Exposure to aromatic amines	All cause mortality	Significant associations (with 95% CI) for : All malignant neoplasms (RR1.30; 1.05-1.60) Respiratory system (RR 1.61; 1.16-2.17) Lung (RR 1.67; 1.2-2.26) Malt genital organs (RR2.01; 1.00-3.60) Prostate cancer (RR2.13; 1.06-3.80)

Multiple Sclerosis, Motor Neurone Disease and Other Neurological Examinations

The purpose of the Multiple Sclerosis and Motor Neurone Disease literature search was to explore evidence of associations between exposure to solvents, and effects on the peripheral nervous system (PNS) and central nervous system (CNS), particularly multiple sclerosis and motor neurone disease. Tables 4 and 5 provide a summary of the literature in this area.

Motor Neurone Disease

Two studies looked at Motor Neurone Disease (MND) as an outcome. The first was a case control study undertaken in Sweden (46) which showed a significant association between exposure to any solvent and MND for men aged 45-59 (OR 3.2). In the second, Schulte (47) conducted a proportionate mortality study in the US over a 10 year period in an endeavour to identify usual occupation associated with early mortality due to neurodegenerative diseases including MND. The study found increased proportionate mortality ratios for firefighters, military personnel, janitors, or others with large exposures to potential toxins.

Multiple Sclerosis

Twelve studies and two meta-analysis papers were located and reviewed that explored the association between organic solvent exposure and multiple sclerosis. No study investigated associations between specific substances; but rather generic organic solvent exposure was explored. The two review papers were both by Landtblom (48, 49), who explored the association between solvent exposure and multiple sclerosis. Landtblom's review specifically targeted studies between 1966 and 1994 that explored if any association existed between occupational exposure to organic solvents and multiple sclerosis.

Thirteen studies were reviewed with varying methodology that included information on solvent exposure of which ten showed an increased risk. Using the best-evidence synthesis techniques three studies were selected for both pooled analysis and meta-analysis. The relative risk point estimates obtained varied from 1.7 to 2.6. This evaluation is consistent with the hypothesis that organic solvents may contribute to multiple sclerosis.

Two studies reviewed were conducted after the Landtblom review. Reis (50) reported a case of multiple sclerosis triggered by exposure to organic solvents. Mortensen (51) conducted a register based case control study which linked occupational solvent exposure status from census data. After a follow-up period of 20 years no increase in incidence of MS was observed although the authors believed the study design had some potential for selection bias.

Other Neurological Outcomes

The major exposure implicated was toluene, of which there were 24 studies. Seven of these were case reports and there was one case series of three patients. The reported central and peripheral nervous system outcomes included: fatigue, irritability, reduced libido, headaches, urinary incontinence, impaired concentration, memory loss, cerebellar signs (intention tremor, gait ataxia, dysarthria) dysphasia, demyelination on Magnetic Resonance Imaging (MRI), myelofibrosis, and reduced nerve conduction velocity. One case described death following a faint and fall from a great height.

Two cohort studies showed differences in the prevalence of neurological and psychological symptoms between exposed and comparison groups. Five other cohort studies explored the association between exposure and performance on neurological and psycho-behavioural testing. These studies found significant differences in dexterity and reaction time prolonged latency and reduced amplitude of visual evoked potentials in the exposed group.

One study described a higher prevalence of organic brain syndrome in the exposed group. However, many of these cohort studies had small sample sizes and were subject to confounding in that there were often significant differences between exposed and unexposed groups.

Five studies involved experimental acute exposure of volunteers to toluene. As with the more chronic occupational exposures, these studies showed significant changes in neuropsychological testing following exposure including decreased manual dexterity, decreased colour discrimination, decreased accuracy in visual perception, adverse performance on digit span, reduced pattern recognition, pattern memory and critical tracking.

Exposures to other solvents were examined in 19 further studies. Three studies of m-xylene showed no significant alteration in neuropsychological performance following short-term experimental exposure. Two studies assessed effects following experimental exposure to methyl ethyl ketone (MEK). These studies reported no statistically significant effects associated with MEK. One study reported reduced performance on dual task and profile of mood states (POMS) on acute exposure to acetone, but not MEK.

Many studies of unspecified “solvents” varied in their findings. Cohort studies of occupational exposures reported more symptoms relating to memory, mood, equilibrium and sleep among those exposed, poorer performances on digit span, complex figures, working memory, dose response increases in dementia, dys-coordination, and cerebral atrophy. Table 4 is taken from a paper by Grasso (52) on the neurotoxic and neurobehavioural effects of organic solvents on the nervous system.

While there is evidence for an association between solvent exposure and both MS and MND, the very low prevalence of these conditions makes it unlikely that any statistically or clinically significant differences in these outcomes between exposure groups will be detectable. While a detailed neurological examination is not warranted, participants should be asked about previous diagnosis of MS and MND.

Table 4 : Summary table of neurotoxic and neurobehavioural efects of organic solvents

Solvent	Observed Effect
n-Hexane	Peripheral neuropathy
Carbon Disulfide	Peripheral neuropathy
Trichloroethylene	Trigeminal nerve Memory and reflection Emotional status
CS2	Neurasthenic syndrome (fatigue, concentration, memory, irritability, alcohol intolerance) Impairment of personality and emotional instability Suicide WAIS sub tests
Toluene	Perception, reaction time - cerebellum and higher integrative functions
Styrene	Rombergs test for balance Manual dexterity
Jet Fuel	Nerve conduction velocity No serious injury to CNS
Painters	Memory, reaction time, intellectual capacity Fatigue, absent mindedness, “dementia”, learning impairment
Wood and furniture	Neuropsychiatric disorder and “dementia”
MEK	Potentiates effects of other solvents (53)

Source : Modified from Grasso P. Occupational Medicine 1988;3(3):525-539.

Several other neurological effects have been linked to solvent exposure, such as peripheral neuropathy, neurasthenic syndrome, emotional instability, memory, reaction time, and intellectual capacity, and should be assessed as part of the General Health and Medical Study. Although there is some overlap between neurological and neuropsychological outcomes, the latter will be discussed more fully in the following section.

Table 5 : Summary of Multiple Sclerosis and Motor Neurone Disease literature review

Author / Year	Study type	No.	Population	Exposure	Outcome	Results
Takeichi, 1986 (54)	Case report	1	Painter	Toluene	Death from faint and fall	
Gupta, 1990 (55)	Cross sectional	45	Electrical manufacturing	Xylene Toluene	Psychological battery of Hanninen and Lindstrom: Visual retention test, Digit symbol test, mirror drawing test	Statistical differences in mean scores between exposed and non-exposed
Welch, 1991 (56)	Case report	1	Painter	Toluene	Memory loss, impaired concentration, fatigue, irritability, reduced libido, headaches, urinary incontinence, tremor, ataxia, dysarthria	N/A
Riihimaki, 1980 (57)	Experiment	8	Healthy male volunteers	m-xylene	Psychomotor (reaction time) and vestibular function (balance and nystagmus)	Temporary increase body sway, prolongation of reaction times
De Rosa, 1985 (58)	Cross sectional	504	504 workplaces	28 different solvents. Mostly toluene, n-hexane. Including MEK	Frequency of encountering certain neurotoxic solvents	Toluene most frequent solvent used (79%), then n-hexane (53%) and cyclohexane (47%).
Morck, 1988 (59)	Cohort	382	Photographic printing plant	Toluene Exposure index	Symptoms, FEV1, FVC, Reaction time	Correlation with memory, dizziness, decreased concentration, sexual disturbance, gastro-intestinal symptoms
Cherry, 1985 (60)	Cohort	44/52	Painters and joiners	Toluene and paint solvents	Dotting test, trail making test, visual search test, digit symbol test, block design test, grooved pegboard test, reaction time, memory test, reading test. Clinical neurological examination, motor conduction velocity	Excess of symptoms but no difference of importance on other measures
Gunnarsson, 1992 (46)	Case-control	112/500	Sweden	Any solvent	Motor Neurone Disease	Significant association only for men aged 45-59

Table 5 continued…

Author / Year	Study type	No.	Population	Exposure	Outcome	Results
Stollery, 1988 (4)	cohort	7,8&10	Female employees of tennis ball factory	Toluene and aliphatic hydrocarbons	Memory test	Slight impairment on resource-competing tasks
Baelum, 1985 (61)	Experiment	43/43	Printers	Toluene	Visuomotor coordination, perceptual speed, higher cortical functions (10 tests)	Decreased manual dexterity, decreased colour discrimination, decreased accuracy in visual perception
Mizutani, 1989 (62)	Case report	1	Solvent sniffer	Toluene	Myoglobinemia and Renal Failure	N/A
Doty, 1988 (63)	Case control	18/18	Volunteers	Multiple chemical sensitivity	Nasal resistance	No association
Ikeda, 1990 (64)	Case report	1	27 yr old man	Toluene	Dementia, cerebellar ataxia, dysarthria, pyramidal signs	N/A
Savolainen, 1985 (65)	Experiment	9	Healthy male volunteers	m-xylene	Body sway, reaction times	Negative correlation
Wennberg, 1981(66)	Cross sectional	NS	Printers	Toluene	Psychiatric interview, EEG, electroneurography, VER, neurological examination	No association
Welch, 1991(56)	Case report	1	38 yr old labourer	Toluene MEK	Impaired concentration, memory loss, cerebellar signs (intention tremor, gait ataxia, dysarthria)	N/A. But did suggest progressive symptoms once exposure was discontinued
Yin,1987 (67)	Cohort	300/130	China- solvent workers	Benzene, Toluene,	Clinical chemistry, Symptoms	No association with clinical chemistry, significantly more symptoms in exposed group
Kraut, 1988 (68)	Cohort	19	Sewage workers	Benzene, Toluene, other solvents	Embedded figures, digit symbol, block design, grooved pegboard, Benton memory test	Lower neurobehavioural scores with increasing years of working at the plant
Kildburn, 1985 (69)	Cohort	76	Histology technicians	Solvents and fixatives	Symptoms	More symptoms of memory, mood, equilibrium and sleep among exposed
Harris, 1987 (70)	Cohort	33/57	Exposed to water from hazardous waste disposal site	Carbon tetra chloride, toluene, benzene	Symptoms: Headache, faintness & dizziness, visual disturbance, tinnitus, loss of taste, paraesthesia, balance, weakness. Signs: hypertension, hepatolmegaly, optic atrophy, peripheral neurological changes	High incidence of abnormal physical symptoms and clinical signs

Table 5 continued…

Author / Year	Study type	No.	Population	Exposure	Outcome	Results
Poungvarin, 1991 (71)	Case report	1	Lacquer sniffer	Toluene	Tremor, dysphasia, demyelination on MRI	N/A
Milanovic,1990 (72)	Cohort	46	Industrial workers in Yugoslavia	Solvents	Attention, visual retention, verbal fluency, digit span, working memory	Poorer performance on digit span, complex figures, working memory
Seppalainen, 1989 (73)	Experiment	9	Male volunteers	m-xylene	Evoked potentials (VEP)	Minor fluctuations
Hjelm, 1990 (74)	Experiment	8	Male volunteers	MIBK & Toluene	CNS symptoms: Swedish Performance Evaluation System; Mood scale; Reaction time test and additions test	Significant increase in symptoms, no effects on mood, no effects on reaction time or additions
Ogawa, 1988 (75)	Case report	1	Paint thinner sniffer	Methyl alcohol	Optical disturbance, dysaesthesia, psychiatric symptoms	N/A
Mergler, 1992 (76)	Experiment	5	Volunteers	Toluene & xylene	Olfactory perception threshold	Significant shift following exposure
Iregren, 1982 (77)	Cohort	38/38	Printers	Toluene	Memory, reaction time, finger dexterity	Significant differences in dexterity and reaction time
Johnson, 1983 (78)	Cohort	233/156	Fibre manufacturers	CS2, hydrogen sulphide, tin oxide, zinc oxide and sulphate, sodium hydroxide, sulfuric acid	Nerve conduction velocity, neurological symptoms	Decrease in amplitude and velocity of nerve conduction for peroneal nerve, sural nerve, but not ulnar. No difference in symptoms
Dick, 1988 (79)	RCT	137	Volunteers (no other description given)	Acetone and methyl ethyl ketone	Eyeblink reflex, visual-vigilance, dual task, reaction time, memory scanning, postural sway, profile of mood states (POMS)	Reduced performance on dual task and POMS on exposure to acetone
Bosch,1989 (80)	Letter (Case Report)	1	60-yr old man	Toluene	Myelofibrosis	N/A
Risberg, 1980 (81)	Case Series	3	Wharf workers	Toluene	Nerve conduction velocity	N/A
Larsen, 1988 (82)	Cohort	22/19	Rotogravure plant workers	Toluene	Psychiatric interview, arithmetic tasks, memory span, abstraction and visuospatial function	Higher prevalence of organic brain syndrome in exposed group

Table 5 continued…

Author / Year	Study type	No.	Population	Exposure	Outcome	Results
Dick, 1988 (79)	Experiment	137	Volunteers	MEK acetone/MEK	Reaction time, visual vigilance, dual task, memory scanning, mood (POMS)	No statistically significant interpretable results
Echeverria, 1989 (83)	Experiment	42	College students	Toluene	Verbal and visual short term memory, perception, psychomotor skill, manual dexterity, mood (POMS) fatigue, verbal ability	Adverse performance digit span. Pattern recognition, pattern memory, critical tracking
Matikainen, 1985 (84)	Cohort	77	"Workers with long standing exposure to organic solvents"	Toluene	Cardiovascular reflex parameters	Lower parameters in exposed group
Foo, 1990 (85)	Cohort	30/30	Female electronic assembly work	Toluene	Visual retention, visual reproduction, trail making, grooved peg board, digit span, digit symbol, finger tapping, reaction time	Poorer performance (dose response) on all tests except reaction time and finger tapping
Urban, 1990 (86)	Cohort	54/46	Rotogravure print workers	Toluene	Visual Evoked Potentials	Prolonged latency and reduced amplitude in the exposed group
Echeveriia, 1991 (87)	RCT	84	Students	Toluene	Verbal skill, verbal short term memory, visual memory, perception, psychomotor skill, manual dexterity, mood (POMS), fatigue	Significant effect on digit span, pattern recognition, manual dexterity, pattern memory
Lash, 1991 (88)	Cohort	46	Airline mechanics	Methylene Chloride paint stripper	Symptoms, special senses, grip strength, event related potential, reaction time, motor speed, short term visual memory, short term verbal memory, attention (digit span, digit symbol, serial addition, trailmaking, STROOP, cancellation task) spatial ability	Solvent exposed group processed reaction time stimuli more slowly, and had lower scores on attention tasks
Peters, 1986 (89)	Cohort	10&5	Grain storage workers	CS2	Neuropsycological and neurobehavioural testing, EMG, nerve conduction velocity, EEG, VER, somatosensory and brainstem auditory responses	Dysfunction of peripheral axons, auditory nerve, optic nerve, extrapyramidal system, altered behaviour and cognitive changes

Table 5 continued…

Author / Year	Study type	No.	Population	Exposure	Outcome	Results
Mikkelson, 1988 (90)	Cohort	85	Painters	Solvent exposure	Dementia and performance, dys-coordination, cerebral atrophy	Dose response increases in dementia, dys-coordination, and cerebral atrophy. Non significant association on performance.
Amaducci, 1982 (91)	Cross-section	86	Patients with diagnosed MS, including Shoe & leather workers using solvents	Exposure to glues containing organic solvents	Multiple sclerosis	Rate in shoe & leather workers statistically significant.
Juntunen, 1989 (92)	Co-twin control study	27,100 pairs, 21 cases	Twins with known zygosity in Finland	Occupational history and estimation of exposure to chemicals including solvents	Multiple sclerosis	Results did not support causal association between exposure to solvents and MS
Flodin, 1988 (93)	Case-referent	93/467	Sweden	Solvent exposure, welding, pets, x-rays	Multiple sclerosis in cases	Association between dog ownership and MS in females, Solvent exposure, especially when also welding associated with MS in males
Gronning, 1993 (94)	Case-control	155/200	Norway	Solvent exposure, welding, other chemical compounds	Multiple sclerosis in cases	No association between MS & organic solvents, organic solvents & welding, organic solvents & other chemical compounds
Landtblom, 1993 (48)	Case-referent	91/348	Sweden	Solvent, ionising radiation & animals	Multiple sclerosis in cases	Association between MS and occupational solvent exposure
Schulte, 1996 (47)	Proportion-ate mortality study	N/A	27 US states	Usual job description	Underlying & contributing causes of death due to presenile dementia, Alzheimer's disease, Parkinson's disease and motor neurone disease.	Neurodegenerative diseases occur more frequently in some occupations with solvent exposures.

Neuropsychology

This aspect of the literature review aimed to explore the published evidence of exposure-related neuropsychiatric disorders, mental symptoms and neurobehavioural performance. A synthesis of the literature review information is shown in Table 6.

A historical background of the studies into the neurotoxic effects of organic solvents was provided by Arlien-Solbørg (95). He reported that occupational exposures to organic solvents have long been a cause of concern. Delpech described the first cases of acute intoxication in workers exposed to carbon disulphide (CS_2) in 1863. He also observed sub-chronic intoxication after weeks to months of occupational exposure, describing impairment of fluctuations in mood, insomnia, memory problems, loss of sensations from different parts of the body, and impotence.

In parallel with industrialisation, a marked increase in the consumption of organic solvents took place, together with an increased exposure of workers. During this period, particularly the 1970s and 1980s, the number of publications concerning neurotoxicity of organic solvents rose rapidly. The early 1970s reports, mainly from the Nordic countries, indicated that long-term, relatively low-level occupational exposure to a number of organic solvents and their mixtures could result in chronic toxic encephalopathy.

The initial reports of neuropsychological effects were seen after exposure to CS_2, however later the neurotoxicity of styrene, white spirit, and other mixtures of solvents were evaluated. From 1964 onwards, hexacarbons were suspected of causing polyneuropathy, both in workers occupationally exposed and, from 1972, in individuals abusing these compounds. Epidemic occurrence of neuropathy was reported from the U.S., Japan, and Europe. This initiated intense studies of the acute and chronic neurotoxic effects of a number of hexacarbons.

Some of the other solvents, in particular toluene, CS_2, and acrylamide, have also been subjected to intense studies, and different theories on the mechanisms of their proven neurotoxic effects have been advanced. Most of these hypotheses are still to be tested although the toxic effects have repeatedly been demonstrated for toluene.

Many of the published papers concentrated on painters as the exposed cohort, seeking to describe and confirm the condition known as “painter’s syndrome”. The majority of studies were cross-sectional in design (as compared with retrospective or longitudinal) and examined relatively small samples of exposed subjects compared with non-exposed comparisons on a number of clinical, neurological, psychiatric and neuropsychological tests. There were a number of recent studies which reported significant differences between solvent-exposed subjects and non-exposed on measures of learning and memory, attention, visuospatial ability, mental flexibility and information processing. Morrow, in particular conducted further dissociative investigation of cognitive impairment and mood disorders (12, 96, 97, 98). In addition to highlighting the need for consideration of other symptomatoloy when studying exposure, the work by Morrow (98) has important implications for SHOAMP, in terms of utilising structured clinical interviews over self report questionnaires alone to obtain a fuller picture of cognitive abilities and mood.

To summarise, the issue of neurological deficit resulting from exposure to chemical substances has been extensively reported in the scientific literature. Based on the standard of studies which report significant differences between exposed and non-exposed cohorts, as well as reports of poor memory by workers to the F-111 Deseal Reseal Interim Health Care Scheme, assessment of neuropsychological function should be made as part of the SHOAMP health examination. Based on those studies included in this review, the minimum tests for inclusion should be tests of attention, information processing, visual construction and recall.

Table 6 : Summary of Neuropsychological literature review

Author / Year	Study type	Population	Exposure	Tests Administered	Evidence of associations between exposure and neuropsychological deficits
Morrow, 2001 (98)	Case-control study	N=38 solvent exposed N=39 non-exposed	3-year organic solvent exposure period vs non-exposure	Pittsburgh Occupational Exposure Test – consisting of learning/memory, visuospatial ability, attention/mental flexibility, psychomotor speed, general intelligence, and clinical interview for DSM-IV diagnoses.	Between groups analysis – statistically significant differences between exp and non-exp for learning/memory, visuospatial and psychomotor speed ($p<0.05$). Within groups analysis – no significant differences ($p>0.05$) between exposure levels and mood disorder diagnoses.
Morrow, 2000 (97)	Cross-sectional case-control	N=38 exposed (categorised into 3 levels of exposure) N=39 non-exposed (all participants were paid a nominal fee for taking part)	Organic solvents in the workplace – most commonly aromatic and halogenated hydrocarbons (eg: toluene, xylene, benzene and trichloroethylene).	Structured Clinical Interview for DSM-IV (interviewers were not blind to exposure status).	Significantly greater number of exposed subjects (71%) met axis 1 diagnosis for psychiatric disorder vs non-exposed (10%), $p<0.001$. Greatest differences existed between groups for anxiety and major depression.
Morrow, 1990 (96)	Cross-sectional case-control	N=32 exposed workers N=32 matched non-exposed controls	Toluene and trichloroethylene most commonly.	Pittsburgh Occupational Exposure Test battery (all subjects) described previously, Minnesota Multiphasic Personality Inventory (exposed only)	Between group analyses – Significantly poorer results for exposed group on learning/memory ($p=0.006$), visuospatial ($p<0.01$), psychomotor speed and manual dexterity ($p<0.025$) and attention and mental flexibility ($p<0.001$). No significant differences on general intelligence ($p>0.20$).
Morrow, 1992 (99)	Case-control study	N=40 exposed N=40 age matched comparisons	Subjects had a history of exposure to organic solvents – toluene, xylene, MEK, styrene.	Verbal-paired associate learning test Digit-paired associate learning test Wechsler Memory scale Visual reproductions WAIR-R digit span Short term memory test	Solvent exposed subjects scored significantly poorer on all paired associate learning tests, digit span test, short term memory and logical memories and visual reproductions ($0.001<p\leq0.05$).

Table 6 continued…

Author / Year	Study type	Population	Exposure	Tests Administered	Evidence of associations between exposure and neuropsychological deficits
Dick, 2000 (100)	Retrospective case-control	N=120 n=78 dockyard painters (consisting of two groups with different reported number of solvent neurotoxicity symptoms) n=42 community controls	Exposures to organic solvents and inorganic lead, from working in paint shop at dockyards for at least one year	Neurobehavioural Evaluation System – continuous performance, paired associate learning, symbol digit substitution, association recall. Trial Making tests, Benton Visual Retention Test, NART, plus physical testing. Genotyping of polymorphic enzymes involved in detoxification.	After adjustment for smoking, age and alcohol intake – - reported evidence of an association between increasing intensity of solvent exposure and poorer performance on some cognitive tests – including visual memory, verbal memory and planning tests. - significant reduction in grip strength in exposed group. - identification of some genetic significant associations with impairment.
Stollery & Flindt, 1988 (4)	Retrospective case-control investigation of memory sequelae	N=7 female factory workers suffering from acute solvent intoxication (occurring over 3 days) N=8 similar workers not suffering intoxication within the same environment N=10 unexposed	Organic solvents from adhesives (toluene and SBP7)	Two test sessions – a) Memory task, paired associate task, serial-position task, Brown-Peterson task. b) Memory task, Beck depression inventory, paired associate task, serial-position task, Brown-Peterson task.	Acute exposed group had higher depression scores ($p<0.01$), tended to learn few word pairs, recalled fewer words during the Brown-Peterson task ($p<0.01$) and errors of omission ($p<0.01$). Very small samples mean low power for the repeated measures analysis.
White, 1995 (101)	2-year prospective cohort study	Screen printers N=30 completed testing over 2 years Categorised as high/low acute exposure and high/low chronic exposure (4 groups)	Mixed solvents such as MEK, hexane, toluene, methanol and ethanol.	Two test sessions one year apart – verbal ability and reasoning, visual construction, reasoning and organisation, attention, motor speed, memory, attention, reaction time, mood and manual dexterity.	After accounting for age, education, gender: Higher acute exposure associated with poor performance on manual dexterity and speed ($p=0.04$) and visual reproductions ($p=0.02$). Higher chronic exposure associated with poor score on visual reproduction ($p=0.02$).

Table 6 continued…

Author / Year	Study type	Population	Exposure	Tests Administered	Evidence of associations between exposure and neuropsychological deficits
Baker, 1988 (102)	Intervention study of the impact of worker education and training program on workplace hazards	N=186 male painters	"solvent containing products"	Neurobehavioural tests – Verbal ability Psychomotor performance Symbol-digit substitution Memory Mood	Chronic mental symptoms correlated highly with higher/lifetime levels of exposure ($0.001<p\leq0.03$). Arm/leg weakness associated with recent exposure ($0.02<p\leq0.05$). Finger/toe numbness associated with lifetime exposure ($p=0.04$). "Other symptoms" (ie; skin rash, nausea) were associated with recent exposure ($0.0001<p\leq0.009$). No clear description of "program of worker education and training" or impact of program
Nasterlack, 1999 (103)	Cross sectional study, with intended follow-up.	N=366 exposed painters N=193 non-exposed construction workers	Described as "solvent exposure" with no further detail of individual chemical components involved.	Questionnaire 16 (for CNS disturbances) Neurotoxic Symptom Score PSE-9 General medical and neurological examination Liver/kidney scans ECG, EEG, EMG, NCV Verbal and actual fluid intelligence, Organic brain dysfunction Concentration Reaction time	Significantly poorer result for vibration sensation at 3 sites for exposed subjects ($0.001<p\leq0.02$). No between-group differences for ECG. Exposed subjects performed significantly worse on visual retention and concentration ($p<0.01$). Within-group differences for "high" versus "low" exposure reported poorer reaction times ($0.01<p\leq0.05$).
Spurgeon, 1994 (104)	Cross-sectional study	N=110 paintmakers N=110 matched comparisons	White spirit, toluene, xylene, MEK, methyl isobutyl ketone, also acetone, isobutyl alcohol, n-butyl acetone and n-butyl alcohol.	Symbol-digit substitution Hand-eye coordination Digit span Associate learning Pattern memory Colour word vigilance Continuous performance Associate recall General health questionnaire Questionnaire 16	No difference in pre-morbid ability ($0.13<p<0.36$). No significant differences between groups. Comparisons performed more poorly on continuous performance ($p<0.05$, CI –75.10 to –14.69) and colour word vigilance ($p<0.05$, CI –56.70 to –5.31).

Table 6 continued…

Author / Year	Study type	Population	Exposure	Tests Administered	Evidence of associations between exposure and neuropsychological deficits
Triebig, 1992 (105)	Cross-sectional study	N=83 spray painters N=42 construction workers, electricians, plumbers with no exposure	Long term solvent exposure	Neurologic investigation Psychiatric analysis using the Present State Examination, psychological testing and CAT scan of the brain.	No significant differences between exposed and non-exposed for neurologic examination (reflexes, hypesthesia, paresis, tremor, vegetative signs) ($p>0.05$). Frequency of syndromes between groups showed significant increases in "special features of depression" and "loss of interest and concentration" (no p-value reported). Also no relationship between these syndromes and level of exposure.
Eller, 1999 (106)	Cross-sectional study	N=30 low exposure N=49 high exposure N=19 non-exposed All current workers in a rotogravure plant (printing magazines)	Toluene	Verbal learning and memory Non-verbal learning and memory Visuo-motor function Visuo-spatial function Attention and concentration Tremor CATSYS test SWAY test	No differences between non-exposed and low exposure groups on neurological tests. High exposure subjects were significantly poorer on finger tap (left hand) test ($p=0.05$) High exposure subjects were significantly poorer on retention test and Bourdon-Wiersman test ($p=0.04$, $p=0.02$).
Gregersen, 1984 (107)	Cross-sectional study	N=65 painters, dry cleaners, boat industry workers and photogravure industry N=33 non-exposed electricians and warehouse workers	Exposure was white spirit, perchloroethylene, stryrene and toluene.	Neurological examination – Tests of sensation, muscle strength, coordination, gait, vibratory perception threshold. Neuropsychological exam – Tests for learning/memory, concentration ability/attention and abstraction functions.	61 final exposed, 29 final non-exposed. No statistically significant differences between types of exposed subjects (ie: painters v's boat workers). "significantly more common" in exposed group were acute work-related symptoms and demential symptoms. No "outstanding symptoms and signs" of sensory and motor peripheral neuropathy between groups ($0.05<p\leq0.10$). Significantly poorer scores for exposed subjects on sentence recall 14 syllables, sorting tests, concentration/attention and abstraction test ($0.01<p\leq0.05$).

Table 6 continued…

Author / Year	Study type	Population	Exposure	Tests Administered	Evidence of associations between exposure and neuropsychological deficits
Bleecker, 1991 (108)	Cross-sectional study to examine "painters syndrome"	N=187male production, maintenance and warehouse workers. No control group.	Toluene, xylene, other alipathic and aromatic hydrocarbons, MEK. Smaller amounts of mixed hydrocarbons (ie; octanes, decanes), and other solvents (ie; butanol, propanol), esters and ketones.	Neuropsychiatric evaluation – Present State Examination Zung Depression Scale Q16 Neuropsychological battery – Visual memory and construction, memory and learning, psychomotor speed, attention and concentration and vibration thresholds.	176 final subjects were categorised into 4 exposure groups. Linear regression to report which neurobehavioural outcome variables were significantly associated with solvent exposure – digit symbol substitution, serial digit learning, truncated reaction time, trail tests A & B and vibration sensation at toe. Study was testing the diagnostic criteria for "painters syndrome", not comparing symptoms with non-exposed.
Mitran, 1997 (109)	Cross-sectional comparative study	Workers from three factories N=71 exp, N=86 comp N=41 exp, N=63 comp N=75 exp, N=85 comp	Exposures were for each factory – Acetone MEK Cyclohexanone	Clinical examination Bio-markers Psychological tests – Reaction times Praga test for attention Woodworth-Mathews personality questionnaire Attention quality test	Exposed groups more likely to experience neurotoxic, irritation, rheumatic and digestive syndromes (frequencies presented only, no analyses). Nerve conduction significantly lower in all exposed groups ($p<0.05$). Psychological results poorly reported, two p-values only reported for – Acetone-exposed displayed delayed reaction time ($p<0.001$) and cyclohexanone-exposed had delayed reaction time to auditory stimuli ($p<0.05$).
Daniell, 1999 (110)	Cross sectional study	N=126 carpenters N=67 painters N=22 aerospace workers All retired, 62-74 yrs.	Solvents	Neuropsychological exam – WAIS-R Wisconsin card sorting test Halstead-Reitan battery WMS-R Rey auditory learning test Benton visual retention test Stroop test Pegboard test Reaction time Beck Depression Inventory	Compared to Carpenters - Painters were significantly lower on – WAIS-R block design test ($p=0.03$) Motor score ($p=0.04$) Aerospace workers were significantly lower on – Wisconsin card sorting test ($p=0.02$) Pegboard test ($p<0.05$) Verbal memory ($p=0.03$) Visuo-motor speed ($p=0.008$) Motor abilities ($p=0.04$)

Table 6 continued…

Author / Year	Study type	Population	Exposure	Tests Administered	Evidence of associations between exposure and neuropsychological deficits
Rosenberg, 2002 (111)	Case control study	N=55 solvent abusers N=61 users of other drugs (cocaine, alcohol)	The most common abuse was from spray painting inhalation (toluene most prevalent solvent). Comparison subjects used cocaine (48%), marijuana (18%), alcohol (8%), amphetamines (10%), opiates (11%) and pain meds (2%).	WAIS-R Brown-Peterson test WMS-R Free recall Word learning test Delayed memory Trail Making Test Parts A & B Digit cancellation Stroop Test Boston Naming Test Boston Diagnostic Aphasia Examination Wisconsin Card Sorting Test Behavioural Dyscontrol Scale MRI's were conducted with both exposed and non-exposed subjects.	Solvent abuse cohort performed poorly on 15 of the 26 measures, versus 1 of the 36 for comparisons. After adjustment for confounding, no between-group differences for Verbal and performance IQ, language/comprehension, information processing, delayed recall measures, Relative to comparison group, exposed were significantly different on digit forward test ($p<0.01$), recall for visual memory ($p<0.05$) and two executive function variables ($0.011<p\leq0.028$). Inhalers were also more likely to have abnormal MRI's than comparisons ($p=0.05$).
Cherry, 1984 (112)	Cohort study	Exposed – N=59 toluene exposed N=42 paint solvent exposed Non-exposed – N=59 matched for toluene N=42 matched for paint exposure	Exposure was to toluene, as part of the manufacture of rubber mats. Paint solvent exposure was from mainly white spirit, from naval dockyard work	NART Reaction time Pegboard test Trail Making Test A & B Digit symbol Visual search Block design Memory	Toluene cohort– Exposed subjects did significantly less well on reading test ($p=0.05$) and pegboard ($p=0.05$). Paint solvent cohort – Exposed subjects did significantly less well on reading test ($p=0.001$), reaction time ($p=0.05$), pegboard test ($p=0.01$), Trial Making B and block design ($p=0.05$) and all memory tests ($p=0.05$).

Table 6 continued…

Author / Year	Study type	Population	Exposure	Tests Administered	Evidence of associations between exposure and neuropsychological deficits
Hanninen, 1976 (113)	Case-control study	N=100 exposed car painters N=101 non-exposed railway workers	Toluene, xylene, buthyl acetate, white spirit, methyl isobuthyl ketone, isopropanol, ethyl acetate, acetone, ethanol	Psychological examination – WAIS Figure identification Wechsler Memory Scale Benton test for visual reproduction Santa Ana dexterity test Finger tapping Reaction times Psychomotor behaviour and ability (Mira test) Rorschach personality test	8 of the 19 tests showed significant differences between exposed and non-exposed ($p<0.001$). When controlled for initial intelligence, only 1 test remained highly significantly different between groups (block design test).
Chen, 1999 (114)	Nested cross-sectional study	N=953 exposed painters N=953 age matched controls	Dockyard paint shop exposures	Questionnaire format to collect symptoms of psychological and neurological disorders	260 final painter questionnaires and 539 controls. Prevalence rate ratios for individual neuropsychological symptoms were significantly higher among exposed subjects. Particularly neurological symptoms, problems buttoning and unbuttoning, hands trembling, and feeling weak/unsteady ($p<0.0001$)
Johnson, 1983 (78)	Cohort study	N=156 male workers from a viscose rayon plant (classified into 3 exposure groups – high, medium and low) N=233 male workers from a polyester-nylon filament plant	Rayon plant – carbon disulfide exposure, hydrogen sulfide, tin oxide, zinc oxide and sulfate, sodium hydroxide and sulfuric acid.	Measure of nerve conduction velocity, maximum motor conduction velocity, sensory conduction velocity. 12-item neurological symptom questionnaire	Significantly decreased nerve conduction in exposed group ($0.01<p\leq0.03$). No significant difference between-groups and within-exposed-group for PNS related symptoms.

Table 6 continued…

Author / Year	Study type	Population	Exposure	Tests Administered	Evidence of associations between exposure and neuropsychological deficits
Tripathi, 1995 (115)	Cohort study	N=100 spray painters N=60 diesel shop workers as reference group N=75 non-exposed workers for controls	Spray painters used mineral spirit, thinner, benzene, toluene and xylene. Diesel workers used diesel oil, no paint. Controls were security workers.	5 psychological tests – Associative recall Critical flicker fusion Letter cancellation Muller-Lyer illusion Card sorting	Significant differences between controls and diesel group for letter cancellation test ($p<0.05$). Significant differences between controls and painter group for alternate critical flicker test, letter cancellation, Muller-Lyer illusion and card sorting design ($0.01<p\leq0.05$). Difference between diesel and painters for alternate critical flicker test ($p<0.01$).
Myers, 1999 (116)	Cross-sectional study	N=228 paint manufacturing workers from 2 factories	Organic solvents	Tests of motor speed Dexterity Clerical speed Attention Vigilance Visuo-spatial function Verbal and visual memory Cognitive flexibility Mood profile of mood states Subjective Symptoms Questionnaire	Weak and inconsistent associations only were reported.

Reproductive Health Effects

The aim of this review was to identify the plausibility of a link between exposures in the F-111 Deseal/Reseal program and birth defects, as well as to identify relevant information that should be collected about other possible perinatal outcomes.

Concern had been raised about the possibility of birth defects in the offspring of workers in the F-111 Deseal/Reseal programs. In view of the anticipated low incidence of such outcomes (0.9 in 1000 for cleft palate, 0.4 in 1000 for neural tube defects in New South Wales, 1993-99) (117) and the limited numbers of births in this cohort, as well as ethical considerations regarding child involvement, it may not be possible to address these concerns in the current study. However it is important to delineate what information could be collected in the current study to shed light on such a possibility.

The literature review yield for birth defects and chemical exposure was relatively low (n=57 papers). A detailed review was conducted using the 10 most relevant papers.

An excellent synthesis of the information was presented in a review article by Tas, (118) and is summarised in Table 7 for 3 major classes of exposures relevant to the deseal/reseal program.

The mechanisms proposed for these effects include:

- Toxin present in the seminal fluid
- Father bringing the toxin into the home environment on work clothes, shoes, skin, etc.
- Neuroendocrine effects in the male
- Genotoxicity (see review of bio-markers)

Table 7 : Summary of Birth Defects and Chemical Exposure

	Sperm abnormalities	Decreased fertility	Foetal loss	Birth defects
Organic solvents	+/-	+	+	-
Ethylene glycols	+/-		+/-	
Aromatic hydrocarbons	+		+/-	+

Legend: + = consistent positive association, +/- = conflicting results, - = consistent negative association, blank =no information

Source : Tas S, et al. Critical Reviews 1996;26(2):261-301.

Experience with Agent Orange in Vietnam veterans (119) indicates that genotoxicity is much more closely linked with childhood cancer than any of the perinatal outcomes above. In particular, genotoxins act differently than teratogens, the former being active later in pregnancy, the latter being active early in development. Several exposures in the F-111 Deseal/Reseal program have been consistently implicated in sperm abnormalities, infertility, foetal loss, and birth defects. It is recommended that the General Health and Medical Study not collect any sperm samples since this might decrease participation rates. This leaves information about fertility and foetal outcomes, which could easily be collected as part of the study. It has been established that husbands are not as reliable a source of information as wives for these sorts of outcomes; men tend to misreport the timing of events, and to under-report low birth weight, spontaneous abortions and induced abortions (120). Interpretation of these outcomes requires knowledge of maternal confounding factors, eg; age of mother, alcohol and smoking habits, and caffeine intake.

In conclusion, the following recommendations are proposed:

1. The inclusion of questions about the following outcomes, pertaining to the time when the participant was involved in the F-111 Deseal/Reseal program(s):
    a) Number of pregnancies and outcomes (eg; spontaneous abortion, miscarriage, stillbirth, live birth).
    b) Weeks of gestation
    c) Birth weight
    d) Maternal complications (eg; pre-eclampsia, eclampsia)
    e) Fertility problems (ie; sub fecundity)
2. Information on confounders: maternal age, smoking and alcohol habits, caffeine intake, and medications during pregnancy.

This section should be filled out by female participants and the female partner of the male participants.

Other health effects

The aim of this section was to explore the evidence of associations between exposure to organic solvents and health effects other than those given *a priori* significance for this report. A separate database search was not performed for this section of the review. Based on information already collected on the health affects of occupational exposure, these studies were recognised as worthy of separate inclusion, and represent an adjunct to the priority health outcome areas. Whilst the main body of this literature review concentrated on cancer, neurologic, neuropsychological and reproductive effects of exposure to organic solvents, a number of other health effects have been reported in the literature. These include olfactory and vibration sensation threshold shift, occupational asthma and mucous membrane irritation, dermatitis, multiple chemical sensitisation, haematological, kidney and liver function changes, sight and hearing changes, and altered clinical and immunological responses. A total of sixteen papers were reviewed and are summarised in Table 8.

Based on the literature and previous worker reports, liver function testing should be considered as part of the SHOAMP health examination process, as should symptoms indicative of respiratory irritation, colour vision deficit and tremor.

Table 8 : Summary of other health effects

Author / Year	Study type	No.	Population	Exposure	Health Effect	Results
Ravnskov, 2000 (121)	Meta-analysis of case control studies	18 studies	Various	Studies of hydrocarbon exposure in glomerulonphritis	Renal Function in glomerulonphritis	Hydrocarbon exposure in glomerulonphritis is associated with the advancement of the disease and inversely associated with renal function. Early elimination of the exposure may, therefore, prevent the process of renal failure in many patients
Paggiaro, 1990 (122)	Review	No specific number (29 references quoted)	Various (human and animal studies included)	Reviewed literature relating to mechanisms of occupational asthma due to low molecular weight compounds such as toluene diisocynate (TDI)	Bronchial hyper-responsiveness – Occupational Asthma	Suggested that while an IgG or IgE immunologic mechanism is not proven, the involvement of inflammatory cells and chemical mediators have been demonstrated in different stages of the disease.
Gralewicz, 1999 (123)	Review	No specific number (64 references quoted)	Animal and human studies	Acute & repeated exposures to some solvents, mainly toluene	Multiple chemical sensitisation as a manifestation of the time dependent sensitisation	Demonstrated from data in the literature reviewed that under circumstances of acute and repeated exposure, some solvents (mainly toluene) exert effect on behaviour and on the functional state of some neurotransmitters systems similar to that exerted by drugs known to induct time dependent sensitisation.
Lemasers, 1999 (124)	Prospective repeated measures study	50 unexposed men evaluated before 1st exposure	US air force aircraft maintenance personnel	Solvent exposure during aircraft maintenance, exposure measured. Jobs were analysed by exposure groups. Exposures were low, below 6 ppm.	Male reproductive effects. Sperm production, structure, and function (sperm concentration, sperm motion, viability, morphology, morphometric, and stability of sperm chromatin)	For most sperm measures, mean values remained in the normal range throughout the 30 weeks of exposure. The paint shop group had a significant decline in motility of 19.5% at 30 weeks.

Table 8 continued…

Author / Year	Study type	No.	Population	Exposure	Health Effect	Results
Tomei, 1999 (125)	Case control study	33 cases and 61 controls	Shoe repairers who work in supermarkets	Solvent mixtures in shoe repairers	Liver damage	Exposed workers had a higher prevalence of elevated mean alanine aminotransferase, aspartate aminotransferase, conjugated bilirubin (P= 0.0001), and alkaline phosphatase (P= 0.004) than controls did. The number of workers who had values outside the upper limit of normal for laboratory was significant (ALT P= 0.034, AST P= 0.037, conjugated bilirubin P= 0.014). Exposed workers all had a ration of ALT to AST greater than 1, with a mean of 1.5; it was > 1.6 in more than half the exposed workers.
Sliwinska-Kowalska, 2001 (126)	Case control study	517 divided into groups according to exposures to noise & solvents or both	Workers of 4 Polish paint and lacquer companies.	Exposure to organic solvents had been measured over the previous 5 years.	Hearing loss to assess the ototoxic effects of solvents at moderate exposure levels	Hearing loss in solvent only exposed group was significant. (RR 4.40) No additional risk in solvent + noise exposure group was found (RR 2.8) Hearing thresholds were significantly poorer in a wide range of frequencies for both groups exposed to solvents, when compared to reference group. The mean hearing thresholds at frequencies 2-4kHz were poorer for workers exposed to solvents + noise than for solvent-only group; Authors suggest this finding suggests an additional effect for noise which had been demonstrated in previous animal studies.
Boogaard, 1993 (127)	Case control study	73 exposed & 35 controls	Male operators employed for an average of 8.2 years in a chemical plant producing chlorinated hydrocarbons	Exposure to a number of chlorinated hydrocarbons. Exposures historically measured were below or near the current threshold limit values.	Kidney & liver function	Long term exposure to a number of chlorinated hydrocarbons at concentrations of below or near the TLV does not lead to clinically significant effects on kidney and liver
Qu, 2002 (128)	Case control study	130 exposed, 51 age/ gender matched controls	Benzene exposed workers	Personal benzene exposure measured by industrial hygienist. Ranged from 0.06 to 122ppm	Haematological Changes	Significant decreased in red blood cells, white blood cells, and neutrophils were observed and correlated with both personal benzene exposures and levels of urinary metabolites and albumin adducts of benzene oxide and 1,4-benzeoquinone

Table 8 continued…

Author / Year	Study type	No.	Population	Exposure	Health Effect	Results
Mergler, 1992 (76)	Experimental control trial	5 volunteers, own controls	5 healthy volunteers	7 hour exposure to toluene and/or xylene in inhalation chamber Olfactory perception thresholds measured	Olfactory perception threshold shift	Study suggests that there is a substantial olfactory threshold shift during 7-hr period, specific to a particular solvent or family of solvents. Receptor-specific saturation is proposed as the underlying mechanism.
Little, 1999 (129)	Controlled trial	20 patients, 16 controls	More than half of the patients had histories of occupational exposure to petroleum-based chemicals, particularly to solvents.	Measured total immunologlobin G and T-cell antigen-binding molecules against an antigen prepared by conjugation of para-aminobenxoic acid to human serum albumin.	Clinical & immunological responses in subjects sensitive to solvents	No significant difference in immunoglobulin G levels to the antigen in the 2 groups, but the levels of T-cell antigen-binding molecules against the para-aminobenzoic acid conjugates to human serum albumin were elevated significantly in subjects sensitive to toluene.
Parkinson 1990 (130)	Cohort study	567 females	Female blue collar workers who were members of the International Brotherhood of Electrical Workers	5 solvent exposure categories were derived. Self-reported neurologic and somatic symptoms as well as neuropsychological performance examined	Neurological performance, depression, severe headaches, light-headedness, room spinning, appetite difficulties, funny taste in mouth, weakness/fatigue, rashes, and abdominal pain.	No difference among groups only for neuropsychological performance. All other self reported symptoms were significant after controlling for the effect of 7 risk factors (age, smoking, moderate-heavy alcohol consumption, severe obesity, history or physician-diagnosed chronic illness, working in a clean room, and exposure to other chemicals.)
Redlich, 2001 (131)	Cross-sectional survey	300 isocyanate body shop workers	Body shop workers exposed to the isocyanate hexamethylene diisocyanate (HDI)	Exposure assessed with exposure matrix, questionnaire and diary. In addition air, surface and skin sampling data were obtained.	Subclinical immunologic and physiologic responses	No clinically apparent asthma cases identified. HDI-specific lymphocyte proliferation in 30% & HDI-specific IgG in 34% of exposed. HDI-specific IgE detected in 2. HDI-specific lymphocyte proliferation, increased methacholine responsiveness, and symptoms of chest tightness and shortness of breath were more common in the most heavily HDI-exposed workers, the painters. The finding demonstrate the presence of HDI-specific immune responses in a large proportion of healthy HDI-exposed workers.

Table 8 continued…

Author / Year	Study type	No.	Population	Exposure	Health Effect	Results
Nijem, 2001 (132)	Cross-sectional survey	137 shoe-factory workers	Workers from 20 manual leather shoe factories in Hebron City, Israel. Workers with less than 1 year employment were excluded	Exposure to different solvents including dichloromethane, n-hexane, toluene, diisocyanate & PVC. Factories generally lacked effective ventilation systems. Workers rarely used personal protective equipment. Health outcomes questionnaire.	Neuropsychiatric & Mucous Membrane Irritation	Workers reported high prevalence of neuropsychiatric and mucus membrane complaints: headache 65%, mental irritability 53%, tingling of limbs 46%, sore eyes 43%.
Bosch, 1989 (80)	Case report	1 patient	Person had been working in direct contact with toluene for 40 years	Had been working 50h a week with a glue made up of 90% toluene	Myelofibrosis	Myelofibrosis not previously reported with toluene exposure. Patient had other previously reported toluene-related complications (neurologic abnormalities and chromosomal aberrations)
Donoghue 1995 (133)	Case series	16 solvent exposed patients	Patients previously diagnosed as having organic solvent induced chronic toxic encephalopathy	Mixture of organic solvents for an average of 5.6 years	Vision – contrast sensitivity	Contrast sensivity was significantly depressed.
Dick, 2000 (100)	Case series	5 painters with neurologic symptoms	Dockyard painter population with solvent exposure between 16-45 years	Xylene, white spirit, MEK, 2-ethoxyethanol, dichloromethane & acetone	Colour vision, Tremor Vibration sensation	Colour vision – blue-yellow deficits Tremor – course tremor Vibration sensation – impaired vibration sensation in legs

Health and the Manufacture and Maintenance of Aircraft

This section provides a review of studies undertaken in the aircraft manufacturing and maintenance industry (refer to Table 9). Aircraft manufacture has been included as a relevant area of interest in this report, as the exposures occurring in this industry are to a large number of solvent mixtures, zinc chromate paints and resins. This is similar to those used generally in aircraft maintenance and in the SHOAMP study population.

Cancer

The literature reports that some workers involved in the manufacture and maintenance of both civilian and military aircraft experience adverse health effects as a result of occupational exposure. The main concern has been increased incidence of various cancers.

Mortality of aircraft manufacturing workers has been described in a number of studies. Garabrant (134) in a cohort of 14,067 subjects employed between 1958 and 1982 found non-significant excesses of cancer of the oesophagus, pancreas, and bladder. The study found no excess of melanoma, mesothelioma, or tumours of the central nervous system. The surveillance study of proportional mortality by occupation in Washington State showed significant excesses for all malignant neoplasms and for some cancer sites (including some digestive organs, haematolymphopoietic system, and melanomas) among aeronautical engineers of different companies and among Boeing officials, managers, and supervisors (135). Aeroplane mechanics, repairmen, and electricians, not necessarily employed at the Boeing Company, showed a significant excess risk of Central Nervous System tumours.

A preliminary investigation of central nervous system neoplasms in Los Angeles County (another US state area of high density of aircraft industry) showed excess risk among aircraft manufacturing employees, in particular engineers (136). A mortality cohort study in a north Italian aircraft factory found no excess either of oesophageal cancer of central nervous system tumours although the authors were concerned that the study follow-up period of 15 years was not sufficient for cancer with long latency periods (130). More recently Boice (137) has reported on a retrospective cohort mortality study of 77,965 employed since 1960 in a California aircraft manufacturing factory. Once again no significant increases in risk were observed for any of the 40 specific causes of death investigated. In all the studies, one of the principal concerns was believed to be the workers' exposure to large numbers and quantities of solvent mixtures.

The use of zinc chromate paints and exposure to chromium was investigated by Dalager (138) in a population of workers at two military aircraft maintenance facilities where spray painting utilised zinc chromate paint. Painters were found to have a significant excess of respiratory tract cancers and elevated rates for cirrhosis of the liver and cerebrovascular disease. Another group of reports investigated the all cause mortality and cancer incidence for aircraft maintenance workers on Hill Air Force Base, Utah between 1952-1956. This group had been working with a mixture of solvents, particularly trichlorethylene. The initial study by Spirtas (139) found some significant excesses of mortality for non-Hodgkin's lymphoma in women and liver and biliary passages in men, however a follow-up study by Blair (17) found no major cancer or mortality excesses.

More recently, concern has surrounded the exposure of those workers with exposure to jet fuels. Lemasters has published a series of papers reporting on various aspects of a study where she looked at exposure to JP-8 jet fuel now used by the United States Air Force and its effects on the sperm of aircraft maintenance personnel. The study found that low levels of exposure containing as little as 6 parts per million (ppm) of benzene, one of the constituents of JP-8, reduced the motility of sperm (124) and an increase in the frequency of sister-chromatid exchanges in a group of painters also exposed to mixtures of solvents (140).

In summary, a number of studies have looked at aircraft maintenance and cancer, although a statistically significant association has not been observed. However, a number of studies have seen non-significant increases in risk. It is therefore likely that a number of cancers will be observed in the SHOAMP population.

Reproductive Effects

The literature also demonstrates that aircraft maintenance, particularly on United States military bases has been of concern for some time. Ducatman (44) investigated a cluster of germ cell tumours of the testicle in a small cohort of aircraft maintenance workers and found a significant association. The men had been engaged in the maintenance of exterior surfaces and electrical components using solvents and paints.

Puhala (141) used industrial hygiene sampling techniques to measure jet fuel exposures on three domestic United States Air Force installations where JP-8 jet fuel was used. He reported that mean exposure concentration in parts per million for aircraft maintenance workers is 0.01ppm. The current Australian time weighted average (TWA) exposure level for benzene of 5ppm is equal to those levels that the Lemasters' studies on male reproductive effects found to have adverse effects. This perhaps means that if the exposures to benzene and naphthas in the fuel tanks were approaching the permissible TWA, adverse reproductive effects could be observed in the SHOAMP study population.

Other Health Effects

A number of other adverse health effects have been recognised in aircraft maintenance personnel. Smith (142) showed a significant association between solvents (benzene, toluene, and xylene) and increased postural sway response, implying subtle influence on vestibular/proprioception functionalities. Hackett (143) reported a case series of 43 aircraft manufacturing workers who reported to him with contact allergic dermatitis on their hands, forearms and faces following the use of resin systems used to seal interstices of aircraft components.

Recently a number of animal studies have been conducted to look at exposures to JP-8 jet fuel as “occupational and environmental exposures… have become a source of public and regulatory concern” (p485) in the United States (144). The studies reviewed, on behalf of the US Air Force Office of Scientific Research, looked at various exposure levels on the cutaneous toxicity (144), nephrotoxicity (145) and long term immunotoxicity (146). The exposures tested were to simulate military occupational exposure. These rates were found to significantly effect protein expression in the kidneys of mice, produce long-term changes in immune status in mice, and increase cutaneous erythema, oedema, epidermal thickness and rete peg depth in the skin of pigs.

Working in Confined Spaces

The civilian aircraft maintenance industry has been concerned about entry to aircraft fuel tanks particularly since TWA Flight 800 exploded shortly after take-off from New York’s John F. Kennedy International Airport. The investigations pinpointed concerns with the 747’s centre-wing fuel tank. As a result the US Federal Aviation Administration issued mandated inspection and maintenance programs for fuel tanks. Whilst the aim of the directives was to make flying safer in the jumbo in the long term, in the short term it presents additional hazards on the ground for aircraft maintenance technicians because the inspection, repair, and maintenance procedures for 747 fuel tanks and other large passenger and cargo planes require that technicians physically enter them. The concern is that a fuel tank is an enclosed or partially enclosed space which, due to its design, has restricted means for entry and exit. It is not intended as a normal place of work; and may have a harmful atmosphere with elevated levels of contaminant or oxygen deficiency (147).

In Australia, changes to Australian Standard 2865-1995, Safe Working in a Confined Space (148) in early 1995 lead Qantas to review working methods in aircraft fuel tanks of its fleet. Yeung (149) conducted a large scale audit to assess procedures for aircraft fuel tank work, with due consideration of factors such as the nature of confined space, method of work, hazards involved, plant used, and emergency response and rescue procedures.

Air monitoring of fuel tank atmosphere showed oxygen remained at 21 percent throughout the test, lower explosive limit levels dropped substantially in a few hours even without purging due to the low evaporation rate of Jet A-1. High airborne concentrations of hydrocarbon vapour were detected in the tank. The level of benzene in the air dropped from 1.3 to 0.1 ppm in the sampling period. Yeung suggested that atmospheric purging of the tank would be necessary to control it to acceptable levels and that additional precautions needed to be taken when hot work, spray painting, or any work that utilises volatile organic solvents is performed inside the fuel tanks.

Co-exposure to several substances

The F-111 Deseal/Reseal program required the use of other volatile organic compounds to be used such as cleaning solvents, sealants, adhesion promoters and isocyanate, zinc chromate and glycol ester paints which may have had an additive or synergistic effect with the benzene exposure from jet fuel.

Table 9 : Studies involving health, exposure and aircraft maintenance

Author / Year	Study type	No.	Population	Exposure	Outcome	Results
Carlton, 2000 (150)	Industrial hygiene survey report	77 workers monitored	US Air Force maintenance personnel at 12 US air force bases	Exposures to jet fuel & benzene during aircraft fuel tank repair through the collection of breathing zone samples	Quantitative measures of exposures to benzene & jet fuel	Highest eight-hour time-weighted average (TWA) fuel exposure was 1304 mg/m^3 Highest 15-minute short-term exposure (STEL) was 10,295 mg/m^3 *(US air force TWA exposure limit is 350 mg/m^3)* Levels of exposure depended on type of aircraft; wether tank contained explosion suppression foam, purging method, ease of efficient ventilation of tank. Study concluded that workers exposure to JP-8 jet fuel are substantial during aircraft fuel tank entry and repair.
Spirtas, 1991 (139)	Retro-spective cohort mortality	14,457	Workers employed in the aircraft maintenance facility on Hill Air Force Base, Utah between 1952-56.	Working with solvents, particularly trichlorethylene	All cause mortality	Significant mortality for: Non-Hodgkin's lymphoma in white women SMR 212 (102-390) Liver & biliary passages in white men SMR 358 (116-836)
Stewart, , 1991 (151)	Retro-spective cohort mortality	14,457	Workers employed in the aircraft maintenance facility on Hill Air Force Base, Utah between 1952-56.	Working with solvents, particularly trichlorethylene	Assessment of exposures	Established exposures with the use of job titles and an exposure matrix and estimates of levels of exposure from historical industrial hygiene data.
Blair, 1998 (17)	Retro-spective cohort mortality	14,457	Follow-up of workers employers in the aircraft maintenance facility on Hill Air Force Base, Utah between 1952-56.	Working with solvents, particularly trichlorethylene	All cause mortality and incidence	No major cancer or mortality excess demonstrated. Non-significant excesses of non-Hodgkin's lymphoma, multiple myeloma, and breast cancer among workers with exposures to various solvents
Boice, 1999 (137)	Retro-spective cohort mortality study	77,965	Workers employed for at least 1 year at a large aircraft manufacturing facility in California on or after 1/1/1960	Exposure to chromate, trichlorethylene, perchlorethylene, and mixed solvents.	Mortality in 40 specific cause categories.	No significant increases in risk were found for any of the 40 specific cause of death category

Table 9 continued…

Author / Year	Study type	No.	Population	Exposure	Outcome	Results
Garabrant, 1988 (134)	Retro-spective cohort mortality study	14,067 mean duration of employ-ment 15.8y	Men & women employed ≥ 4 years, 1958-1982 at an aircraft manufacturing company in San Diego County. Male 85%, Female 15%	Estimated to prevalence of exposure to a variety of materials including: Paints, toluene Methyl ethyl ketone, trichloroethylene, 1,1,1-trichloroethane, methylene chloride	All cause mortality, including cancer of the testes, brain & nervous system, malignant melanoma,	Based on 1,804 deaths where 2,399 were expected. No excesses of mortality had occurred. Non significant excesses were noticed for oesophagus, pancreas, and bladder Study had power to find excesses greater than two fold for all but testicular cancer that had low power (28%) of detecting a risk greater than two-fold. Authors note that the study would not have been adequate to detect excess risk that would not have been detectable with less than 20-30 yr of follow-up.
Ducatman, 1986 (44)	Retro-spective cohort incidence study	153	Men engaged in the exterior surfaces and electrical components of aircraft	A histologically verified testicular germ cell cancer following at least 3 years of working at an airframe	Germ cell tumours of the testicle	Statistically significant result. No point estimates provided.
Dalager, 1980 (138)	Retro-spective cohort mortality study	997 male painters, 276 male electro-platers	Painters and electroplaters from 2 large US government-owned (military) aircraft maintenance bases where spray painting utilised zinc chromate primer paint. Both bases had electroplating operations.	Exposure to zinc chromate paints and electroplating in aircraft maintenance.	Cancer mortality measured as proportionate cancer mortality	Electroplaters had no relative excess of cancer. Painters had a significant excess of cancer, particularly of the respiratory tract (PMR 1.84). PMR's elevated for cirrhosis of the liver, and for cerebrovascular disease, and depressed for cardiovascular disease.

Table 9 continued…

Author / Year	Study type	No.	Population	Exposure	Outcome	Results
Costa, 1989 (152)	Retro-spective cohort study of Mortality	8626	Workers employed between 1954 and 1981 in a aircraft-manufacturing factory in northern Italy. Median duration of follow up from the date of first employment was 16 years	Aromatic nitro & amino organic compounds in cutting fluids and as constituents of rubber plastic paint dye. Other aromatic and halogenated organic compounds in solvents; chromates and other heavy metal salts in paints and welding fumes. Epoxy resins, other plastics with amine hardeners in fibre sheet preimpregnated materials, in paints & enamels, in adhesive materials; fibres (asbestos, man-made mineral fibres) in insulating materials, composite materials; ionising radiation in non-destructive testing.	All cause mortality SMR calculated on Italian national mortality rates. Particular focus on oesophageal cancer & CNS tumours.	All cause SMR was 85 (n=685 deaths). No excess for either oesophageal cancer for CNS tumours. The study had 56% and 71% power to detect any significant risk greater than twofold at the 5% significance level for these two cancer sites respectively. There was a significant excess of mortality for melanoma, SMR 561. This was recognised in the younger workers, employed more recently and working in manufacturing areas. Exposure to a specific chemical or other cause was difficult given that multiple exposures existed. No specific excess of mortality was found in specific jobs or work areas.
Lemasters, 1999(124)	Prospective repeated measures study	50 un-exposed men evaluated before 1st exposure 8 controls	US air force aircraft maintenance personnel	Solvent exposure during aircraft maintenance, exposure measured. Jobs were analysed by exposure groups. Exposures were low, below 6 ppm.	Male reproductive effects. Sperm production, structure, and function (sperm concentration, sperm motion, viability, morphology, morphometric, and stability of sperm chromatin)	For most sperm measures, mean values remained in the normal range throughout the 30 weeks of exposure. The paint shop group had a significantly decline in motility of 19.5% at 30 weeks.

Table 9 continued…

Author / Year	Study type	No.	Population	Exposure	Outcome	Results
Lemasters, 1997 (140)	Prospective repeated measures study	50 un-exposed men evaluated before 1st exposure 8 controls	US air force aircraft maintenance personnel	Solvent exposure during aircraft maintenance, exposure measured. Jobs were analysed by exposure groups. Exposures were low, below 6 ppm.	Genotoxic changes, sister-chromatid exchanges (SCE) and micronuclei (MN) frequency were measured	A small but statistically significant increase in the frequency of SCE occurred after 30 weeks of exposure for sheet metal workers (p=0.003) and for painters (p=0.05). The MN frequency in the sheet metal workers initially showed a statistically significant increase but by 30 weeks had decreased. Authors feel findings suggest that small increases in SCE's in particular may serve as a sensitive biologic indicator of low level hydrocarbon exposure in as much as statistically significant changes occurred in the highest exposed groups but not in the low or no exposure groups.
Lemasters, 1999 (153)	Full shift industrial hygiene sampling	8 volun-teers with job duties involving use of solvents	US air force aircraft maintenance personnel at Hill air force base.	1,1,1-tricloroethane (TCA), xylene, toluene, methyl ethyl ketone (MEK) and methylene chloride.	Comparison of internal dose measures of solvents in breath, blood & urine & genotoxic changes	Industrial hygiene air samples and internal breath measures taken on the same day were highly correlated for measuring TCA (r=0.93) and toluene (r=0.90) but was not as well correlated for other compounds. Breath measures were more sensitive for measuring low level exposure than were either analyses in blood or 23-hr urine samples; these latter two measures were usually below the limits of detection.
Puhala, 1997 (141)	Industrial hygiene report	3 US AF install-ations	At 3 USAF installations breathing zone samples collected from 3 general job categories at each location: aircraft maintenance, fuel handling, and flightline positions	Naphtas, benzene, heptane, m-Xylene, o-Xylene, p-Xylene, toluene.	Quantified exposures	Aircraft maintenance Benzene = 0.01 ppm, naphthas/jet fuels = 1.33 ppm. Fuel handling Benzene = 0.01 ppm, naphthas/jet fuels = 0.61 ppm Flightline positions Benzene = 0.004 ppm, naphthas/jet fuels = 0.33 ppm

Table 9 continued…

Author / Year	Study type	No.	Population	Exposure	Outcome	Results
Smith, 1997 (154)	Case control study	27 / 25	USAF employees at 2 bases.	Cases exposed to jet fuels for an average of 12 years. Results interpreted with mean cumulative exposure levels.	Postural Balance	Showed a statistically significant association between solvents (benzene, toluene, and xylene) and increased postural sway response. For all solvent exposures, the “eyes closed, on foam” test provided the strongest association between sway length and JP-8 benzene, implying subtle influence on vestibular/proprioception functionalities.
Pleil, (155) (from abstract)	Case control study	63 controls, 215 JP-8 related	Various groups of air force personnel	JP-8 exposure Ambient air & collected breath	Assessment of exposure levels	Found a demonstrable JP-8 exposure for all subjects, ranging from slight elevations as compared to control group to > 100 [multiple] the control values.
Hackett, 1999 (156)	Case series	43 patients	Workers who reported to workplace occupational physician with allergic contact dermatitis	Aircraft manufacture.	Allergic contact dermatitis on hands, forearms & face	Most of the patients were associated with resin systems used to fabricate aircraft components or resins used in sealing interstices of assembled components.
Witzmann, 2000 (145)	Animal study to simulate JP-8 jet fuel exposure	30 mice	Male Swiss-Webster mice	Mice exposed 1 h/day for 5 days to aerosolised JP-8 jet fuel at a concentration of 1000 mg/m3, simulating military occupational exposure	Nephrotoxicity	Demonstrated significant but comparatively moderate JP-8 effects on protein expression in the kidney and provides novel molecular evidence of JP-8 nephrotoxicity. Human risk is suggested by these data but conclusive assessment awaits a noninvasive search for biomarkers in JP-8 exposed humans.

Table 9 continued…

Author / Year	Study type	No.	Population	Exposure	Outcome	Results
Harris, 1997 (146)	Animal study to simulate JP-8 jet fuel exposure	Not specified	Female mice	Mice exposed for 1h/day for 7 days to moderate (1000 mg.m3) and a high (2500 mg/m3) concentration of aerosolized JP-8 jet fuel for 28 days	Long term immunotoxicity	It was observed that decrease in viable immune cell numbers and immune organ weights found at 24h after exposure persisted for extended periods of time. Further, JP-8 exposure resulted in significantly decreased immune infection, as analysed by mitogenesis assays which persisted for up to 4 weeks post-exposure. Thus short-term exposure to mice to JP-8 jet fuel caused significant toxicological effects on the immune system, which were long lasting and persistent. It appears that the immune system may be the most sensitive indicator of toxicological damage due toJP-8 exposure. Such long-term changes in immune status may have significant effects on the health of the exposed individuals.
Monteiro-Riviere, 2001 (144)	Animal study (pigs) to simulate jet fuel exposure	16 female Yorkshire pigs	Pigs were used as they are an accepted animal model for human skin.	Exposed to low-dose (25 μl) or high-dose 335 μl Jet A, JP-* and JP-*+100 under occluded (Hill Top or cotton fabric) and non-occluded conditions for 5h, 24h and 5 days. To mimic occupational exposure, fuel-soaked fabric (high dose) was used.	Cutaneous toxicity of three fuels used in both civilian and military aircraft. Erythema, oedema, transepidermal water loss (TEWL) and epidermal thickness were quantified	The high-dose fabric soaked exposure at 5 days to all fuels caused the greatest increase in cutaneous erythema, oedema, epidermal thickness and rete peg depth compared with high dose non-occluded or low-dose exposure under Hill Top occluded conditions.

Measurement of exposure and outcomes

Bio-markers

The aim of this review was to identify the best bio-marker of pre-clinical cancerous disease. It was anticipated that with the limited sample size and young ages of those involved in the F-111 Deseal/Reseal programs, the numbers of clinically overt cancers, even for the most common types (eg; colon) would not allow sufficient power to detect statistically significant differences between exposed and comparison groups. A literature review was conducted to identify a quantitative bio-marker that would indicate an increased risk of cancer at a population level, and which could be used with the SHOAMP population. The main requirement was that such a bio-marker should be measurable in blood and not be invasive, eg; colonoscopy. The paradigm used was that of genotoxicity, i.e. the underlying mechanism of cancer is fundamentally DNA damage and mutations.

Synthesis of the information was organised according to the matrix shown in Table 10. This table differs in format and content to previous tables and will therefore be described in detail. Along the left hand side are the criteria judged to be necessary for a bio-marker to be suitable as a marker of pre-clinical cancer:

a) Blood assay reflects tissue damage: this refers to the fact that DNA damage to the susceptible organ, ie; the organ in which cancer is likely to develop, has been correlated to DNA damage in the peripheral blood cells. For example, DNA adduct levels in peripheral blood lymphocytes reflect DNA adduct levels in lung tissue for the risk of lung cancer.
b) Related to cancer: this refers to the minimum criteria that the presence of the bio-marker has been shown to be related to the future risk of cancer in a cohort or longitudinal design.

c) Related to environmental toxins: that the bio-marker has been shown to relate to exposure levels of environmental toxins of the kind that were used in the Deseal/Reseal program, eg; organic solvents, etc.

d) Related to radiation: related either to major exposure, eg; Hiroshima, Chernobyl, or occupational exposure, eg; radiation workers in industry or hospital.

e) Ability to discriminate exposed versus non-exposed: this refers to the spread of values of the bio-markers between exposed and non-exposed persons, and the amount of overlap in the 2 sets of values. In other words, is the spread of bio-marker values tight enough that one can use the bio-marker to define the exposure groups?

f) Level of mutation: refers to the absolute value of the bio-marker.

g) Ease of assay: a subjective grading from easy (+) to difficult (+++).

h) Persistence over years: a key criterion is that exposure in the remote past should cause a bio-marker that persists to the present time. For example, DNA-adducts are markers for acute exposure, but the adducts are either repaired by DNA repair enzymes or cause cell death; in either case, the adducts do not persist beyond a few months.

Along the top of the graph are the various bio-markers considered.

a) Chromosomal aberrations: these reflect chromosome deletions, translocations, duplications, etc. and are seen at the cytogenetic level, eg; using a light microscope. Lymphocytes are obtained and grown in culture, then a spread of chromosomes are obtained on a slide.

b) Micronuclei: these are extra bits of chromosomes that are sequestered apart from the rest of the cell nucleus and are observable by light microscopy.

c) Sister chromatid exchange: this refers to the fact that each member of a chromosome pair exchanges some bits of DNA with its “sister” chromosome. For this to be observed, live lymphocytes need to be cultured in radioactive material to tag the strands of DNA.

d) Adducts: refers to chemical cross-linking of a toxin to DNA or protein, eg; benzo-a-pyrene adducts in DNA.

e) GPA: Glycophorin A is a protein on the surface of red blood cells and comes in 2 isoforms, M and N. Approximately 50% of people have both forms on the surface of their red blood cells (RBC). Mutagens can knock out one or the other of the M or N gene, causing a sub-population of RBCs which are only M or N, in a background of predominantly MN cells. Results are expressed as variant frequency.

f) HPRT: is a gene involved in DNA synthesis. In the presence of functional copies of HPRT, the cells can take up a toxin which kills them. Those that have mutations in the HPRT gene (which knock out function), can grow in the presence of the toxin.

g) TCR: refers to the T Cell Receptor which in principle is the same as the GPA but is expressed on the surface of lymphocytes.

h) p21 or p53 or p185: these are oncogenes. Oncogenes are proteins involved in the cell cycle, which have been found to be mutated in tumour tissue; they are in the pathogenic pathway of cancerous growth. Although the proteins are usually found in tumour tissue, cells may make excess protein which can be detected in the serum.

Only one marker meets the essential criteria of being related to cancer in cohort studies and of persistence: chromosomal aberrations. In a series of papers pooling thousands of subjects in Nordic countries and Italy, the presence of chromosomal abnormalities were linked to a ~3 fold risk in all cancers. This risk was graded, and present despite the bio-marker being graded in various labs with no standardisation. This risk was found on long-term follow-up of the cohort (10-15 years) and the bio-marker was measured at a fixed point in time, often many years after the exposure of interest. This bio-marker has been well linked to environmental exposures and has the advantage of being standard methodology in any genetic pathology lab. Although the methodology used standard cytogenetics and Giemsa staining, the advent of Fluorescence In-Situ Hybridisation (FISH) has the potential to make this method even more sensitive.

Some of the other markers which may potentially be useful:

a) Serum Oncogenes:

These have only been related to PVC exposure, and most of the work relating them to cancer (lung, breast, colon) has been in people with clinically overt cancer. Only a fraction (up to 25% at most) of cancer patients have circulating levels of oncogenes, but in these people remission and recurrence seems to correlate with oncogene levels. Establishing the presence of the oncogene many months or years before the clinically overt presentation of cancer has not been reported in the literature. Verbal communication with a leader in the field confirmed that it would be premature to use this bio-marker in the SHOAMP project (Brandt-Rauf, personal communication).

b) GPA

The advantages of this assay are that it is easy to perform, well established, and there are groups with the expertise in Australia. The negatives are that data will only be available on half of the sample, and the association with environmental toxins is somewhat contradictory. Most of the work has been with radiation exposure and in this case the GPA variant frequency is statistically related and persists for years. Most of the work with environmental toxins has been with chemotherapeutic agents, and it appears that GPA levels with this exposure do not persist beyond 6 months. The relation to cancer has only been established in genetic cancer syndromes, eg; Bloom's syndrome, where people with this condition have higher levels of GPA than controls.

<u>Recommendations</u>

A bio-marker with the desired properties is at the cutting edge of the field of molecular epidemiology and needs to be considered experimental. Nevertheless:

1. Chromosomal aberrations are the most suitable marker at present. Aberrations may be detected using two different methods:

- *Karyo-typing*: Giemsa staining is used to stain chromosomes into bands, and a trained technician looks for any translocations, deletions or duplications etc. The resolution of the bands is in the range of 10-30 million base pairs.
- *Fluorescence In-Situ Hybridisation (FISH)*: DNA probes with various fluorescent dyes are hybridised to a chromosome spread and an interferometer is used to collate the coloured hybridisation pattern. Various filters are used so that each chromosome is "painted" a different colour. The resolution is at least one order of magnitude greater, in the range of 0.5-2 million bases.

Traditional karyo-typing costs ~$180 per person and is a Medicare Benefits Scheme listed item. FISH would be closer to $400-500 per person and is still a research method. The increased resolution obviously allows for greater sensitivity, such that "micro" deletions, translocations and duplications, missed by karyo-typing can be detected by FISH. There are hundreds of reports in the literature using FISH in prenatal diagnosis, tumour histology, and hematological malignancies, showing that it has greater sensitivity than traditional karyo-typing, however these are all case reports or small series, and to date no-one has reported a head to head comparison in a large series of samples; hence it is difficult to quantify the advantage of the newer methods in terms of percentage gain in the number of aberrations detected, or indeed if there is any advantage. Bayani reviewed recent advances in the detection of chromosomal aberrations using spectral karyotyping (157).

2. We recommend that samples should be stored for future analysis, in the event that new bio-marker assays are developed. This involves two considerations –
    - Storage of samples for possible future processing. Although limited in amount, serum and DNA may be stored for a limited number of future analyses.
    - Immortalisation of lymphocytes. This would enable a renewable and unlimited source of DNA, should future analyses or tests be required. This

needs to be performed with fresh lymphocytes and hence needs to be incorporated into the present protocol if desired.

3. The SAC may wish to consider funding the development of a new bio-marker of cancer risk, such as mitochondrial DNA mutations (refer to Appendix G).

Table 10 : Summary of Assay Information

CRITERIA	Chromosomal Aberrations	Micronuclei	SCE	Adducts	GPA	HPRT	TCR	P21, P53 or P185
Blood assay reflects tissue damage	+ Bonassi (158, 159)		+	+			-	
Related to cancer	+ Bonassi (158, 159); Liou (160)	- Bonassi (158)	- Bonassi (158)		- / + cancer prone syndrome, At/Bloom Cole (161)	+ / - cancer prone syndromes Albertini (162)	+ / - cancer prone syndrome Albertini (162)	+ / - Brandt-Rauf (163) Small numbers, no cohort, silicosis
Related to environmental toxins	+ Sorsa (164)	+ / - Tucker (165) Surralles (166)	+ Sorsa (167); Tucker (165)	+	+ / - Smith (168)	+ Albertini (169)		+ (PVC) Wong (170)
Related to radiation	+ Tucker (165)	+ Muller (171)	+	-	+ Ha (172)	+ Akiyana (173)	+ Akiyana (173)	
Ability to discriminate exposed v's non-exposed	- Liou (160)	- Muller (171)	- Sorsa (167)	-	- Lots of variability Bigbee (174); CV ~ 30-40% Cole (161)	- 2 – 8 fold variation Cole (161)		+ / -
Level of mutation	10^{-2} – 10^{-3} Liou (160) (chromatid); Bender (175) (chromosome)		1 – 10^{1}	1 x 10^{-6-7} nucleotides	1 – 10 x 10^{-6} Bigbee (174)	1 – 5 x 10^{-6} Morley (176)	10^{-4} Akiyana (173)	~ 10% - 20% Wong (170)

Table 10 continued…

CRITERIA	Chromosomal Aberrations	Micronuclei	SCE	Adducts	GPA	HPRT	TCR	P21, P53 or P185
Ease of assay**	++ cultured 48-72 hrs Bonassi (159)	+	+++	+	+	++	+	+
Persistence over years	+ Bonassi (159)	- Muller (171)	-	-	+ / - Ha (172); Akiyama (173); Langlois (177); Wones (178); Cole (161	- Albertini (169) (1-4 yrs) Compton (179)	- 1-4 yrs Compton (179); Cole (161)	
Additional comments		Neg may be due to lab variability. Currently being standardised, only useful in splenectomized people for red blood cells.	Theoretically unknown mechanism. Link to cancer can be induced by non-mutagens.		Radiation effect persists but chemo reverses after 3 months.			Case control +/- for serum p21 and lung, colon and breast cancer.

** For “ease of assay” criteria only - + easy, ++ moderate, +++ difficult, - Does not meet criteria, + Does meet criteria, + / - Equivocal

Measurement of Neuropsychological Deficits

The published scientific literature identified through the current review provided evidence for the assessment of neurological deficit following a period of exposure to organic solvents. While there were some studies which reported conflicting or non-significant results in terms of between-groups differences following exposure, the data did not entirely refute the view that exposure to solvents does not lead to chronic organic or functional damage. Therefore, we recommend that the issue be explored by comprehensive assessment as part of SHOAMP.

As part of the General Health and Medical Study, neuropsychological testing is recommended for all consenting individuals from both the exposed and comparison cohorts. A number of individuals previously involved in the F-111 Deseal/Reseal programs have reported cognitive difficulties, and the Scientific Advisory Committee for the study support the assessment of cognitive functioning, motor functioning, mood and personality assessment and behavioural effects. Therefore the issue of how best to assess neuropsychological function also needed to be reviewed as a separate topic to whether there was evidence for adverse neuropsychological affects alone.

The literature supported the use of a battery of tests, rather than use of symptom questionnaires alone (180, 181). A report by the World Health Organisation (1986) in conjunction with the United Nations Environment Programme and the International Labour Organisation outlined principles for the assessment of neurotoxicity associated with chemical exposure. In addition to descriptions of animal investigations, they discussed the issue of applying a battery of tests to assess various aspects of behavioural, neurological and autonomic status. The literature reviewed as part of the neuropsychological aspect of SHOAMP also supported the use of a battery of tests for completeness. Table 11 provides a summary of the tests employed by different researchers to assess cognitive abilities.

Neuropsychological search terms were cross-checked against chemical terms, in order to establish evidence for the most appropriate domains for testing and the best measures to use. Each participant in the study should undergo a series of examinations, selected specifically to detect and report meaningful differences between exposure and comparison cohorts. For this review of neuropsychological measurement literature, the main points for attention were:

- Important confounders such as pre-morbid intellect, age and alcohol consumption;
- Domains most commonly affected being memory/learning (verbal/non-verbal), psychomotor speed, and manual dexterity;
- Frontal/executive domain did not seem to be consistently affected, at least using tests currently used; and
- Primary language function seemed resistant, but some caution about the true stability of “hold tests” were dependent on this.

Moreover, additional issues important for consideration when evaluating neuropsychological measurement for the SHOAMP General Health and Medical Study were:

- Consideration of the brevity of each test and the overall battery of tests together, so that study participants could combine their nursing and medical examinations in similar time periods;
- Establishment of pre-morbid intellect where possible (very few papers reviewed included any mention or conduct of tests for pre-morbid ability);
- The potential for inclusion as part of the overall examination of susceptibility factors, including indication of alcohol intake, family medical history (particularly of depression and/or dementia), APOE, and slow/fast metabolisers; and
- With regard to Psychopathology – the value of probing for past history.

Table 11 : Summary of Tests Used for Neuropsychological Assessment

NEUROPSYCHOLOGICAL DOMAINS IMPAIRED	AUTHOR / YEAR	AGENTS	COMMENTS	INSTRUMENT / MEASURE
Auditory Verbal Memory	Baker (19)	Trichlorethylene, toluene, other	Case report (CR)	WMS
	Baker (19)	Perchlorethylene	CR	WMS
	White (182)	Mixed solvents	CR 'Chronic encephalopathy'	WMS
	Hanninen (113)	Mixed solvents	Premorbid data from military	WMS, Benton
	Morrow (98)	Solvents	Community Controls	Verb pair`assoc, Del verbal
	Bowler (183)	Organic solvents	Munitions workers	WMS (log memory, word list)
	Reinvang (184)	Organic solvents	Exposed vs non-exposed	Paired associate learning
	Ng (2)	Organic solvents	Depression, irritability also	Paired associate learning
	Hanninen (185)	Mixed solvents	Monozygotic twins	Paired associate learning
	Welch (56)	Toluene, methylethylketone	CR 2-d exp, chronic sequelae	WMS
Working Memory	Stollery (4)	Toluene aliphatic hydrocarbons	Post acute intoxication	Brown Petersen task
	Reinvang (184)	Organic solvents	Exposed vs non-exposed	Digit span
	Chia (186)	Mixed solvents	Select from cohort	Digit span
	Hanninen (185)	Mixed solvents	Monozygotic twins	Digit span
Visual Memory	White (101)	Toluene + others	2-yr prospective	WMS visual reproduction
	Morrow (98)	Solvents	Community controls	WMS-R visual reproductions
	Chia (186)	Mixed solvents	Select from cohort	WMS visual reproduction
Psychomotor Speed	Hanninen (113)	Mixture of solvents	Premorbid data from military.	Santa Anna Dexterity Test
	Bowler (183)	Organic solvents	Munitions workers	Digit symbol grooved pegboard
	Reinvang (184)	Organic solvents	Exposed/non-exposed	Digit symbol
	Kishi (187)	Organic solvents	Age education matched	Digit symbol
	Chia (186)	Mixed solvents	Selected from cohort	Digit symbol, Santa Anna
	Ng (2)	Organic solvents	Depression, irritability also	Digit symbol
	Bleecker (108)	Organic solvents	Life time weighted av exp	Digit symbol, Trails A

Table 11 continued…

NEUROPSYCHOLOGICAL DOMAINS IMPAIRED	AUTHOR / YEAR	AGENTS	COMMENTS	INSTRUMENT / MEASURE
Executive Functioning	Hanninen (113) Bleecker(108)	Mixture of solvents Organic Solvents	Premorbid data from military Life time weighted ave	Block design, similarities Trails B
Malingering in Memory	-	-	-	-
Subjective Memory	Ng (188) Rammussen(189)	Spray paint Halogenated hydrocarbons	Headache also Metal workers	'often need to go back and check on things'. Endorsed by exposed in both studies
Mood / Depression	Chen (114) White (101) Capurro (190) Morrow (97) Dryson (191) Condray (192) Daniell (110) Kishi (187) Morrow (12)	Dockyard solvents Toluene, + others Solvent vapours Organic solvents Solvents Organic solvents Solvents Organic solvents Organic solvents	Dose effect with #symptoms 2-yr prospective study case reports exposed-non-exposed adverse prognostic feature Well controlled Comparison of occ groups Exposed v nonexposed Comparison of instruments	Single item Profile of mood states (POMS) clinical evaluation SCID Clinical SCID Structured interview 'easily depressed without reason' SCL-90, POMS,BDI
Anxiety	Chen (114) Morrow (97)	Dockyard solvents Organic solvents	Dose effect with #symptoms Depression and anxiety	Single item SCID
Somatoform and Dissociative Disorders	Rassmussen (189) Chen (114)	Halogenated hydrocarbons Dockyard solvents	Metal workers Symptoms proport to exposure	Somatic complaints questionnaire

SUMMARY OF RESULTS AND IMPLICATIONS FOR GENERAL HEALTH AND MEDICAL STUDY

This Section summarises the main findings from the literature review in terms of the implications for the SHOAMP General Health and Medical Study. The summary is presented separately for each of the outcomes, and includes the most appropriate method of measurement of outcomes where relevant.

Cancer

Among exposures examined, known carcinogens were benzene, strontium chromate, zinc chromate (hexavalent chromium) and silica. Probable carcinogens included white spirit, naphtha and stoddard solvent. Possible carcinogens were carbon black and lead chromate. It is important to include cancer incidence and mortality as an endpoint. Although record linkage should be a quick way to investigate this outcome, we highlight the fact that low power, long latency and insufficient control of confounders will make the result of such a study difficult to interpret. It is recommended that participants be asked, in the postal questionnaire, to provide information on previous diagnosis of cancer. A breast examination should be included as part of the General Health and Medical Examination, and participants be provided with a take home self administered Faecal Occult Blood Test kit. Assessment of chromosomal aberrations is also suggested.

Multiple Sclerosis, Motor Neurone Disease and other Neurological Effects

Solvent exposure has been linked to Multiple Sclerosis, Motor Neurone Disease and other neurological outcomes such as peripheral neuropathy, neurasthenic syndrome, emotional instability, memory, reaction time, and intellectual capacity.

It is recommended that a full neurological examination NOT be undertaken as part of the General Health and Medical Study, but instead that participants be asked about previous diagnosis of these conditions.

Birth Defects

It is recommended that information on number of pregnancies and outcomes (eg; spontaneous abortion, miscarriage, stillbirth, live birth), weeks of gestation, birth weight, maternal complications (eg; pre-eclampsia, eclampsia), fertility problems, maternal age, smoking and alcohol habits, caffeine intake, and medications be obtained for pregnancies which occurred during the participant's involvement in F-111 Deseal/Reseal. It is further suggested that, in the case of male participants, this information be obtained from the female partner.

Neuropsychology

Neurological deficit resulting from exposure to chemical substances has been extensively reported in the scientific literature. The minimum outcomes which should be measured as part of the General Health and Medical Study should reflect attention, information processing, visual construction and recall.

The suggested domains to be measured are Auditory Verbal Memory, Working Memory, Visual Memory, Psychomotor Speed, Executive Functioning, Malingering in Memory, Subjective Memory, Mood and Depression, Anxiety, Somatoform and Dissociative Disorders. Measures include WMS, Paired Associated Learning, Digit Span, Santa Anna Dexterity Test, Digit Symbol, Pegboard, Trails A and B, Block Design and CIDI. Where possible a measure of pre-morbid intellect should be obtained. Susceptibility factors, including indication of alcohol intake, family medical history (particularly of depression and/or dementia), APOE, and slow/fast metabolisers; and should be included, in addition to report of past history of psychopathology.

Other Health Effects

Based on the literature and previous worker reports of poor health symptoms, liver function testing should be considered as part of the SHOAMP General Health and Medical Examination process, as should symptoms indicative of respiratory irritation, colour vision deficit and tremor.

Biomarkers

Chromosomal aberrations are the most suitable marker at present. Aberrations may be detected using Karyo-typing or Fluorescence In-Situ Hybridisation (FISH). It is recommend that blood samples should be stored for future analysis, in the event that new bio-marker assays are developed. This should involve Immortalisation of lymphocytes to enable a renewable and unlimited source of DNA.

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APPENDICES

Appendix A : List of chemical products

Appendix B : Search terms representing chemical substances to which F-111 DSRS workers were potentially exposed

Appendix C : Search terms for indicators of adverse outcomes of occupational exposure

Appendix D : List of resources used for literature search

Appendix E : Silica and other substances in relation to malignancies

Appendix F : Benzene exposure in relation to malignancies

Appendix G : Mitochondrial disease and solvent exposure

Appendix A : List of chemical products

CHEMICAL PRODUCT	COMPONENTS	SYNONYMS	CAS Code **
SR-51	Petroleum Solvent (high flash aromatic)	Methacrylic Acid, Methyl Ester, 2-Methylacrylic Acid Methyl Ester, Methyl Methacrylate Monomer, Methyl Methylacrylate, Methyl Alpha-Methylacrylate, Methyl 2-Methyl-2-Propenoate, 2-Methyl-2-Propenoic Acid Methyl Ester, Diakon, Methyl Methacrylate Monomer Inhibited, Methyl Methacrylate Monomer Uninhibited, MME, “Monocite” Methacrylate Monomer, NA1247, NCI-C50680, RCRA Waste Number U162, UN1247, 2-Methyl-2-Propenoic Acid Methyl Ester, Acrylic Acid, 2-Methyl-, Methyl Ester, 2-Propenoic Acid, 2-Methyl-, Methyl Ester	80-62-6
	Thiophenol	Thiophenol (Benzenethiol)	108-98-5
	Dimethyl Acetamide	Acetdimethylamide, Acetic Acid Dimethylamide, Dimethylacetamide, N N-Dimethylacetamide, Dimethylacetone Amide, Dimethylamide Acetate, DMA, DMAC, NSC 3138, U-5954, Acetyldimethylamine	127-19-5
	Triethyl Phosphate	Phosphoric Acid Triethyl Ester, Ethyl Phosphase, TEP	78-40-0
SR-51A	Petroleum Solvent (aromatic)	Separate list for search results was provided.	
	Thiophenol	Previously described (page 1, under “SR51”)	
	Dimethyl Acetamide	Previously described (page 1, under “SR51”)	
	Triethyl Phosphate	Previously described (page 1, under “SR51”)	

*** CAS = Chemcial Abstract Service*

Appendix A continued…

CHEMICAL PRODUCT	COMPONENTS	SYNONYMS	CAS Code
AIRTECH 23	Octylphenol Ethoxylate	No results found using online National Toxicology Program	2315-62-0
	Sodium Dodecylbenzenesulfonate	List of synonyms too lengthy to include here	25155-30-0
	Alcohols C9-11 Ethoxylated	Detergent Range Alcohol Ethoxylate	68439-46-3
	Sodium Alkyl Carboxylate	Aminobenzene, Aminophen, Aniline Oil, Aniline Oil Liquid, Benzenamine, Benzidam, Blue Oil, CI 76000, CI Oxidation Base 1, Cyanol, Drystallin, Kyanol, NCI-C03736, Phenylamine, Anyvim, Benzene Amino, RCRA Waste Number U012, UN1547, Arylamine.	62-53-3
	Sodium Metasilicate (Anhydrous)	Disodium Metasilicate, Sodium Silicate, Sodium Metasilicate, 9-Hydrate, Sodium Metasilicate, Anhydrous Soluble Glass, Waterglass	6834-92-0
	Sodium Hydroxide	Separate list for search results was provided.	
	Sodium Nitrite	Nitrous Acid Sodium Salt, Anti-Rust, Diazoting Salts, Erinitrit, Filmerine, NCI-C0284	7632-00-0
ED-500	Ethyl Glycol Monobutyl Ether	BUCS, Butoxyethanol, N-Butoxyethanol, 2-Butoxyethanol, 2-Butoxy-1-Ethanol, Butyl Cellosolve, O-Butyl Ethylene Clycol, Butyl glycol, butyl oxitol, dowanol EB, ektasolve EB, ethylene glycol N-butyl, gafcol EB, glycol butyl ether, glycol ether EB, glycol ether EB acetate, glycol monobutyl ether, jerrersol EB, monobutyl ether of ethylene glycol, monobutyl glycol ether, 3-Oxa-1-heptanol, poly-solv EB, UN2369	111-76-2
	Monophenol Polyethylene Glycol	No results found using online National Toxicology Program	
	Sodium Dodecyl Benzene Sulfonate	List of synonyms too lengthy to include here	25155-30-0
	Distilled Water	Did not search	Not applicable

Appendix A continued…

CHEMICAL PRODUCT	COMPONENTS	SYNONYMS	CAS Code
ME767 (Mil-Spec) also referenced as MIL-C-38736	Aromatic Naphtha	Naphthalin, Tar Camphor, Naphthene, Naphthaline, Moth Balls, Moth Flakes, White Tar, NCI-C52904, Camphor Tar, Mighty 150, Mighty RD1, RCRA Waste Number U165, UN1334, UN2304.	91-20-3
	Ethyl Acetate	Separate list for search results was provided.	
	Methyl Ethyl Ketone	2-Butanone, Butanone, Ethyl Methyl Ketone, Ketone Ethyl Methyl, Methyl Acetone, MEK, Meetco, RCRA Waste Number U159, UN1193, UN1232	78-93-3
	Isopropanol	Isopropyl Alcohol, Dimethylcarbinol, 2-Hydroxypropane, Propan-2-Ol, 2-Propanol, Sec-Propyl Alcohol, Alcojel, Alcosolve, Avantin, Avantine, Chromar, Combi-Schutz, Hartosol, Imsol A, Isohol, Lutosol, Petrohol, Pro, N-Propan-2-Ol, Propol, 2-Propyl Alcohol, Spectrar, Sterisol Hand Disinfectant, Takineocol, UN1219, Alcosolve 2.	67-63-0
MEK	Methyl Ethyl Ketone	Previously described (page 3, under “ME767”)	
	Water	Did not search	Not applicable
T4460 (Mil-Spec) also referenced as MIL-C-38736	Aromatic Naphtha	Previously described (page 3, under “ME767”)	
	Ethyl Acetate	Separate list for search results was provided.	
	Methyl Ethyl Ketone	Previously described (page 3, under “ME767”)	
	Isopropanol	Previously described (page 3, under “ME767”)	
ZI-400	Alkylbenzene sulfonic acid as dodecylbenzenesulfonic acid	List of synonyms too lengthy to include here	25155-30-0
	Organic Sulfonates (unspecified)	No results found using online National Toxicology Program	

Appendix A continued…

CHEMICAL PRODUCT	COMPONENTS	SYNONYMS	CAS Code
ZI-400	Alcohol Ethoxylate as Alcohols C9-11 Ethoxylated	No result from online National Toxicology Program for C9-11 ethoxylated. For alcohol ethoxylate, list of synonyms too lengthy to include here.	9002-92-0
	Sodium Xylene Sulfonate	Dimethylbenzenesulfonic Acid Sodium Salt, Sodium Dimethylbenzenesulfonate, Sodium Xylenesulfonate, Conco SXS, Cyclophil SXS30, Eltesol SX 30, Hydrotrope, Naxonate, Naxonate G, Stepanate X, Surco SXS, Ultrawet 40SX, NCI-C55403, Sodium Xylene Sulfonate, Calsoft SXS 96, Alkatrope SX-40, Carsosulf SXS, Eltesol SX93, Reworyl NXS40, Richonate SXS, Witconate SXS, Benzenesultonic Acid Dimethyl- Sodium Salt	1300-72-7
	Nonionic Surfactant as Polyethylene Glycol Mono-P-Nonylphenyl Ether	No results found using online National Toxicology Program	
	Impurities (unspecified)	Did not search	
	Water (not specified)	Did not search	
MIL-P-23377	Toluene	Methylbenzene, Methacide, Phenylmethane, Methylbenzol, Toluol, Tolu-Sol, RCRA Waste Number U220, UN1294, Antisal 1A, NCI-C07272, Benzene Methyl, Methane Phenyl.	108-88-3
	Isopropanol 2-Propanol Dimethyl Carbinol	Isopropyl Alcohol, Dimethylcarbinol, 2-Hydroxypropane, Propan-2-Ol, 2-Propanol, Sec-Propyl Alcohol, Alcojel, Alcosolve, Avantin, Avantine, Chromar, Combi-Schultz, Hartosol, Imsol A, Iisohol, Lutosol, Petrohol, Pro, N-Propyl Alcohol, Spectrar, Sterisol Hand Disinfectant, Takineocol, UN1219, Alcosolve 2	67-63-0
	Xylene Dimethylbenzene Xylol	Component 1 – Xylenes, Dimethylbenzenes, Xylol Component 2 – Ethyl Benzene	1330-20-7
	Ethyl Benzene	EB, Ethylbenzol, Phenylethane, NCI C56393	100-41-4
	Polyamide Resin	Separate list for search results was provided.	
PR1560	Not specified.	Need advice on which term to search further on, if applicable	
DESOTO 823-707	Not specified.	Need advice on which term to search further on, if applicable	

Appendix A continued…

CHEMICAL PRODUCT	COMPONENTS	SYNONYMS	CAS Code
Alodine 1200S	Chromium Trioxide	Chromium Oxide, Chromic Acid, Chromic Acid Solid, Chromic Acid Solution, Chromic Anhydride, Chromic Trioxide, Chromic VI Acid, Chromium (6+) Trioxide, 5 Chromium Trioxide Anhydrous, Chromium VI Oxide, Monochromium Oxide, Monochromium Trioxide, Puratronic	1333-82-0
	Potassium Fluoborate	Potassium Tetrafluoroborate, Potassium Borofluoride	14075-53-7
	Potassium Ferricyanide (III)	Potassium Ferricynate, Tripotassium Hexacyanoferrate, Ferrate (3-), Hexacyano, Tripotassium	13746-66-2
	Sodium Fluoride	List of synonyms too lengthy to include here	7681-49-4
	Potassium Fluozirconate	Zirconium Potassium Fluoride	16923-95-8
A3598	Not specified.	Need advice on which term to search further on, if applicable	
PR-148	Toluene	Previously described (page 5, under “MIL-P-23377”)	
	Distillate Petroleum Solvent Dewaxed Light Naptha	No results found using online National Toxicology Program	
	Ethyl Acetate	Separate list for search results was provided.	
	MEK	Previously described (page 3, under “ME767”)	
	Isopropanol	Previously described (page 3, under “ME767”)	
	Tetraoctyl Titanate as Titanium(IV) 2-Ethylhexoxide	No results found using online National Toxicology Program	1070-10-6
EC-3580 B/A	Part A: Polyaminopolyamide	No results found using online National Toxicology Program	
	Ball Clay (Kaolin)	Separate list for search results was provided.	
	Aluminium Silicate	No results found using online National Toxicology Program	12141-46-7

Appendix A continued…

CHEMICAL PRODUCT	COMPONENTS	SYNONYMS	CAS Code
EC-3580 B/A	Silica Dimethylsiloxane (treated)	No results found using online National Toxicology Program	
	Carbon Black	Separate list for search results was provided.	
	Part B: Bisphenol A/ Epichlorohydrin Resin Liquid	No results found using online National Toxicology Program	25068-38-6
	Ball Clay	Separate list for search results was provided.	
	Silica	Separate list for search results was provided.	
	dimethylsiloxane treated	No results found using online National Toxicology Program	
666-2003-427 (also referenced as MMS-425)	Bisphenol A/ Epichlorohydrin Resin, Solic	Bisphenol A – Araldite 6010, 2 2'-((1-Methylethylidene)Bis(4 1-Phenylenexymethylene)) Bisoxirane, 4 4-Isopropylidenediphenol Epichlorohydrin Resin, Bisphenol A-Epichlorohydrin Condensate, 2 2-Bis (P-(2,3-Epoxypropoxy) Phenyl) Propane, 2 2-Bis (4-(2,3-Epoxypropyloxy) Phenyl) Propane, Bis (4-Glycidyloxyphenyl) Dimethylmethane, 2 2-Bis (P-Glycidyloxyphenyl) Propane, 2 2-Bis (4-Hydroxyphenyl) Propane Diglycidyl Ether, Bis (4-Hydroxyphenyl) Dimethylmethane Diglycidyl Ether, 2 2-Bis (P-Hydroxyphenyl) Propane Diglycidyl Ether, D.E.R. 332, Diglycidyl Bisphenol A Ether, Diglycidyl Ether of 2 2-Bis (P-Hydroxyphenyl) Propane, Diglycidyl Ether of 2 2-Bis (4-Hydroxyphenyl) Propane, Diglycidyl Ether of Bisphenol A, Diglycidyl Ether of 4 4'-Isopropylidenediphenol, 4 4'-Dihydroxydiphenyldimethylmethane Diglycidyl Ether, P P'-Dihydroxydiphenyldimethylmethane Diglycidyl Ether, Epi-Re2 510, Epoxide A, ERL-2774, 4 4'-Isopropylidenediphenol Diglycidyl Ether	1675-54-3

Appendix A continued…

CHEMICAL PRODUCT	COMPONENTS	SYNONYMS	CAS Code
666-2003-427 (also referenced as MMS-425)	Bisphenol A/ Epichlorohydrin Resin, Solic	Epichlorohydrin – 1-Chloro-2 3-Epoxypropane, 3-Chloro-1 2-Epoxypropane, (Chloromethyl) Ethylene Oxide, Chloromethyloxirane, 2-(Chloromethyl) Oxirane, Chloropropylene Oxide, Gamma-Chloropropylene Oxide, 3-Chloro-1 2-Propylene Oxide, Alpha-Epichorohydrin, (DL)-Alpha-Epichlorohydrin, Epichlorophydrin, 1 2-Epoxy-3-Chloropropane, 2 3-Epoxypropyl Chloride, Glycerol Epichlorohydrin, ECH, RCRA Waste Number U041 Skekhg, UN2023	106-89-8
	Inert Pigments and Strontium Chromate	Chromic Acid Strontium Salt, CI Pigment Yellow 32, Strontium Yellow, Deep Lemon Yellow, Strontium Dichromate, Strontium Chromate (VI)	7789-06-2
	N-Butyl Acetate	Acetic Acid Butyl Ester, Acetic Acid N-Butyl Ester, N-Butyl Acetate, Butyl Acetate, 1-Butyl Acetate, Butyl Ethanoate, UN1123	123-86-4
	MEK	Previously described (page 3, under “ME767”)	
	Toluene	Previously described (page 5, under “MIL-P-23377”)	
EC-2216	Part A: Amine Terminated Polyether/Carboxylic Acid Reaction Produce	No results found using online National Toxicology Program	
	Kaolin	No results found using online National Toxicology Program	1332-58-7
	Carbon Black	Separate list for search results was provided.	
	Part B: Bisphenol A/ epichlorohydrin resin	Previously described (page 7, under “666-2003-427”)	
	Liquid	Did not search	
	Kaolin	No results found using online National Toxicology Program	1332-58-7

Appendix A continued…

CHEMICAL PRODUCT	COMPONENTS	SYNONYMS	CAS Code
EC-1945 B/A	Part A: Isopropyl Alcohol	See attached list for search results.	
	Toluene	Previously described (page 5, under "MIL-P-23377")	
	MEK	Previously described (page 3, under "ME767")	
	Xylenes (O-,M-,P-isomers)	Component 1 – Xylenes, Dimethylbenzenes, Xylol. Component 2 – Ethyl Benzene	1330-20-7
	Ethyl Benzene	Previously described (page 5, under "MIL-P-23377**")**	
	Ethylenediamine	1 2-Ethanediamine, 1 2-Diaminoethane, Dimethylenediamine, Ethylendiamine, 1 2-Ethylenediamine, Beta-Aminoethylamine, NCI-C60402, UN1604	107-15-3
	N-(3- (Trimethoxysilyl) Propyl)	No results found using online National Toxicology Program	1760-24-3
	2,4,6-Tris (Dimethylamino Methyl) Phenol	No results found using online National Toxicology Program	90-72-2
	Volatile Organic Content	Did not search	
	Part B: N-Butyl Acetate	Previously described (page 7, under "666-2003-427")	
EC-1945 B/A	Zinc Chromate	Hydroxyoctaoxodizincatedichromate(1-) Potassium, Buttercup Yellow, Chromic Acid Potassium Zinc Salt (2:2:1), Citron Yellow, Potassium Zinc Chromate Hydroxide, Zinc Chrome, Zinc Yellow	11103-86-9
	Talc (containing asbestos)	Talc (Non-Asbestos Form), Talc Non-Asbestos Form Silica, Talcum, French Chalk, Soapstone, Steatite, Hydrous Magnesium Silicate, Mineral Graphite, Non-Asbestiform Talc, Non-Fibrous Talc	14807-96-6
	Epichlorohydrin, Bisphenol A	Previously described (page 7, under "666-2003-427")	
	Toluenediisocyanate Polymer	Tolylene Diisocyanate, Diisocyanatotoluene, Isocyanic Acid Methyl-M-Phenylene Ester, 1 3-Diisocyanatomethylbenzene, Diisocyanatomethylbenzene, Methylphenylene Isocyanate, Tolylene Isocyanate, Isocyanic Acid Methyl Phenylene Ester, Methyl-Meta-Phenylene Diisocyanate, Desmodur T100, Niax Isocyanate TDI, TDI, UN2078, Mondur-TD, Mondur-TD-80, Nacconate-100, Rubinate TDI, Rubinate TDI 80/20, T100, TDI-80, TDI-80-20, Hylene-T, RCRA Waste Number U223	26471-62-5
	Titanium Dioxide	See attached list of synonyms, it's too lengthy to include all here	13463-67-7

Appendix A continued…

CHEMICAL PRODUCT	COMPONENTS	SYNONYMS	CAS Code
EC-1945 B/A	MEK	Previously described (page 3, under “ME767”)	
	2-Ethoxyethyl Acetate	2-Ethoxyethanol Acetate, Acetic Acid 2-Ethoxyethyl Ester, Cellosolve Acetate, Ethoxyethyl Acetate, 2-Ethoxyethylacetate, Ethylene Glycol Ethyl Ether Acetate, CSAC, Ektasolve EE Acetate Solvent, Ethoxy Acetate, 2-Ethoxyethanol Ester with Acetic Acid, Beta-Ethoxyethyl Acetate, Glycol Ether EE Acetate, Glycol Monoethyl Ether Acetate, Oxytol Acetate, Poly-Solv EE Acetate, UN1172	111-15-9
	Lead Chromate	See attached list of synonyms, it’s too lengthy to include all here	7758-97-6
	Cyclohexane	Hexahydrobenzene, Cycloshexane (DOT), Hexamethylene, Hexanaphthene, Benzenehexahydride, Benzene Hexahydride	110-82-7
	Volatile Organic Content	Did not search	
SS-4004	Benzene	Benzene (D6), D6-Benzene, (D6) Benzene, Benzal-D6, Cyclohexatriene-D6, Phene-D6, Phenyl Hydride-D6, Pyrobenzole-D6	1076-43-3
	Tetraethyl Silicate	No results found using online National Toxicology Program	
	Acetone	See attached list for search results.	
	N-Butyl Alcohol	See attached list for search results.	
	Isopropyl Alcohol	See attached list for search results.	
	Toluene	Previously described (page 5, under “MIL-P-23377”)	
	(C10-13) Alkylbenzenesulfonic Acid	No results found using online National Toxicology Program	
	Triethanolamine	Trihydroxytriethyl Amine, 2 2’ 2’’-Nitrilotrisethanol, 2 2’ 2’’-Nitrilotriethanol, 2 2’ 2’’-Nitriloethanol, Daltogen, Nitrilo-2 2’ 2’’-Triethanol, Sterolamide, Thiofaco T-35, Triaethanolamin-NG, Triethanolamin, 2 2’ 2’’-Trihydroxytriethylamine, Triethylolamine, Tri (Hydroxyethyl) Amine, Tris (2-Hydroxyethyl) Amine, Trolamine, Tea, T-35	102-71-6
	Volatile Organic Compound	Did not search	

Appendix A continued…

CHEMICAL PRODUCT	COMPONENTS	SYNONYMS	CAS Code
PRO-SEAL 899	Not specified.	Need advice on which term to search further on, if applicable	
PR-1750	Part A: Hydrogenated Terphenyls	No results found using online National Toxicology Program	61788-32-7
	Manganese Dioxide	See attached list for search results.	
	Diphenyl Guanidine	Diphenylguanidine, N N'-Diphenylguanidine, DPG, Melaniline, Sym-Diphenylguanidine, NCI-C60924, DPG Accelerator, USAF EK-1270, USAF B-19, Vulcacid D, Vulkacit D/C, Vulkazit	102-06-7
	Carbon Black	See attached list for search results.	
	Part B: Limestone	No results found using online National Toxicology Program	
	Titanium Dioxide	See attached list of synonyms, it's too lengthy to include all here	
PR-1750	Toluene	Previously described (page 5, under "MIL-P-23377")	
	MEK	Previously described (page 3, under "ME767")	
	Trichloropropane/Sodium Polysulfide Copolymer (not specified).	No results found using online National Toxicology Program	
PR-2911	White Part A: Propylene Glycol Monomethyl Ether Acetate	No results found using online National Toxicology Program	
	Alpha-Isome	No results found using online National Toxicology Program	
	Diethyltoluenediamine	No results found using online National Toxicology Program	68479-98-1
	Silica	See attached list for search results.	
	Dimethylsiloxane (treated)	No results found using online National Toxicology Program	
PR-2911	Titanium Dioxide	See attached list of synonyms, it's too lengthy to include all here	13463-67-7
	White Part B: Polyurethane Repolymer as Polythioether Polymer with H12MDI	No results found using online National Toxicology Program	
	Monomeric Methylene Bis (4-Cyclohexylisocyanate)	No results found using online National Toxicology Program	
	Propylene Glycol Monomethyl Ether Acetate	No results found using online National Toxicology Program	

Appendix A continued…

CHEMICAL PRODUCT	COMPONENTS	SYNONYMS	CAS Code
PR-2911	Alpha-Isome	No results found using online National Toxicology Program	
	Black Part A: Propylene Glycol Monomethyl Ether Acetate	No results found using online National Toxicology Program	
	Alpha-Isome	No results found using online National Toxicology Program	
PR-2911	Carbon Black	See attached list for search results.	
	Diethyltoluene-Diamine	No results found using online National Toxicology Program	
	Silica	See attached list for search results.	
	Dimethylsiloxane (treated)	No results found using online National Toxicology Program	
	Polyether Polyol (extended)	See attached list for search results.	
	Black Part B: Polyurethane Prepolymer as Polythioether Polymer with H12MDI	No results found using online National Toxicology Program	
	Monomeric Methylene Bis (4-Cyclohexylisocyanate)	No results found using online National Toxicology Program	
PR-2911	Propylene Glycol Monomethyl Ether Acetate,	No results found using online National Toxicology Program	
	Alpha-Isome	No results found using online National Toxicology Program	
PR-1826	Not specified.	Need advice on which term to search further on, if applicable	
QR-2817	MethyltrIacetoxysilane	No results found using online National Toxicology Program	4253-34-3
	Ethyltriacetoxysilane	No results found using online National Toxicology Program	17689-77-9
	Red Iron Oxide	See attached list for search results.	
	Hydrophobic Amorphous Fumed Silica	No results found using online National Toxicology Program	
	Methyl-3,3,3-Trifluoropropylsiloxane Hydroxy Termi	No results found using online National Toxicology Program	
94-002/9	Not specified.	Need advice on which term to search further on, if applicable	

Appendix B : Search terms representing chemical substances to which F-111 DSRS workers were potentially exposed

- Other -
2-Butanone
2-Butoxy-1-Ethanol
2-Butoxyethanol
2-Ethoxyethanol Acetate
2-Ethoxyethyl Acetate
2-Hydroxypropane
2-Propanol
2-Propyl Alcohol

- A -
Acetic Acid Butyl Ester
Acetone
Alcohol Ethoxylate
Aluminium Silicate
Amorphous Silica

- B -
Benzene
Benzene Methyl
Benzenethiol
Bisphenol A
Epichlorohydrin
Butanone
Butoxyethanol
Butyl Acetate

- C -
Carbon
Carbon Black
Chromium 6+ Trioxide
Chromium Oxide
Chromium Trioxide
Chromium VI Oxide
Cyclohexane

- D -
Diethyltoluenediamine
Dimethylacetamide
Dimethylbenzenes
Dimethylbenzenesulfonic Acid Sodium Salt
Dimethylcarbinol
Dimethylsiloxane
Diphatic Petroleum Naphtha
Diphenylguanidine
Disodium Metasilicate
Dodecylbenzenesulfonic Acid

- E -
Ethyl Acetate
Ethyl Benzene
Ethylbenzol
Ethyl Glycol Monobutyl Ether
Ethylenediamine
Ethyltriacetoxysilane

- F, G -
Fibrous Talc
Glycol Butyl Ether

- H, I, K, L -
Iron Oxide
Isopropanol
Isopropyl Alcohol
Kaolin
Lead Chromate
Limestone

- M -
Manganese Dioxide
MEK
Methane Phenyl
Methyl Ethyl Ketone
Methylbenzene
Methyltriacetoxysilane
Monobutyl Glycol Ether
Monochromium Oxide
Monochromium Trioxide
Monomeric MethyleneBis Monophenol Polyethylene Glycol

- N, O -
N N-Dimethylacetamide
N N'-Diphenylguanidine
N-Butoxyethanol
N-Butyl Acetate
N-Propan-2-O
Naphtha
Octoxynol 9

- P -
Petroleum Ether
Petroleum Naphtha
Petroleum Solvent
Phenylmethane
Phosphoric Acid Triethyl Ester
Polyamide Resin
Polyaminopolyamide
Polyol
Potassium Borofluoride
Potassium Fluoroborate
Potassium Fluorozirconate
Potassium Tetrafluoroborate
Propan-2-Ol
Propylene Glycol Monomethyl Ether Acetate

- S -
Sec-Propyl Alcohol
Silica
Silicate
Sodium Alkyl Carboxylate
Sodium Dimethylbenzenesulfonate
Sodium Fluoride
Sodium Hydroxide
Sodium Metasilicate
Sodium Monofluoride
Sodium Nitrite
Sodium Salt
Sodium Xylene Sulfonate
Sodium Xylenesulfonate
Solvent
Soot
Strontium Chromate
Strontium Chromate (VI)
Strontium Dichromate
Stoddard Solvent

- T -
Talc
TDI
TEA
TEP
Tetraethyl
Tetraethyl Silicate
Thiophenol
Titanium Dioxide
Toluene
Toluenediisocyanate
Triethanolamine
Triethyl Phosphate
Trihydroxytriethyl Amine
Tripotassium

- U, V, W, X, Y, Z -
White Spirit
Xylene
Xylol
Zinc Chromate
Zirconium Potassium Fluoride

Appendix C : Search terms for indicators of adverse outcomes of occupational exposure

BIOMARKERS	TOXICOLOGY	NEUROPSYCHOLOGY	CANCER	BIRTH DEFECTS	MS & MN DISEASE
Biological markers Mutation DNA damage Sister chromatid exchange Micronuclei Chromosome aberrations Ploidies Polyploidy Genes, P53 Genes, ras Hypoxanthine phosphoribosyl transferase Genes, suppressor, tumor Oncogenes Neoplasms Carcinogens Carcinogens, environmental Mutagens Mutagenesis Tumor Neoplastic disease Cancer (text word)	Toxicology Toxic response Toxic effects Dose response Dose effect Metabolism Mixed function oxidases Cytochrome P450 Mono-oxygenases Enzyme Excretion Absorption Elimination Metabolite(s) Biological markers Biological monitoring Health effect(s)	Cognitive impairment Dementia Alzheimer's disease Memory Cognition Concentration Neuropsychology Neurobehaviour Depression Mood Anxiety Psychosis Fatigue Epilepsy Stroke Cerebrovascular disease Parkinson's disease	Cancer Neoplasm Tumour Carcinoma Sarcoma Carcinogen Malignant/malignancy	Congenital disease Birth defects Birth defects congenital disease Chromosomal abnormalities Birth Injuries	Demyelinating Autoimmune disease Multiple sclerosis, chronic progressive, relapsing-remitting Neuromyelitis optica Myelin dysfunction Polyradiculoneuritis Guillain-barre syndrome Chronic inflammatory poly-radiculoneuropthy Brain diseases Spinal cord diseases Paresthesias Dysarthria Spasticity Ataxia Myelitis, transverse Optic neuritis Demyelination Neurodegenerative diseases Amyotrophic lateral sclerosis Bulbar palsy, progressive Muscular atrophy Poliomyelitis Heredodegenerative disorders Nervous system Peripheral nervous system diseases Muscle hypertonia Amyotonia congenita Polioviruses human 1-3 Sarcoidosis

Appendix D : List of resources used for literature search

NAMES OF DATABASES / SEARCH FACILITIES

- Cumulative Index to Nursing and Allied Health
  http://www.library.ucsf.edu/db/cinahl.html
- ACP Journal Club
  http://www.acpjc.org
- Cochrane Database of Systematic Reviews
  http://www.cochrane.org
- Database of Abstracts of Reviews for Effectiveness (DARE)
  http://nhscrd.york.ac.uk/darehp.htm
- Medline
  http://www.ncbi.nlm.nih.gov/entrez/query.fcgi
- Australian Institute of Health and Welfare
  http://www.aihw.gov.au
- PsycINFO
  http://www.apa.org/psycinfo
- ClinPSYC
  http://www.ovid.com/products/databases
- NSW Health Clinical Information Access Program
  http://www.ciap.health.nsw.gov.au
- World Health Organisation
  http://www.who.int
- Epidemiology Information System
  http://www.nlm.nih.gov/pubs/factsheets/toxlinfs.html
- Hazardous Materials Technical Center
  http://www.dscr.dla.mil/htis/htis.htm
- Australian Bureau of Statistics
  http://www.abs.gov.au
- Newcastle Institute of Public Health
  http://www.niph.org.au
- Australian Federal Information
  http://www.nla.gov.au/oz/gov/
- Development and Reproductive Toxicology
  http://www.nlm.nih.gov/pubs/factsheets/dartfs.html
- Australian Chemical Trauma Alliance Inc.
  http://members.ozemail.com.au/~actall
- Swedish National Chemicals Inspectorate
  http://www.kemi.se/default_eng.htm
- Federal Research in Progress
  http://www.nisc.com/factsheets/qfdr.htm
- Toxic Substances Control Act Test Submissions
  http://esc.syrres.com/efdb/TSCATS.htm
- CANCERLIT
  http://www.cancer.gov/search
- Canadian Centre for Occupational Health and Safety
  http://www.ccohs.ca
- Center for Health Effects of Environmental Contamination
  http://www.cheec.uiowa.edu
- Poisonous Plants Bibliography
  http://www.calacademy.org/research/library/biodiv/biblio/poison.htm
- Canadian Task Force on Preventive Care
  http://www.ctfphc.org/
- International Pharmaceutical Abstracts
  http://www.silverplatter.com/catalog/ipab.htm
- United Nations Environment Programme
  http://www.unep.org/
- Toxicological Aspects of Environmental Health
  http://www.biosis.org/products_services/toxline.html
- International Programme on Chemical Safety
  http://www.who.int/pcs/
- American College of Occupational and Environmental Medicine
  http://www.acoem.org/

Appendix E : Silica and other substances in relation to malignancies

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Axelson, 1979 (214)	Case-control study	2313	Various occupations in Helsingborg (Southern Sweden) an industrial city	Iron oxide dust	Cancer incidence	No excess of cancer has been observed with exposure to dust of iron oxide
Bansal, 1997 (200)	Genetic research	N/A	N/A	N/A	Genetic research	Maturation analysis of the coding sequences of MEK-1 and MEK-2 genes in human lung cancer cell lines
Bauer, 2000 (233)	Letter	N/A	N/A	Silica dust	Lung cancer	Remains unclear whether silica is on the causal pathway between exposure to silica and lung cancer.
Beirne, 1982 (211)	Abstract only	?	Cellular	Polycyclic aromatic hydrocarbons	Oral cancer	NA
Boffetta, 2001 (196)	Population based study	1066	Residents in Montreal Canada	Titanium dioxide	Risk of lung cancer	No association between exposure to titanium dioxide (paints) and increased risk of lung cancer
Brockman, 1998 (216)	Review of literature	N/A	N/A	Carbon black	Cancer	No increased risk
Browne, 1992 (259)	Letter	N/A	N/A	Silica and asbestos	Lung cancer	Non-smokers at greater risk if they have grade 3 asbestos
Carta, 1994 (254)	Review	N/A	Sardinian metal miners	Exposed to silica and low levels of radon daughters	Lung cancer mortality and airways obstruction	No relation between crystalline silica and lung cancer; slight association between lung cancer mortality and exposure to radon daughters

Appendix E continued…

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Checkoway, 1997 (243)	Historical cohort mortality study	2342	Diatomaceous earth industry, California	Silica	Non-malignant respiratory disease and lung cancer	Strong dose-response relationship between silica and NMRD. Lung cancer less convincing.
Checkoway, 1999 (237)	Cohort analysis	2342	White males diatomaceous earth industry workers	Crystalline silica	Radiological silicosis, and lung cancer mortality	Suggests silicosis is not necessarily a co-condition for silica related lung carcinogenesis.
Checkoway, 2000 (232)	Review of epidemiologic literature (10 studies)	N/A	Exposed workers	Silica	Is silicosis required for associated lung cancer	Silicosis and lung cancer as distinct entities whose cause/effect relations are not necessarily linked
Cherry, 1998 (242)	Cohort	5115	Men born 1915-45 employed in the pottery, refractory and sandstone industries of Stoke	Crystalline silica	Risk of lung cancer	Positive association between silica and lung cancer
Chulasir, 1984 (209)	In vitro	N/A	Tumor cells in vitro	Petroleum ether and chloroform extracts from Ceylon Cinnamon barks	Carginogenic effects	Showed cytotoxic effects of KB and L1210 cells.
Cocco, 1994 (253)	Mortality cohort study	526	Female workers in two lead and zinc mines in sth/west Sardinia (Italy)	Exposed to silica	Lung cancer	Low statistical power of the study does not allow conclusion to be drawn on the aetiology
Cocco, 2000 (231)	A nested case-control study	1372	Chinese workers in mines and factories	Silica	Non-malignant respiratory diseases and lung cancer	Modest association of silica and cumulative exposure to silica with lung cancer
Cocco, 2001 (228)	A nest case-control study	1672	Workers in Chinese mines and pottery factories	Silica	Lung cancer risk and silicosis	Future studies should incorporate detailed information on exposure other than workplace to lung carcinogens.

Appendix E continued…

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Dalager, 1980 (138)	Cohort	202	US, male, spray painters in the aircraft maintenance industry	Zinc chromate	Cancer mortality	Significant excess of cancer, primarily of the respiratory tract.
Davies, 1984 (210)	Cohort	1152	Workers at three English chromate pigments factories	Lead chromate and zinc chromate pigments	Lung cancer mortality	Results indicate that moderate or heavy exposure to zinc chromate may give rise to severe risk of lung cancer
De Klerk, 1995 (252)	Cohort	1971	Western Australian gold miners employed underground for greater than 40 years	Silica	Lung cancer mortality	Slight but non-significant increase in the lung caner risk
De Klerk, 1998 (240)	Cohort	2297	Western Australian goldminers	Silica	Silicosis and lung cancer	Silicosis clearly related to silica exposure and significant increase in risk for subsequent lung cancer
Dong, 1995 (250)	Retrospective cohort mortality study	6266	Chinese refractory plants	Silica dust	Lung cancer	Increased lung cancer risk attributed to the silicotics
Duffus, 2000 (235)	Letter	N/A	NA	Silica	Lung disease	Radon is carcinogenic, metallic nickel is not and possibly elemental arsenic is also not
Fayerweather, 1997 (199)	Case-control study	1160	Tetraethyl lead manufacturing plant in Deepwater, New Jersey	Tetraethyl lead	Cancer risk	Possible association between colorectal cancer and TEL manufacturing process at this plant

Appendix E continued…

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Fillmore, 1999 (239)	A death certificate study	N/A	Women with probable exposure	Probable exposure to silica	Cancer mortality in women	Women had elevated proportional mortality ratios (PMRs) for thyroid ca, multiple myeloma, digestive organ cancers
Finkelstein, 2000 (234)	Quantitative review of literature	N/A	Variety of industries	Silica	Silicosis and lung cancer	A lifetime risk of silicosis and lung cancer at an exposure level of 0.1mg/m3 is high
Finkelstien, 2001 (229)	Letter	N/A	NA	Silica	Silicosis and lung cancer	Re Hessel and colleagues. "The authors have overlooked data from Ontario that clearly demonstrate a relationship between the presence of radiographic silicosis and the later diagnosis of lung cancer" (p199).
Forastiere, 1986 (274)	A case-referent study	391	Italian ceramic workers	Silica	Silicosis and lung cancer	Increased risk of lung cancer with silica exposure
Gibbs, 1998 (241)	Letter	N/A	N/A	Silica	Non-malignant respiratory disease and lung cancer	Re: Checkoway and asbestos – findings may be diluted and influenced the conclusion of no asbestos effect
Hagmar, 1993 (204)	A cohort based case-reference study	7023	9 Swedish polyurethane foam manufacturing plants.	Toluene diisocyanate and methylene diphenyldiiso-cyanate	Incidence of cancer	Negative or no association for high exposure and prostate, colon, non-Hodgkin's lymphoma or rectal cancer.
Heppleston, 1985 (275)	Comment piece	N/A	N/A	Silica	pneumoconiosis and carcinoma of the lung	Weight against evidence of carcinogenic role for uncombined silicon dioxide

Appendix E continued…

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Hessel, 1986 (272)	Case-control study	399	White South African gold miners	Silica	Silicosis and lung cancer	No association
Hessel, 1987 (270)	Letter	N/A	NA	Silica	Silicosis and lung cancer	Re: Forastier - claimed an association between silica exposure and silicosis and lung cancer.
Hessel, 1990 (263)	A necropsy study (case control)	549	White South African gold miners	Silica	Silicosis and lung cancer	No association between lung cancer and silica exposure
Hnizdo, 1991 (260)	Mortality study	2209	South African gold miners	Silica and tobacco	Mortality from lung cancer	Association between lung cancer and silica dust effect modification by smoking
Hnizdo, 1997 (244)	Nest case-control study	2260	South African gold miners	Exposure to silica dust, silicosis and uranium	Lung cancer	Results cannot be interpreted definitively in terms of causal association
Kerslake, 1997 (198)	In vitro model	N/A	N/A	Phorbol esters	In vitro model – abstract only	In vitro model of iron oxide particle toxicity
Klein, 1995 (249)	Review	N/A	N/A	Crystalline silica	Threshold carcinogen	Insufficient evidence
Koskela, 1994 (255)	Cohort plus census-based target populations	1026 +	Finnish granite workers + census-based target populations from the same regions	Silica dust	Lung cancer	Increased lung cancer with silica exposure
Lebowitz, 1981 (276)	Review of extent of morbidity	N/A	N/A	Silica	Silicosis and lung carcinoma	No conclusive evidence of a definite relationship between silicosis and lung carcinoma
Liu, 1997 (217)	Retrospective cohort study	6635	Male factor workers in China	Carbon black	Cancer mortality	Numerous deaths correlated with cola tar pitch volatiles

Appendix E continued…

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Lynge, 1986 (273)	Incidence register results	N/A	Nordic Foundry workers and Swedish miners	Silica dust	Lung cancer	Workers exposed to high concentrations of silica dust showed a significant excess lung cancer risk
Lynge, 1990 (262)	Comparative analysis	N/A	Nordic Foundry workers and Swedish miners	Silica dust	Cancer mortality and incidence	Excess lung cancer risk for foundry workers
Mastrangelo, 1988 (269)	A case-referent study	309	Belluon, Italy. Workers in quarrying, tunnelling and other occupations involving exposure to silica	Silica dust	Lung cancer	Exposure to silica appears to increase risk of lung cancer but only in the presence of silicosis.
McDonald, 1989 (268)	Editorial	N/A	N/A	Silica	Silicosis and lung cancer	Limited evidence for the carcinogenicity of crystalline silica in man
McDonald, 2000 (230)	Editorial on IARC	N/A	N/A	Silica	Lung cancer	"Crystalline silica in the form of quartz or cristobalite from occupational courses is carcinogenic to humans.
McLaughlin, 1992 (258)	Nested case-control study	1668	Workers in Chinese pottery workers, tungsten, copper-iron and tin miners	Silica	Lung cancer	Increasing trend of lung cancer with increased exposure to silica
McLaughlin, 1997 (193)	Book chapter	N/A	N/A	Amorphorous silica	Health effects with particular reference to cancer	Data on cancer outcomes associated with amorphorous silica are scanty and mostly negative.

Appendix E continued…

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Meijers, 1990 (265)	A case control study	761	Male Dutch fine ceramic industry workers	Silica	Lung cancer	No association
Merlo, 1991 (261)	Retrospective cohort study	1022	Refractory brick workers, Genoa, Italy	Crystalline silica	Mortality from lung cancer	Mortality from lung cancer and resp disease elevated in workers employed longest
Merryman, 1997 (197)	Lab investigation	N/A	N/A	N/A	Small cell lung cancer	Carbon dioxide an important messenger molecule
Morgan, 1996 (247)	Letter	N/A	N/A	Silica exposure	Lung cancer	Comment on Weills and McDonald
Moulin, 1989 (220)	Review of studies	2417	Carbon electrode manufacturing workers in France	Carbon Black	Lung, larynx, pharynx and buccal cavity cancers	No association
Neuberger, 1990 (264)	A prospective study	1621	Viennese men working in foundries, other metal, glass, ceramic, brick, stone and other dusty industries	Silica dust	Respiratory disease and lung cancer	Relation between exposure to respirable particles and mortality from lung cancer and chronic lung disease
Ng, 1994 (256)	Viewpoint	N/A	N/A	Silica	Lung cancer	Association between lung cancer in workers with occupational silica is confounded by exposures to cigarette smoke.
Nurminen, 1992 (257)	Risk estimation	N/A	N/A	Silica	Estimate risks of silicosis and lung cancer associated with lung cancer	Prediction formulas to predict occurrence of silicosis and lung cancer
Pan, 1999 (236)	Nested case-control study	375	Various Industrial workers	Silica and other dusts	Oesophageal cancer	Positive association between silica and

Appendix E continued…

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Parent, 1996 (218)	Case-control study	3730	Various exposures	Carbon black	Lung cancer	Association between exposure to carbon black and lung cancer
Park, 2002 (222)	Quantitative risk assessment	?	California diatomaceous earth industry workers:	Crystalline silica	Silicosis and lung disease other than cancer	Crystalline silica risk lung disease other than cancer far in excess of what is considered acceptable.
Partenen, 1995 (251)	Review	N/A	Various hazardous industries	Silica	Silicosis and cancer	Suggests that silica dust also causes lung cancer
Petrone, 1987 (207)	Cohort mortality study	4000	Oklahoma commercial dry cleaning plants 1941-1985	Stoddard solvent	Mortality due to cancer	Increase in resp and pancreatic cancers
Rice, 2001 (224)	A quantitative risk assessment	2342	California diatomaceaous earth industry workers	Crystalline silica	Lung cancer mortality	There was significant risk of mortality from lung cancer that increased with cumulative exposure to respirable crystalline silica dust
Robertson, 1989 (221)	A case-control study	345	Carbon black workers in the United States	Carbon Black	Circulatory, malignant and respiratory morbidity	No association
Rønneberg, 1995 (203)	Cohort study of cancer incidence between 1953 and 1991	1137	Norwegian aluminium smelter workers	Prebaked carbon anodes	Mortality from circulatory and respiratory diseases	Data supports previous finding: increased IHD and support for increased resp mortality in potroom workers
Rønneberg & Anderson, 1995 (202)	Cohort study of cancer incidence between 1953 and 1991	1137	Norwegian aluminium smelter workers	Prebaked carbon anodes	Mortality and cancer morbidity	Increased bladder, lung, kidney cancer and exposure to tar pitch volatiles. Latency period of 30-40 years

Appendix E continued…

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Rood, 2001 (195)	A Stochastic estimate	N/A	Rocky Flats Environmental Technology Site	Carbon tetrachloride	Cancer risk	Carbon tetrachloride considered a probably human carcinogen
Seaton, 1997 (246)	Letter	N/A	N/A	Silica exposure	Risk of cancer	– re Morgan and Reger.
Shabad, 1980 (213)	Guest editorial	N/A	N/A	Carcinogenic polycyclic aromatic hydrocarbons	Cancer prevention	Good historical background to chemical carcinogenesis
Sheffet, 1982 (212)	Cohort - 1296 white & 650 non-white men	(refer left)	Pigment plant workers in Newark	Lead and zinc chromates	Cancer mortality	Increased risk of lung, stomach and pancreatic cancer
Simonato, 1990 (267)	Not a study	N/A	N/A	Silica dust	Lung cancer	IARC – 3 main findings: 1) silica is carcinogenic in experimental systems (IARC 1987); 2) lung cancer risk is increased among workers exposed to silica; 3) when investigated separately, lung cancer risk is concentrated among the subpopulation of exposed workers who develop silicosis
Sjogren, 2001 (225)	Letter	N/A	US industrial sand workers	Crystalline silica	Lung cancer	Refers to Steenland re IHD.
Sorahan, 1989 (206)	Cohort	953	Workers in a factory, 1961-84	Chlorinated toluenes	Lung cancer mortality	Lung cancer may result from occupational exposure to certain chlorinated toluenes
Spivack, 1990 (266)	Letter	N/A	N/A	Silica	Comment	Re Rivard – “the implication of a causative role for silica exposure in the development of lung cancer must remain speculative”

Appendix E continued…

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Steenland, 1997 (245)	Meta-analysis	N/A	Various industries	Silica, asbestos, man-made mineral fibers	Cancer	Little evidence for lung cancer for either glass wool or rock slag wool. Asbestos well established as carcinogen for lung and mesothelium.
Steenland, 2001 (223)	IARC multicentre study	65980	Various exposed workers – gold miners, diatomaceous earth, pottery and granite workers	Silica	Lung cancer	IARC to classify silica in occupational settings as a carcinogen.
Steenland, 2001 (226)	Cohort	4626	US industrial sand workers	Crystalline silica	Lung cancer	Supports the labelling by the International Agency for Research on Cancer of crystalline silica as a human carcinogen.
Stober, 1996 (201)	A critical appraisal of epidemiolog-ical studies	N/A	N/A	Diesel soot particles in ambient air	Lung cancer	No consistent association with lung cancer or bladder cancer
Straif, 2000 (215)	Cohort	8933	Rubber workers	Nitrosamines, carbon black, asbestos and talc	Mortality from stomach, lung and laryngeal cancer	Increased mortality from lung and stomach cancer associated with exposure to asbestos and dust respectively. No association between nitrosamines and stomach or lung cancer.
Sutton, 1985 (208)	Letter	N/A	N/A	Sodium fluoride	Oral carcinogen	Referring to Tsutsui (1984) on fluoride as a cause mouth cancer
Thomas, 1987 (271)	Cohort mortality study	2055	US pottery workers	Silica and talc	Lung cancer and respiratory disease	Talc and lung cancer association

Appendix E continued…

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Thomas, 1993 (205)	Descriptive epidemiology	N/A	N/A	N/A	Breast cancer in men	Little evidence re chemical exposure
Tsuda, 2001 (227)	A case-control study	726	Deaths in the Tobi area of Japan	Silica	Gastric cancer and esophageal cancer	Results suggest gastric and oesophageal cancer were related to silica exposure and silicosis.
Ulm, 1999 (238)	Case-control study	1042	Workers in German stone quarrying and ceramic industries	Silica dust	Lung cancer	No association between exposure to crystalline silica and lung cancer
Valberg, 1996 (219)	Quantitative comparison	N/A rats	NA	Carbon-black	Lung cancer	Using rat inhalation bioassay data for carbon black to estimate lung tumor risk in humans must be seriously questioned
Weill, 1996 (248)	Review	N/A	N/A	Exposure to crystalline silica	Risk of lung cancer	Epidemiological evidence has become stronger in suggesting a link between exposure to silica and lung cancer.
Yamada, 1997 (194)	Case control	211	Non-occupational females in urban areas of Japan	Talc and amosite/ crocidolite	Non-occupational female lung cancer	Fibrous talc in urban environments may be a candidate for carcinogenic factors of female lung cancer

Appendix F : Benzene exposure in relation to malignancies

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Aksoy, 1982 (296)	Chapter 5	N/A	N/A	Benzene	Leukaemia and Malignant Lymphoma	Benzene capable of inducing a variety of haematology and lymphatic malignancies as well as damaging the bone marrow.
Budinsky, 1999 (278)	Evaluation of modelled benzene exposure and dose estimates	N/A	Workers in China	Benzene exposure	NA	Suggest increased risk of acute nonlymphocytic leukaemia at relatively low benzene concentrations and associations with cancers not previously associated with benzenes exposure.
Cronkite, 1988 (293)	Mice	N/A	N/A	Benzene	Induced hematopoietic neoplasms	Benzene causes and promotes malignant process in mice
Gerin, 1998 (29)	A case-control study	4236	Cancer patients and controls	Benzene, toluene, xylene and styrene	Several sites of cancer	Limited evidence of increased risk for associations of oesophagus-toluene, colon-xylene, rectum-toluene, rectum-xylene and rectum-styrene.
Hayes, 1997 (283)	Cohort study	110633	Industrial workers in 12 cities in China	Benzene	Hematologic neoplasms	Benzene known to cause leukamia, particularly acute nonlymphocytitic leukemia and perhaps other haematological neoplasms.
Ireland, 1997 (282)	Cohort mortality study	4172	Male workers at the Monsanto Company plant in Sauget.	benzene exposure	Cancer mortality	Elevated (albeit imprecise) rates of leukemia and multiple myeloma.

Appendix F continued…

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Jarvholm, 2000 (277)	Letter	N/A	N/A	Benzene from traffic and petrol stations	Letter.	Disputes the conclusions reached in the Harrison study
Krekel, 1978 (298)	Presentation transcript	N/A	N/A	Benzene	Cancer Risk demands cancer control	Some history
Li, 1994 (289)	Cohort	110000	Benzene-exposed workers in China	Benzene	Gender differences in hematopoietic and lymphoproliferative disorders and other cancer risks by major occupations group	No significant differences in relative risks for total mortality between male and females benzene exposed workers. Both sexes had increased risk for all haematopoietic and lymphoproliferative (HLP) malignant and nonmalignant disorders.
Linet , 1996 (287)	Follow-up of Chinese cohort	110633	Benzene-exposed workers in China	Benzene	Clinical features of hematopoietic malignancies and related disorders	Validating diagnoses of leukemia and other haematopoietic and lymphoproliferative malignancies and related disorders (HLD)
Maltoni, 1983 (295)	Long term bioassays	N/A	N/A	Benzene	A multipotential carcinogen	There is the need for more research.
Nurmien, 1984 (294)	Cohort	?	Carbon disulfide-exposed workers	Carbon disulfide	Cancer mortality	Mortality rate not statistically significant
Paci, 1989 (291)	Cohort	2013	Male and female workers in a show manufacturing plant	Benzene.	Aplastic anaemia, leukaemia and other cancer mortality	Benzene is a well documented carcinogen for hematic and lymphopoietic system. Excess risk of aplastic anaemia for men observed.

Appendix F continued…

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Petralia, 1999 (280)	Case-referent study	301	Women over 40 with premenopausal breast cancer in New York State.	Occupational exposure to polycyclic aromatic hydrocarbons and benzene	Risk of premenstrual breast cancer	Association between risk and occupational exposure to benzene. However, low-response rates and small numbers of exposed persons
Rothman, 1997 (284)	Case-control study	11177	Shanghai workers in benzene exposed jobs	Benzene poisoning	Haematological malignancy	Evidence of human susceptibility to benzene related disease
Schnatter, 1996 (288)	Nested case-control study	155	Canadian petroleum distribution workers	Benzenes	Lymphohaemato-poietic malignancies and quantitative estimates of exposure	No relation between lymphohaematopoietic cancer and long term, low level exposures to benzene
Smith, 1999 (281)	Commentary	N/A	N/A	Benzene NQO1	Genetic susceptibility to cancer	Possible link between lack of or lowered NQO1 activity may make individuals vulnerable to leukaemia secondary to chemical exposure.
Steineck, 1990 (290)	Population based case-referent study	541	Men born between 1911-45 living in the County of Stockholm	Benzene and exhausts	Increased risk of urothelial cancer	Exposure to benzene (any annal dose) gave a relative risk (with 95% CI) of 2.0 (1.0 – 3.8).
Van de Berghe, 1979 (297)	Two patients case study	2	Men with histories of working with benzene	Presumably by benzene	Chromosome analysis in two unusual malignant blood disorders	Generally accepted that chronic exposure to benzene may induce leukaemia in man. Early reports in 19th century followed by “abundant literature” on the subject.
Wong, 1999 (31)	A critique of the exposure assessment	N/A	Workers in China	Benzene-exposed	NA	Believes many of the results in the CAPM-NCI study are unreliable.

Appendix F continued…

Author	Study type	n=	Population	Exposure	Outcome	Results/Evidence
Yin, 1989 (292)	Retrospective cohort	28460 + 16621 controls	Benzene workers	Benzene	Study of leukemia and other cancers	For certain cancers increased mortality was noted among benzene exposed males
Yin, 1996 (285)	Cohort	110633	Benzene-exposed workers in China	Benzene	Cancers	Employment in benzene associated occupations in China associated with wide spectrum of myelogenous and lymphocytic malignant disease and related disorders.
Yin, 1996 (286)	Expanded cohort study	110633	Benzene-exposed workers in China	Benzene	Cancer	Results as above
Zheng, 1999 (279)	Case-control	490	Connecticut women with breast cancer	β-Benzene hexachloride in breast adipose tissue and risk of	Breast cancer	Results support the hypothesis that increasing adipose tissue levels of β-BHC area associated with an increased risk of breast carcinoma in females.

Appendix G : Mitochondrial disease and solvent exposure

As part of the F-111 DSRS Interim Health Care scheme, one RAAF member who had been involved in deseal/reseal activities was assigned a possible diagnosis of MELAS, a syndrome of mitochondrial encephalopathy, lactic acidosis, and stoke, that usually manifests in childhood or adolescence. The syndrome may be accompanied by psychosis, cardiac myopathy, or arrythmias, and in most cases (ie;over 80%) is due to a particular mutation in mitochondrial DNA. This created speculation that mitochondrial disease may be related to exposures during deseal/reseal activities. Hence, the TUNRA team was asked to examine this in its literature review.

The search was carried out as follows: the following MeSH headings were entered in MEDLINE (from 1966 to July 2003), joined by “OR”:

Hydrocarbons
Hydrocarbons, acyclic
Hydrocarbons, alicyclic
Hydrocarbons, aromatic
Hydrocarbons, brominated
Hydrocarbons, chlorinated
Hydrocarbons, cyclic
Hydrocarbons, fluorinated
Hydrocarbons, halogenated
Hydrocarbons, iodinated
Polycyclic hydrocarbons
Polycyclic hydrocarbons, aromatic
Solvents
Environmental exposure
Occupational exposure
Organic chemicals

And crossed with:
MELAS

Fifty nine references were found, none of which were relevant to solvent exposure. In addition, the incidence of the most common mutation for MELAS is between 10-16 per 100,000 (299), and not all of these develop the clinical syndrome; this would lead to an expected number of MELAS cases in our exposed group (~1000) of 0.1. Thus, no evidence of a relationship between solvent exposure and mitochondrial disease has been found, and the rarity of this condition would not recommend it as a possible outcome in the General Health and Medical Study.