Public Health and Environmental Impacts of Monosodium Methanearsonate as used in Bark Beetle Control in British Columbia

Prepared for
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by

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Summary

This report examines the potential health and environmental effects of monosodium methanearsonate (MSMA), as used in British Columbia to create lethal trap trees for control of bark beetle infestation.

MSMA is applied as a frill injection to individual trees. The highest dosage of use is about 40 ml of MSMA product per tree, depending on tree size. Approximately 750 kg of MSMA product are applied in British Columbia each year on average. The area of use is widely dispersed covering most of the interior of the province where bark beetle infestations may occur. The average annual total area of treatment is 650 hectares. In any one landscape drainage infested with bark beetles, it is unlikely that, of the many thousands of trees that may exist there, more than 50 trees would be treated with MSMA.

Existing evidence indicates that use of MSMA in bark beetle control does not impose measurable risk on applicators, the public or wildlife.

Burning of slash or mill waste, or use of treated trees as firewood also does not represent a health threat, as judged through comparison of expected arsenic levels in smoke with other markers of air contamination.

Arsenic concentration in various parts of trees treated with MSMA or the related cacodylic acid has been measured in several studies. A worst case situation where only treated trees enter a mill, with contaminated sawdust in air at the maximum allowable *wood dust* concentration, would lead to arsenic intake 2000-5000 fold lower than permitted by British Columbia industrial health and safety regulations.

These conclusions have been reached after review and consideration of, in the context of bark beetle control, (a) the toxicology of MSMA and related compounds, (b) the disposition of these substances in the body, (c) the behavior of MSMA in the environment, and (d) exposure of workers, the public and lower species. All of the information has been integrated in an assessment of risk associated with this use of MSMA. The information reviewed includes both publications in the open literature and summaries of manufacturer's confidential registration data made available for the purpose of this report.

The toxicity of MSMA is limited. It has some potential for mild skin and eye irritation, and when ingested in sufficient amounts causes gastrointestinal erosion. Studies of its cancer causing potential have been negative, and it has a limited and questionable ability to cause mutation. Reproductive effects appear only at dose levels that cause evident maternal injury.

MSMA is excreted rapidly by mammals, including humans. Exposure of applicators has been determined to be low, and their intake of MSMA is far below thresholds of toxicity. However, it is evident that better use of basic protective garments, training and work discipline can lower exposures still further.

In nature, inorganic arsenic salts are continuously converted to methylated acids and oxides, including MSMA, which are much less toxic than inorganic arsenic compounds. Formation of methylated derivatives is also a primary means of detoxication in mammals. Soil microorganisms slowly produce the corresponding arsines from the oxygen-bearing acids and oxides, but the reaction is rapidly reversed in air. While the arsines are relatively toxic, they disappear quickly enough that concentrations do not become significant. Reversion of MSMA to inorganic arsenic in plants or mammals, including humans, apparently does not occur to a measureable extent. Some microorganisms are able to accomplish this reaction.

Because MSMA is either injected or applied directly to cuts in the bark at the base of selected trees in a stand, there is very little environmental contamination. Measurement of MSMA application to agricultural soil at several times normal application rates over multiyear periods shows that soil buildup and offsite movement do not occur, even under such extreme conditions. Measurement of arsenic in streams through treated forests has not detected increases over background levels. A spill of MSMA is unlikely to contaminate water sources unless lost directly into or immediately adjacent to a water body. Exposure of the public using the forest is extremely unlikely.

Acknowledgements

The initial effort in development of this report was a survey and review of available literature, commercial information and unpublished reports by Marnie Duthie, a student at the University of Victoria in a Cooperative Education Project with the Silviculture Branch, MOF. John Henigman of Silviculture Branch, MOF prepared the section on methodology and patterns of MSMA use and provided critical review from the perspective of forest insect control. Dr. John Manville, Pacific Forestry Centre, Canadian Forest Service and Dr. K.J. Reimer, Department of Chemistry, Royal Roads Military College reviewed the report and provided extremely valuable assistance and advice. A critique by Dr. E.M. Belletts, Chemical Consultants International, of toxicological and chemical considerations of the report was very helpful.

This report could not have been completed adequately without access to recent data generated for re-registration of MSMA in the United States. The cooperation and generosity of the manufacturers of MSMA, collectively identified as MAA Task Force Three, in making the findings available, is acknowledged with thanks, as is the efforts of Dr. Belletts in expediting our access.

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Introduction

The Ministry of Forests is constantly reviewing and revising its worker and environmental protection policies for all aspects of forest management. This report on the impacts of use of the pesticide monosodium methanearsonate (MSMA) for bark beetle control is a part of that program. Everyone involved in use or management of British Columbia forests should understand the safety and risks associated with the kinds of work necessary for forest maintenance. The people of the province should have access to reliable information about the effects of forestry activities on workers, the public and the environment.

MSMA is a paradoxical pesticide. It is a widely used agricultural herbicide in the United States, but in Canada it is used only for forest insect control. It is a synthetic or manufactured pesticide, but MSMA and several similar arsenical pesticides are also universally formed in nature. They are formed by many living organisms, including humans, from the inorganic arsenic that is a normal component of soil, water and foodstuffs. MSMA is a relatively benign chemical, but is based on an element used and feared as a poison throughout recorded history. The legends about arsenic as a poison lead to a tendency to lump all forms of arsenic together, but organic arsenicals are very much less toxic than the inorganic forms. Curiously, the formation of methyl arsenicals in the body, including MSMA, is the mechanism for detoxifying inorganic arsenic.

In the case of MSMA as it is used in bark beetle control the essential questions are:

1. How much MSMA (or its degradation products) reaches humans, by any route?
2. Are the amounts sufficient to imaginably cause harm, or are the levels so low that they cannot be expected to approach a harmful level?
3. Does the use of MSMA in bark beetle control adversely affect populations of non-target organisms in the forest?

In other words, what exposures of workers and the public result from this use of MSMA, and what does the scientific information about MSMA and similar arsenical compounds tell about the potential effect of the exposures?

MSMA has been used in control of several species of bark beetles since the sixties, using a variety of protocols. In British Columbia, spruce, mountain pine and Douglas-fir bark beetles cause major economic losses in the forests. To control the former mentioned beetles, MSMA is applied in shallow cuts through the bark at the base of individual trees selected as traps in infested areas. Application is either before (for spruce) or after (for lodgepole pine) the beetles attack the treated trees. An attractant bait is used with lodgepole pine to improve trapping efficiency. The pesticide translocates through the xylem and into the phloem, resulting in the death of the tree. The dying, treated tree attracts beetles away from viable trees that would otherwise be attacked, and the arsenical pesticide distributed in the tree apparently has a direct lethal effect on the insect. Manville et al. (1988) have reviewed the various factors that influence the effectiveness of the approach, and have elucidated much of the behavior of MSMA after administration to trees.

The use of MSMA as a stem injection limits its potential for adverse human or environmental effect. Virtually all of the applied pesticide reaches its target directly, and when properly applied, little MSMA reaches soil or other vegetation as a result of application.

The most important health concern is exposure of applicators, who handle MSMA in concentrated form. Research has shown that application by stem injection or hack and squirt can be made virtually exposure-free through training and supervision, and even workers with imperfect discipline can be well protected by proper clothing and gear. Nonetheless, consequences of exposure, should it occur, must be evaluated.

From an environmental perspective, the primary concern is distribution of MSMA or arsenic derived from MSMA through the tree and the potential for the applied material to move from fallen foliage and from roots into other compartments of the environment.

The public health concern is the possibility of exposures from handling treated trees in logging and milling, use of treated trees for firewood, and disposal of trees or mill waste containing MSMA.

The last mechanism for potential impact is mishandling and spillage of MSMA.

The information reviewed in preparation of this report has been obtained from the published scientific literature and from a summary of studies submitted to the US Environmental Protection Agency for purposes of re-registration of MSMA and DSMA (disodium methanearsonate). Such information is maintained as corporate confidential documents in the hands of regulatory agencies. The data has been made available under a confidentiality agreement to F.N. Dost on behalf of the British Columbia Ministry of Forests, by a Task

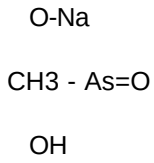
Force consisting of the U.S. registrants of MSMA. In references, the source of this material is identified as MAA Task Force Three (1993).

Review of the published data that applies to MSMA, as well as re-registration data developed by the industry, indicates that use of this pesticide in bark beetle control does not impose discernible health or environmental risk.

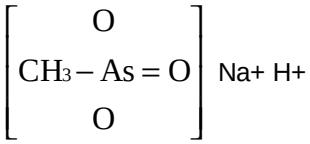
Background

Chemistry

MSMA has the chemical structure:



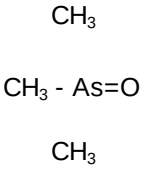
In solution the structure is more accurately represented by showing the electronic structure, because the bonds to the three oxygen atoms are essentially interchangeable:



For the purposes of this report the simpler representation is adequate and easier to follow.

In solution MSMA is in equilibrium with monomethylarsonic acid (MMAA) and the disodium methane arsenate (DSMA). At relatively neutral pH, it is mostly in the form of MSMA. As the solution becomes more acid, MMAA predominates, with the sodium ion (Na+) replaced by hydrogen ion (H+). If the solution becomes more basic, the hydrogen of the second hydroxyl (OH) group is replaced by sodium to form DSMA. These relationships are illustrated in Figure 1. (In the literature MMAA is sometimes identified as MAA; the abbreviation MMAA will be used when referring to such work to avoid confusion with the convention used here.)

The closely related pesticide cacodylic acid has a structure similar to that of MSMA, with a hydroxyl group replaced by a second methyl group (CH3):



Inorganic arsenic is ubiquitous in nature and is found in soil and all organisms; at one time it was thought that arsenic was an essential element in biological processes. Woolson (1977a) has reviewed data on presence and fate of arsenic in various compartments of the environment. Among the levels reported are concentrations of 1-40 parts per million (ppm) in soil, up to 0.0023 ppm in the Great Lakes, up to 0.006 ppm in sea water, and 0.010 and 0.030 mg/m3 in rural air and urban air respectively. Because of the wide variation in natural deposition of arsenic, and the existence of many industrial sources, environmental concentrations also are widely variable. Cullen and Reimer (1989) have prepared a comprehensive review of the chemical forms and interconversions of arsenic compounds in the environment. More recently Tamaki and Frankenburger (1992) have also reviewed the biochemistry of arsenic emphasizing microbial, fungal and algal interactions.

Arsenic is found in many forms that interchange readily in biological systems. These relationships in nature are illustrated in Figure 1, modified from Manville *et al.* (1988) and Cullen and Reimer (1989).

The first three structures in Figure 1 are inorganic arsenicals, having no carbon (Figure 1, 1). Microbial systems such as those of soil tend to favor formation of DMAA through MMAA, with some formation of TMAO (Figure 1, 11). Microorganisms also slowly convert MMAA, DMAA and TMAO to methyl arsines (Figure 1, 111), which are volatile and move into the atmosphere, then are rapidly oxidized in air back to the corresponding acids. DMAA is the predominant metabolite of arsenic in mammals as well as in soil. Oxidation

of the methylated forms (II) back to inorganic arsenic W with formation of C02 from the methyl groups has been demonstrated by cultures of soil microorganisms (Von Endt *et al.,* 1968). The process is slow and incomplete and the inorganic arsenic is then subject to re-methylation.

MSMA has a place in the natural arsenic cycle because at the pH of the body, MMAA ionizes and is associated with sodium to form the sodium salt, MSMA. For this reason, research on the toxicology of MSMA given orally often utilizes MMAA. As shown in Figure 1, if MSMA is fed to an animal, the low pH (high acidity) of the stomach causes it to hydrolyze to MMAA. Administration of MMAA is therefore identical to administration of MSMA. After absorption into blood and tissues, where the pH is about 7.4, it has the form of MSMA.

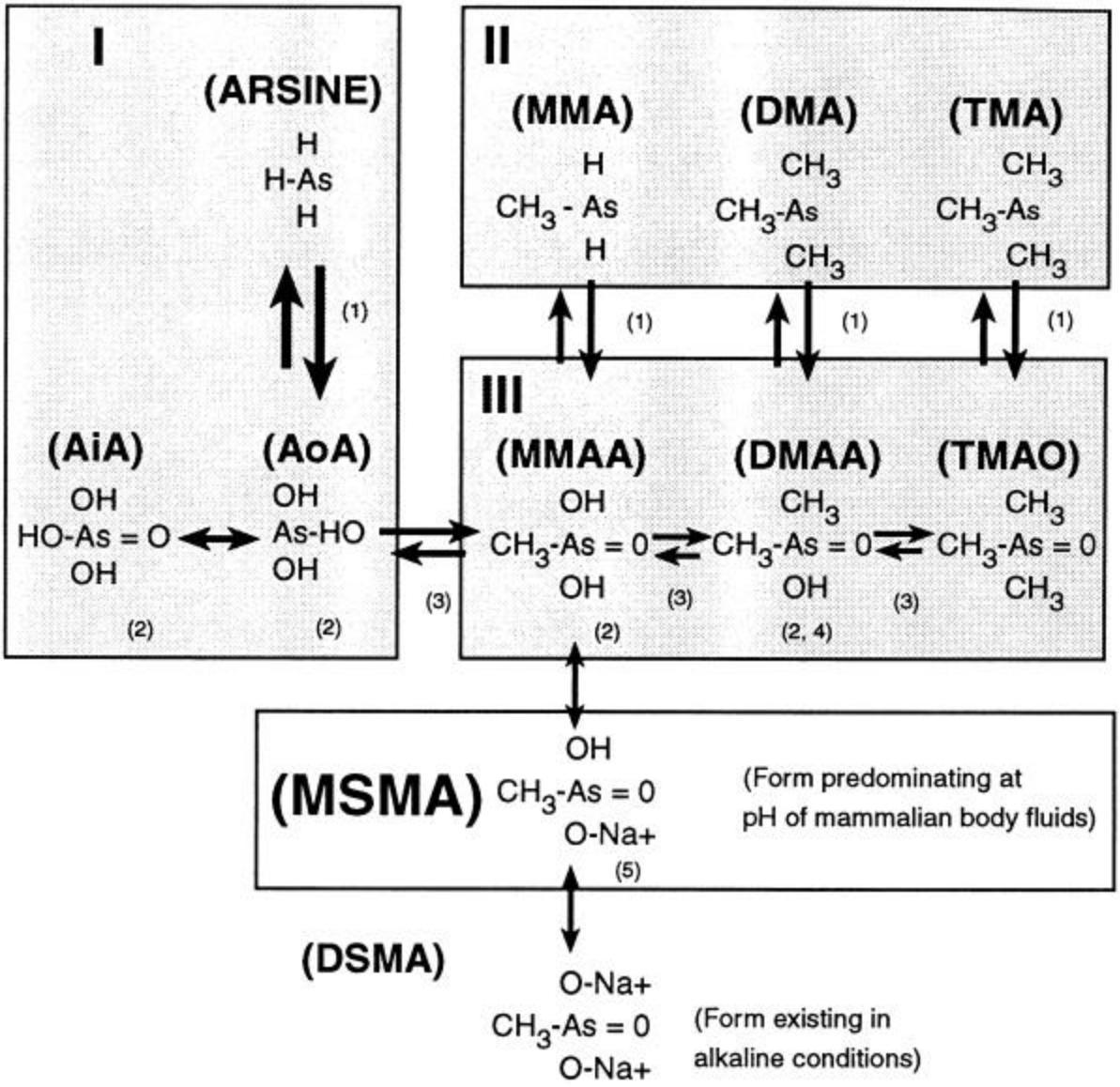
The discussion above is to illustrate the ease of conversion in nature among the various organic and inorganic forms of arsenic. The inorganic acids of arsenic tend to be removed from contact with biological systems because they become tightly bound to soil, particularly through the iron and aluminum ions in clays.

Several of the organic arsenicals found in nature are registered as herbicides, including DMAA and MSMA, shown in Figure 1. Substitution of a sodium for hydrogen on the OH of cacodylic acid, a second sodium on MSMA or an ammonium instead of sodium on MSMA also make effective herbicides. These are not discussed further. However, biological effects and environmental behavior are fairly consistent among the organic arsenicals, and data on any one has some application to all.

There are many commercial formulations of MSMA because it is not protected by patent. Formulations used in forestry are water based solutions containing MSMA in concentrations ranging from 30 to 45%. A surfactant is usually added to lower the surface tension of water, making the herbicide solution spread more easily on surfaces, and translocate more easily when absorbed from application on tree stems. Surfactants used in pesticide formulations are usually similar to household detergents, such as are found in shampoos and dish soaps.

Some formulations include a polysaccharide gum to hold the pesticide in place by increasing viscosity, giving the opposite effect from a surfactant. Dyes are usually used to indicate treated sites and to show applicators the quality of their work practices. Because MSMA is synthesized from inorganic precursors, traces of inorganic arsenic may be present.

The only formulation used in Canadian forestry is Glowon®. The constituents of the formulation are water, a polysaccharide gum, 6.66 lbs MSMA/gallon, pH adjusted to 5.6 with hydrochloric acid, Cab-o-Sil (a suspending agent) Tamol (a wetting agent) and A-14-N Fire Orange dye. A specimen label can be found in Appendix A, and a copy of the Material Safety Data Sheet is in Appendix B.



Acronyms:

MMA, monomethyl arsine; **DMA**, dimethyl arsine; **TMA**, trimethyl arsine.
AiA, arsinic acid; **AoA**, arsenous acid; **MMAA**, monomethyl arsonic acid; **DMAA**, dimethyl arsinic acid (cacodylic acid);
TMAO, trimethyl arsine oxide.
MSMA, monosodium methane arsonate; **DSMA**, disodium methane arsonate.

(1) Arsines are readily oxidized in presence of atmospheric oxygen and are found only in traces in the atmosphere.
(2) These are the most common forms in nature.
(3) There is some demethylation to inorganic arsenic by soil and gut microorganisms, not by plants or animals.
(4) DMAA is the predominant excretory form in mammals.
(5) Among MMAA, MSMA and DSMA, MSMA is the form that will predominate in mammalian systems.

Figure 1. MSMA and other components of the natural arsenic cycles. Boxes I, II and III refer to discussion in text.

Basis for control of bark beetle

Bark beetles of the genus *Dendroctonus* are the most damaging of forest insects in western North America. Species of greatest concern in British Columbia are the mountain pine beetle, *D. ponderosae* Hopk., the spruce beetle, *D. rufipennis* (Kirby), and the Douglas-fir beetle, *D. pseudotsugae* Hopk. These insects periodically reach outbreak levels and attack and kill large volumes of large diameter, mature pine, spruce, and Douglas-fir respectively.

Management agencies employ a variety of strategies and treatments to reduce losses to these insects. Some of the treatments include directed harvesting, use of semiochemicals, and single tree disposal. Treatments for mountain pine beetle and spruce beetle also include the use of systemic insecticides such as MSMA in a number of use patterns.

The mountain pine beetle is responsible for much of the mortality of mature lodgepole pine in western Canada and northwest United States. Epidemic infestations of the mountain pine beetle have been recorded in British Columbia since the turn of the century with the first attempts at controls occurring in the 1920's. Since that time, infestations have occurred in all Forest Regions in the province at various times, frequencies, and intensities. The last major outbreak began in the mid-1970's and has continued in various areas into the 1990's. Extensive tracts of pine have been killed and harvesting and other management activities have been directed at beetle infestations at the expense of other long-term management plans. Effective management of mountain pine beetle requires the coordinated use of all available treatments.

Spruce beetle attacks mature and overmature stands of Engelmann and white spruce in the interior of British Columbia. While infestations of this insect are not as chronic as those of mountain pine beetle, substantial losses of high value spruce forests have occurred in periodic large infestations in the province. Past efforts at management have resulted in extensive progressive clearcuts in several regions in the province. This practice is unacceptable under proper forest management and disrupts normal harvesting plans. As with mountain pine beetle, reduction of losses to spruce beetle requires the application of a variety of treatments in a coordinated fashion.

Limited directed harvesting of stands infested by mountain pine or spruce beetle remains a major tool in reducing losses to these insects. However, other methods that allow removal or destruction of small patches of infested material or allow suppression of small infestations in isolated areas serve as preventive treatments, removing small, incipient infestations before they can expand and cause major impacts. These treatments include small patch or selective harvesting, falling and burning individual infested trees, and the use of MSMA.

Patterns of MSMA use in British Columbia forestry

MSMA is used to control both mountain pine and spruce beetles. About 2000-3000 litres (640-960 kg of MSMA) of the Glowon® product is used annually in the province. It is applied by small crews of forest workers to individual mature pine or spruce trees by hacking a frill around the base of the tree and squirting a measured amount of Glowon® into the frill.

Treatment of pine with MSMA requires three different, though related, activities. Normally the same workers are involved in all three activities. During June and July pheromone baits are placed on specific trees in order to predispose these trees to attack. Later in July and August workers survey forest stands for recently attacked trees. If baiting has been successful the baited trees and others located close to them will be attacked. MSMA is then applied in July or August to the mass attacked trees to kill the beetles. In any one location occupied by many thousands of trees, 10-50 trees may be treated. On average, it will take 10 minutes to treat a tree with MSMA.

The treatment of spruce beetle is somewhat different. As with pine, crews survey and identify attacked trees in July or August. In April or May of the following year the crews treat with MSMA a number of unattacked trees close to the infestation. Two weeks later, after the pesticide has translocated and before beetle flight, the trees are cut down to mimic blown down trees, which are preferred by spruce beetle. Beetles in the local area will be drawn to the treated and downed trees and will be killed.

In treating a pine or spruce tree, a worker first cuts a continuous frill around the base of a tree with an ax. The cuts must just penetrate the cambium layer of the bark. MSMA is squirted into the frill evenly around the circumference to achieve the appropriate dosage rate for the tree species and size. For pine, 1 n-d of 90% Glowon® in water per 2.5 cm of tree bole circumference is applied, and for spruce 1 ml of 25% Glowon® in water per 2.5 cm of tree bole is applied.

MSMA is originally supplied in 20 litre pails and is eventually dispensed into 1 litre bottles for use in the forest. Each bottle, at the time of its use is fitted with a squeeze bottle applicator orifice. Each applicator would carry up to two one litre bottles into the forest from the helicopter or truck. Prior to the bark beetle control season, staff dilute the Glowon® product to a concentration of 90% or 25% with water for use to control respectively mountain pine beetle or spruce beetle. Where available, clean-up rinsate water from the previous year is used for the dilution. The resultant mix is dispensed into 1 L plastic bottles for use in the field. This mixing is normally undertaken in a forest district compound on a plastic tarp where clean-up facilities are close at hand. All pesticides, including MSMA are stored in specially constructed pesticide storage facilities.

Workers in the MSMA program include both sexes and all age groups. Some of the workers are trained and certified pesticide applicators, who will supervise the other workers in the pesticide application. Depending on the size of the treatment project, the crew size will typically be two or three persons.

During late July to the end of August when MSMA is applied to pine, workers wear normal bush clothing and rubber gloves. Each crew would have at least one litre of water available for washing and cleaning small splashes on their clothing or equipment. The crew would walk into the forest between 100-1000 metres away from the truck or helicopter.

For isolated treatment locations crews often are carried in by helicopters. In this case the helicopter will land near the trees on a pre-constructed helipad or natural opening. All equipment and MSMA is left with the crew at the helipad and later in the day the crew and all equipment and MSMA are retrieved.

At the end of the control season empty MSMA pails are cleaned and disposed. The procedure for cleaning is to initially rinse each pail with about 1 L of water to remove the majority of MSMA residue. This rinsate is stored for next year's Glowon® dilution. The pails are then triple rinsed, punctured and taken to a local landfill. The secondary rinsate, as well as any rinsate from equipment cleaning, is temporarily stored and then drained into clay or silt soil on an MSMA permitted treatment area. The location of the rinsate disposal is far removed from surface or ground water as required by the Waste Management Act Regulation.

Other methods of bark beetle control

Pile and burn

The pile and burn treatment process to control bark beetles has similarities to the MSMA treatment technique. The baiting and probing activities are the same. The piling and burning activity, which replaces the MSMA treatment, occurs during the non-fire hazard season (approximately December 1 to March 30). Crews locate, fell and buck infested trees. The bucked trees are piled and burned. Liquid or gelled gas is used to carry the fire. On average each tree will take about one hour to burn. Like the use of MSMA, piling and burning can be done in isolated locations.

The individuals involved in piling and burning may be the same as those involved with MSMA use. The minimum crew size is three. One or more of the crew will be a certified faller. The gear used by the crew will include chain saws, axes, gasoline and peevees. As well, fire fighting equipment, such as shovels and "piss" cans, will be available. The fallers will wear Workers' Compensation Board approved safety gear for falling.

Sanitation logging

Spread of the beetle can be limited by sanitation logging individual or groups of specific baited and mass attacked trees that have previously been located by probing. In the Cariboo Forest Region a few beetle control projects involved either a horse logging team or a small helicopter. Once on the landing, the logs must soon be removed by truck to a mill in order to prevent the escape of the beetles to new trees. This " of specialized logging can act to limit the spread of the beetle.

Large-scale salvage logging of beetle damaged trees, or those at high risk, is not a control treatment. Rather, this logging is an attempt to save the timber for the mill. This logging does not impede the spread of the beetle.

Environmental behavior of MSMA

To evaluate the potential for exposure of workers or others after application of MSMA to tree stems, it is necessary to understand what happens to the pesticide at the time it is applied and afterward. Interpretation of the behavior of synthetic methyl arsenicals introduced into the environment by human activity is complicated by the fact that natural biological processes methylate native soil arsenic to form some of the same chemicals used as pesticides. Even mammals, including humans, are able to produce methylated arsenic compounds. Also, until relatively recently, arsenic determinations were usually as total arsenic; the arsenic arising from an application of MSMA could not be distinguished from that already present in nature unless it produced statistically valid evidence of increased levels.

The environmental distribution and fate of MSMA as it is used in insect control is constrained by the method of application. Only a small percentage of trees in a stand are treated and the material is administered directly into the tree stem by making a cut frill as low on the tree bole as possible. Because there is no broadcast spraying, there is no direct distribution on soil or litter which reduces or eliminates exposure of animal life and movement to watercourses. As with other pesticide use, the consequence of spills must still be considered.

Obviously, exposure of applicators can occur directly while handling the herbicide. For exposures through milling of treated trees, it is necessary to know how MSMA or its products are distributed in the tree stem, and whether they can be transferred to the hands or clothing. Is a logger or millworker who handles wood containing MSMA exposed significantly? If treated wood is burned, how much arsenical is released to the atmosphere in smoke, and in what form, and what exposures are possible?

Movement to other native or domestic crops must be considered. Does MSMA move to roots and then into adjacent soil where berries, mushrooms or forage are growing? If arsenic does move into soil, will plants take it up and pass it on to ultimate human or animal consumers?

The study most immediately applicable to the question of environmental movement of MSMA after tree injection is by Norris *et al*. (1983). They measured total arsenic in the organic matter of the forest floor, soil and vegetation near trees treated in thinning operations, and in streams flowing through treated forests in eastern Washington State. Samples were taken of herbs, browse, forest litter and soil at points 0.5, 2 and 4 crown radii from the stem of selected trees. Sample times were prior to treatment, and approximately eight weeks, one year and two years after treatment.

In the earlier studies of the fate of MSMA it was not possible to differentiate among the several forms of arsenic that might be present. Analyses of environmental samples measured total arsenic, including MSMA, inorganic arsenate and arsenite, and any metabolic derivatives of MSMA. However, despite the lack of specificity, when levels of total arsenic are found to increase in an orderly manner related to application of MSMA, it may be fairly assumed that MSMA is the source. Recent investigations in which the form of arsenic can be specified are obviously more informative.

Norris *et al*. (1983) found that following the Douglas-fir injection treatment there was an increase in levels of total arsenic in undergrowing herbiage in the samples closest to the trees at all sampling times. The amounts of arsenic in the initial samples in this sequence were highly variable, and while the mean concentration of 1.72 ppm was quite high compared to the pretreatment level of 0.18 ppm, the large variability reduced statistical significance. In browse, statistically significant arsenic elevation appeared two years after application at the closest sampling point. There was a highly variable but not statistically significant elevation in forest litter total arsenic concentration that probably resulted from needle drop. There was modest change in soil arsenic levels at the sampling point closest to the stem at one and two years after treatment.

Findings after ponderosa pine treatment were similar but less pronounced except for the higher arsenic concentration in forest litter close to the tree, possibly because of a higher turnover of needles. Concentration in litter rose to almost 1.2 ppm at two months, compared to 0.5 ppm prior to treatment. At one year after treatment the level was very high, averaging 43.2 ppm which declined over the following year to 9 ppm.

In the western larch treatment there was some increase in arsenic concentration in litter that appeared to be sustained over the time of the study. Neither pine nor larch treatments altered soil arsenic levels. Although measurements were of total arsenic rather than MSMA as such, the pattern overall indicates tight binding of MSMA in foliage with little movement to soil. Whether the modest increases in arsenic in herbaceous foliage under treated trees originated from litter or deeper soil is unclear. The levels found do not appear to be biologically significant.

The water sampling by Norris et al. (1983) was conducted during thinning operations in which stem-injected MSMA was used to eliminate unwanted young trees, during storms and during the spring run-off as much as nine months after application. In two of the areas, MSMA was used on both sides of the stream. There was no indication of a buffer area between treated trees and streams. Four samples contained arsenic at the detection limit of 0.01 ppm; in all others arsenic could not be detected. These measurements indicate that there is not significant intrusion into forest watercourses after stem treatment with MSMA.

Microbiological processes in soil slowly form volatile arsines, which are shown in Figure 1. Woolson (1977b) incubated sodium arsenate, cacodylic acid and MSMA in soil, both with and without oxygen. Over a period of 160 days, 12.5% of methyl 14C-labeled MSMA applied to soil under aerobic conditions was converted to dimethyl or trimethyl arsine, which volatilized from the soil and was trapped for analysis. The rate of production appeared to be relatively linear, which means that about 0.09% of the applied MSMA was converted to a volatile form each day. In other words, the amount produced each day was about the same, even though the amount available for conversion became less and less as time progressed.

This linear effect probably occurred because the soil micro-organisms were converting MSMA at capacity, even at the lower soil concentrations. Volatile methylarsines plus soil bound radioactivity accounted for about 80% of the applied MSMA. The remaining radioactivity probably emerged as $^{14}C0_2$, formed from the labeled methyl carbon. (See discussion of work by von Endt *et al.,* 1968, below.) There was no evidence of formation of arsine gas (AsH_3). This is quite important, because arsine is highly toxic. In nature both inorganic and organic arsines react readily with oxygen in the atmosphere and are converted back to the corresponding acids (Arsenic acid, MMAA, DMAA and TMAO). (See Figure 1.) Because the methyl arsenicals do not migrate far in soils, most of the microbial activity of interest is probably aerobic. In further unpublished work by Woolson referenced by MAA Task Force Three (1993), the residual arsenic in soil was found to be arsenate ion, with some cacodylate.

Microorganisms can also convert organic arsenic back to inorganic forms, although the process is usually slow. Von Endt *et al.* (1968) found that one species of soil bacterium isolated in pure culture converted almost 20% of the ^{14}C of labeled MSMA to carbon dioxide in three days, if oxygen and an energy source were supplied. Other kinds of organisms converted much smaller amounts, and also required other nutrients. Unlike the pure cultures, microbes in soil carry out this reaction very slowly. It took 60 days for normal microbial populations of four incubated, nonsterile soils to convert 1.7 to 10% of applied radiolabeled MSMA to carbon dioxide over a 60-day period. The authors concluded that even though the carbon of MSMA could slowly be oxidized to carbon dioxide, it could not be used as a nutrient source in the way that many organic chemicals can be.

These papers indicate that emergence of methyl arsines from MSMA in a natural soil environment is a slow process. Even at the most unfavorable dilution in airspace over a treated area of soil, the slow production of arsines and their conversion forms commonly found in soil means that atmospheric concentrations will not violate even highly conservative safety factors. In trees that are not decaying, bacterial and fungal populations are low, which means that conversion to arsines should be further minimized. In addition, the arsines have very sensitive odour thresholds and can be detected at levels much lower than will produce adverse effects. For example, the odour threshold for trimethyl arsine in the air over a dilute solution is reported to be 0.000002 mg/kg (Yamauchi and Yamamura, 1982, in Cullen and Reimer, 1989). In other words, trimethyl arsine in aqueous solution at a concentration of two parts per billion would be detectable by odour.

The levels of MSMA found in herbaceous foliage and browse after tree injection can be compared with data from studies of crop uptake after field applications of MSMA. Norris *et al.* (1983) found that soil close to treated Douglas-fir trees contained about 1 ppm arsenic prior to treatment and gained another part per million over the sampling period after two years. Total arsenic concentration in plants growing in that soil increased from a maximum of about 0.4 ppm to almost 0.8 ppm in one case, with one apparently anomalous finding of 1.7 ppm. Almost all of the increases observed were not statistically significant. Johnson and Hiltbold (1969) applied MSMA to a field at 2.23,4.47 and 8.95 kg/ha, producing arsenic concentrations in the upper 5 cm of soil of 15.1, 20.9 and 21.8 ppm respectively. Note that soil concentrations of total arsenic did not increase in proportion to application rate. Clover, oats and vetch acquired the lowest arsenic concentrations, and oil seeds accumulated the highest. The tables in the paper are difficult to understand and there is no information on background concentrations, but the data suggest that if total arsenic concentration at the soil surface is 15 ppm, foliage concentrations may be about 1.5 ppm. The finding of Norris *et al.* (1983) of foliar concentrations of much less than 1 ppm at soil concentrations of up to 2 ppm is consistent with the data on field crops.

When dealing with low numbers in a highly variable matrix such as soil, even two-fold differences are unlikely to have much meaning. Studies of very heavy applications of MSMA are instructive in resolving this uncertainty. For example, Hiltbold *et al.* (1974) measured arsenic levels in soils after six annual MSMA applications of 10, 20 and 40 kg/ha, which are 2.5, 5 and 10 times normal agricultural application rates. Total arsenic applied as MSMA over six years was 110 kg/hectare at the highest rate. Even at such remarkable application rates, almost all of the arsenic found was within 30 cm of the surface, and that found in the 15-30 cm depth was moved to that zone by plowing, not leaching. Cotton seed from treated areas contained only traces of arsenic. Movement of arsenic into seed

was also found to be very slight after application to wheat plants (Domir *et al.,* 1976). In a study somewhat comparable to that of Hiltbold *et al.* (1974), Robinson (1975) found that application of up to 36 kg MSMA/hectare did not increase soil arsenic concentrations.

These observations show empirically that the vastly smaller amounts of MSMA that may translocate from a treated tree will have little influence on arsenic levels in forest soils. It is likely that the limited change resulting from extensive application of MSMA in the above studies is a reflection of the very active "arsenic cycle" mentioned earlier. (See Figure 1 and associated comments.) Slow microbial transformation of organic arsenicals to volatile arsines moving into the atmosphere, followed by quick reaction with molecular oxygen and eventual precipitation back to the surface results in almost infinite redistribution of applied material into the much larger pool of naturally occurring arsenic.

Hiltbold (1975) reviewed the literature on behavior of organoarsenicals in plants and soils. His terminal paragraph is quite useful to our purpose here: "Sustained use of methanearsonates at rates recommended for weed control does not appear to result in hazardous accumulation of As in harvested crops. Methanearsonates are extensively adsorbed in soil and subject to little movement in leaching. Loss from treated fields may occur where erosion is severe. Volatilization of methylated As appears to be a significant loss process that limits As accumulation in soil and probably accounts for the ubiquitous occurrence of As in soils generally. The organoarsenicals are oxidized microbiologically producing arsenate. While arsenate is subject to methylation and volatile loss, much of the residual As in soil reverts to progressively less soluble forms with aluminum and iron compounds."

This statement reflects findings indicating that even if MSMA is lost from roots into soil, uptake by plants is possible but limited, which in turn limits any further transmission to browsing or grazing animals. The absence of significant movement into plants is supported by L. Anderson *et al.* (1978) who compared residues in tomatoes, cucumbers and pinto beans in plots treated with MSMA in water applied by either sprinkler or furrow irrigation, at rates equivalent to 0.11 or 1.1 kg/ha. Treatment was timed after blooming but before set of fruit. Furrow application did not cause an increase in arsenic levels of the plants, but application by sprinkler increased concentrations as much as three-fold over controls. Marcus-Wyner and Rains (1982) also found that uptake from soil was limited while absorption from foliar application was substantial.

Reference was made earlier to Norris *et al.* (1983), who showed small elevations of total arsenic levels in vegetation a short distance from the stem of trees treated with MSMA. Other research indicates that after use of MSMA there is little movement of any form of arsenic from soil into crop plants. However it seems likely that the small increase in total arsenic found by Norris *et al.* in plants adjacent to treated trees did translocate from roots or dropped needles, to soil, then to plants. The standard deviations of the data were not large, indicating reasonable consistency among samples. If the source was accidental spillage near the trees, erratic findings would be expected. Movement of ^{14}C from roots of wheat plants after foliar application of ^{14}C-MSMA was demonstrated by Domir *et al.* (1976). There was very slow formation of $^{14}C0_2$ to the extent of 0.8% of the applied MSMA. About 0.1 % was trapped as arsines. The rate of translocation was limited because volatiles were not detected until two weeks after application. It would probably be impossible to identify movement of MSMA arsenic from Douglas-fir, because natural arsenic translocates selectively into Douglas-fir to levels many times those found as background in other species. It has been suggested that arsenic levels in fir trees might serve as an indicator of gold and silver ores, since gold and silver are sometimes found with arsenic (Warren *et al.,* 1968).

Residues in fruit of blackberries subjected to MSMA spraying during roadside application increased to as much as 30 ppm, some of which could be washed off, suggesting both surface application on the fruit and translocation from leaves and stems (Anderson *et al.*, 1980).

The use of MSMA appears to offer little potential for movement in the environment to non-target vegetation or water sources. Slight increases in arsenic concentration, whether as MSMA or any other form in vegetation near treated trees is not sufficient to significantly expose livestock or herbivorous large game. The lack of lateral movement, and limited leaching as observed in very heavy agricultural applications indicates that small spills, such as from broken equipment will not result in water contamination. However, it must be considered possible that in unusual circumstances such as a heavy spill or a container of concentrate left in an accessible location, mammals might ingest a lethal amount of the pesticide. Because of the behavior of MSMA and similar materials in the environment, any accident will be confined to the site of occurrence.

Norris (1977) took a practical approach to the question of uptake of arsenic derived from MSMA by grazing or browsing animals. He measured arsenic in the hair of cattle foraging in forest plantations which had been thinned with MSMA. Inorganic arsenic moves selectively to hair and then remains in the segment of hair growing at the time of exposure. He found no differences between animals feeding in treated and untreated areas, which indicates that MSMA treatment did not contribute to available inorganic arsenic at the site. Norris (1974b) has also examined small mammals. Mice, chipmunks and shrews in treated areas were monitored over a 30 day

period following application of MSMA. Findings were quite variable in the various study areas, with a number of whole body burdens above 1 ppm total arsenic, and in many areas a high percentage of non-detectable residues. High or low levels appeared to be consistent with time in each area, suggesting that access to the arsenical depends on how it is handled by applicators. Mention is made of a single dead hare containing a concentration of arsenic considered sufficient to cause death, although most trapped hares contained low residues. The formulation is stated to have a salty taste that may be attractive to animals if it is accessible, as in a spill. The smaller mammals did not seem to be deterred by a rabbit repellent added to the MSMA.

Although the cattle surveyed did not seem to have acquired appreciable arsenic after use of MSMA, there has been a report of a deer assumed by the authors to have been killed by ingestion of MSMA within three days after stem treatments (Mathews and Porter, 1989). Pathological evaluation found lesions that were thought to be consistent with effects of high doses of MSMA in small animals, and with the results of treatment of steers described by Dickinson (1972). Levels of tissue total arsenic were also somewhat similar. It was suggested that since no spill was found near the storage site, the deer was attracted by a supposed salty taste of the formulation and had licked the material from treated trees. Older formulations contained significant amounts of sodium chloride; the taste of MSMA itself is apparently not on record. The authors assumed that a lethal dose would be similar to that reported by Dickinson (1972), who treated steers, some of which died, with 10 mg MSMA/kg/day for 10 days. Dickinson's study is discussed later. Mathews and Porter estimated that the deer would have had to lick all of the applied MSMA from 25-34 treated trees.

There is no point in arguing the arithmetic or suppositions used to reach the conclusion that the animal acquired the MSMA by licking trees; with a single animal and unknown time of death, one supposition is as good as another. However, the deer in question died between application and three days later. Such an immediate response suggests a very high dose, as does the pathology. After application into frills cut in the bark of the trees, the herbicide is physically difficult to reach, and absorption of MSMA by treated trees should further reduce its accessibility, even a short time after application. The use of MSMA for stem treatment has been very common and the number of deer who might have opportunity for exposure to treated stems must be very large. If exposure by licking stems is significant, it is surprising that there have not been other similar reports. Two alternative explanations for the case seem more plausible. The most likely is a spill at some location removed from the storage facility. It is also possible that individual deer, as do some cattle, may acquire pathological tastes leading to fervent search for the desired substance, which could result in a unique kind of exposure.

No reference has been found to measurements of arsenic or suspected intoxication of predatory species such as coyotes or foxes in areas treated with organic arsenicals. Even if in an extreme case several small animals were affected and consumed by a predator there would be no effect on the population. Because of rapid excretion it is questionable whether the predator itself would be injured.

Metabolic fate of MSMA and other methyl arsenicals

There is relatively little data in the literature describing the metabolic disposition of MSMA administered as such to mammals, but studies of the metabolism of monomethyl arsonic acid (MMAA) are directly applicable in judging disposition of MSMA. At the pH of the body, MMAA is almost entirely in the form of the univalent ion (MSMA) (Hiltbold, 1975; MAA Task Force Three, 1993), which is therefore predominant in body fluids. The cells and fluids of the body are rich in positive sodium (and potassium) ions. Sodium associates with the negative MMAA ion formed when hydrogen is removed from one OH, effectively forming MSMA.

Studies of metabolism of inorganic arsenic in mammals also provide direct information about MSMA disposition. They show excretion of some inorganic arsenic and a relatively irreversible transformation of the remainder to MMAA, followed by formation of DMAA and excretion. MMAA corresponds to MSMA at physiological pH. The proportions of the excretory forms depend on dose and species differences. In the paragraphs below, the term "inorganic arsenic" is used for simplicity. It has been shown in several studies (for example, Tam *et al.,* 1979; Vahter, 1981; Marafante *et al.,* 1987) that arsenate (arsenic, valence V) is converted to arsenite (arsenic, valence III) in the body, which is subsequently methylated. Methylation is the mechanism of detoxifying inorganic arsenic. Arsenic V that is not reduced to arsenic III is excreted unchanged. Curiously, the marmoset monkey, among the various mammals so far studied, apparently does not methylate arsenic (Vahter *et al.,* 1982).

The interchange among MMAA, MSMA and DSMA at various pH is shown in Figure 1.

Yamauchi *et al.* (1988) administered MMAA to hamsters in single oral doses of 5, 50, or 250 mg/kg, and 50 mg/kg intraperitoneally. Almost all of the 50 mg/kg oral dose was excreted in its original form in both urine (29%) and feces (60.5%). It is likely that most of the fecal MMAA had not been absorbed from the digestive tract after oral administration. When the same dose was injected into the peritoneal space (into the abdomen, among the viscera) more than 80% appeared in urine as MMAA by 48 hours after administration, and only about one percent was found in feces over the five days of the study. Very small amounts were converted to other methyl derivatives.

As would be expected, concentrations in the kidneys were highest among organs because they are the primary route of excretion.

Particular attention was paid by Yamauchi *et al.* (1988) to levels of DMAA, which was never present in urine at more than a small fraction of MMAA levels in the animals given 50 and 250 mg MNL4.A/kg. Urinary MMAA as the fraction of administered dose remained more or less constant at all doses, but at the lowest dose the percentage of DMAA increased to about 22% of the total. The sharp difference between doses suggests that at still lower doses the percentage conversion to DMAA would be greater yet. A small amount of trimethylated arsenic was found.

An important finding was that little if any MMAA was demethylated to the inorganic form of arsenic; the small amounts of inorganic arsenic found could be accounted for by the known arsenic contamination of the MMAA used in the study. (The authors also attempted to degrade MMAA, DMAA and TMAO chemically, without success.) The absence of demethylation is consistent with work on DMAA in other species (Stevens *et al.,* 1977; Yamauchi and Yamamura, 1984; Vahter, 1981; Vahter *et al.,* 1984). Absence of demethylation is important because it provides assurance that MSMA acquired through occupational or environmental exposure will not be converted to the much more toxic inorganic forms.

Metabolic studies in human volunteers given radio-labeled inorganic arsenic show that during the first day, about half of the excreted arsenic is inorganic, presumably in the form ingested. After that time most of the excreted arsenic is methylated, primarily to DMAA (Tam *et al.,* 1979). Crecelius *et al.* (1977), Smith *et al.* (1977) and Johnson and Farmer (1991) also showed a predominant conversion of inorganic arsenic to DMAA and MMAA in humans. In a portion of the latter study, intake of 22 nanograms inorganic arsenic by a single individual three times a day over 10 days resulted in steady-state daily excretion of about 21% inorganic arsenic, 14% MMAA and 65% DMAA. A day after last intake, DMAA exceeded 80% of the daily excretion, and by day 16 represented about 100% of excreted arsenic.

Study of other species provides similar information about the conversion of ingested arsenic to methylated forms, although the pathway in the rat is less efficient than in other species. (Odanaka *et al.,* 1980; Vahter and Envall, 1983; Charbonneau *et al.,* 1979; Lakso and Peoples, 1981).

Charbonneau *et al.* (1979) administered labeled arsenic acid to dogs, then followed the concentrations of inorganic and organic arsenic in plasma, red blood cells and urine. Red cells have a high affinity for arsenic. At 50 minutes after administration of arsenic acid

about 60% of the arsenic in red cells was inorganic and more than 30% was DMAA. After 400 minutes only about 7.5% was inorganic and more than 90% was DMAA. In plasma the organic fraction was even greater. Excreted arsenic in the urine was almost entirely DMAA. It would have been helpful to know what fraction of the administered dose was represented by these levels, but the conclusion must be that all or virtually all of the arsenic was methylated, and that there was no measurable reversal of the sequence. In the hamster, a similar experiment showed that a major fraction of the excreted arsenic had not been methylated, however (Charbonneau, *et al.,* 1980). Presumably, this occurred because the administered material was excreted rapidly, before methylation could take place.

In the two studies by Charbonneau *et al.,* arsenic was administered at very low doses; the labeled material was essentially free of unlabeled arsenic. Lakso and Peoples (1975) administered sodium arsenate and potassium arsenite to dogs at considerably higher doses, and found that urinary inorganic arsenic was comparable with the amounts of methylated arsenic. Cows converted a greater fraction to methyl arsenic. It is likely that the ability of both species to methylate arsenic was exceeded by the amounts administered.

Even though most arsenic is methylated, human tissues contain small amounts of background inorganic arsenic. Yamauchi and Yamamura (1983) analyzed healthy tissues from autopsied human cadavers (deaths not due to intoxication) to determine the distribution of the various chemical species of arsenic in normal humans. Most levels were in the range of hundredths of a part per million. About 90% of residual arsenic was inorganic; the remainder was predominantly DMAA.

The findings on residues in human tissues and other data discussed here indicates that most of the "normal" dietary arsenic intake is converted to the methylated forms and is excreted readily. When larger amounts of inorganic arsenic are encountered, much of the intake is initially excreted in the inorganic form and as time passes a greater fraction is methylated. A small amount of the inorganic arsenic that is not converted binds in tissues and remains for long periods. Arsenic bound in this fashion is not readily available and represents little or no potential for biological effect although it may serve as an indicator of past exposure. This cycle of rapid metabolism and excretion, with a minuscule storage of arsenic protects against almost all exposures to inorganic arsenic.

The biochemistry of the methylation reactions has been examined by Buchet and Lauwerys (1985,1987,1988) and Buchet *et al.* (1984). The metabolic scheme in the latter paper indicates that the equilibrium is in the direction of the dimethyl derivative, with both mono- and dimethyl metabolites emerging in urine; it is therefore unlikely that inorganic arsenic would be formed from the methylated species. Most of the methylation reaction occurs in the liver, and is dependent on adequate glutathione levels.

Glutathione is a sulfur-bearing tripeptide found in all cells and is important in oxidation-reduction reactions and detoxication. Some of the inorganic arsenic taken in by mammals is suggested to be trapped by glutathione and excreted in bile. The same workers have observed the methylation sequence in cultured mouse fibroblasts (Fischer *et al.,* 1985), and in rat tissue slices (Georis *et al.,* 1990) with formation of MMAA and DMAA from inorganic arsenic. Cells preconditioned with inorganic arsenic were more efficient in methylating arsenic than cells with no previous exposure. The tissue slice studies showed that As III diffuses through the cell wall, facilitated by reduced glutathione, and binds to intracellular components. Arsenic V is not readily brought into the cell, accounting for the need for reduction to As III prior to metabolism, as well as the greater toxicity of As III.

The indirect evidence that organic arsenic is not converted to inorganic forms was confirmed by observations of Marafante *et al.* (1987) who showed that 80 to 85% of DMAA administered to mice and hamsters at a dose of 40 mg As/kg was eliminated unchanged. In mice 3.5% was eliminated as TMAO (see Figure 1); hamsters produced 6.4% in this form. In a single male human, 80% was excreted as DMAA and 4% as TMAO. There was no demethylation of DMAA to inorganic arsenic. In the laboratory animals 13-15% of the dose was excreted as an unidentified complex of DMAA. The same group (Vahter *et al.,* 1984) had shown earlier that contrary to the rapid excretion by mice, rats excrete DMAA very slowly.

The pharmokinetic behavior (movement in the body) of MSMA in sheep and goats has been studied by Shariatpanahi and Anderson (1984) with the objective of judging the safety of consuming meat and milk from animals exposed to MSMA used in agriculture. In both species, after oral doses of 19.45 mg MSMA/kg, clearance was more than 97% complete in five days, and only very small amounts appeared in milk. The data indicated that most of the arsenical was present in a free form in the circulation and tissue fluids and was easily excreted by the kidneys. A small fraction is bound to cellular and probably plasma protein and is released more slowly to account for most of the later phase of excretion.

The arsenic content of marine fish is an interesting special case, although it is only peripherally related to questions of MSMA use. Many species of marine fish carry high natural burdens of arsenic. Arsenic found in fish tissues is almost entirely organic (Edmonds and Fransesconi, 1977; Crecelius, 1977), and is more complex than a simple methylated form. Because the chemical species have not been firmly identified in all cases, and because they appear to be excreted unchanged when ingested by mammals, they have acquired identity as "fish-arsenic." An extensive list of aquatic species in which high arsenic levels have been found is included in the review by

Cullen and Reimer, 1989 who point out that arsenobetaine is the most abundant arsenical in most marine species. Tam *et al.* (1982) have briefly reviewed the question in a paper describing metabolism of fish-arsenic in 15 human volunteers. Following ingestion of 200 grams of fish containing 50 ppm arsenic (10 mg total), about 80% of the arsenic intake was eliminated in eight days, apparently unchanged. Johnson and Farmer (1991) have reported similar behavior. Freeman *et al.* (1979) observed six human volunteers who ate a total of 385 grams of fish containing a total of slightly more than 5 mg of arsenic in two consecutive meals. Excretion of total arsenic was almost complete in three days after the second meal.

It is quite clear that MSMA and other methylated arsenicals are excreted expeditiously from the body, and that formation of inorganic arsenic from methylated arsenicals is very limited, if it occurs at all.

Toxicology of MSMA

MSMA has been registered in the United States for many years although until recently there were extensive regulatory data gaps. In spite of the interest in the biochemistry of the organic arsenicals, they are not extensively discussed in the published toxicology literature.

Clinical observations in humans

There have been few clinical observations of humans known to have been exposed to MSMA or closely related compounds. Allard (1974) evaluated 14 clinical laboratory measurements in workers applying MSMA and cacodylic acid. Mean urinary arsenic levels ranged from 0.01 to 0.07 ppm prior to exposure and up to 0.8 ppm after a week at work. Higher concentrations were evident in less well-trained crews. There were no departures from normal ranges in any of the clinical indices, even in the crew with relatively high exposures. In some cases there were small differences from the values found in the control groups, as distinguished from the normal ranges for the population at large.

Peoples *et* al. (1979) reported on a series of 34 incidents of agricultural exposures to MSMA and cacodylic acid. Twelve of these involved MSMA, but the similarity of the two compounds makes both pertinent to concerns about MSMA. Nine exposures were systemic, presumably by ingestion and resulted in vomiting and diarrhea caused by gastrointestinal irritation, which is characteristic of large intakes of this group of compounds. One individual was sufficiently intoxicated to experience temporary partial paralysis and respiratory distress. The remainder of the exposures were eye or skin contact, resulting in mild, transient irritation. Recovery was prompt in all cases, including the most severe systemic intoxication.

There is long term epidemiological data on oral exposure, notably that of Tseng (1977), showing a dose related incidence of non-carcinogenic skin lesions in Taiwan, as well as skin cancer.

There appears to be no question that the various systemic effects of arsenic are threshold related, and that threshold may be a function of ability to methylate inorganic arsenic. The studies cited earlier on methylation, arguing that MSMA is identical to detoxication products of arsenic in mammals, show that methylation capacity must be exceeded to elevate arsenic levels. Similar findings in humans (Valentine *et* al., 1979) indicate that daily oral intake must exceed 0.2 mg per day in humans (0.004 mg/kg/day for 50 kg person) before blood arsenic levels begin to rise.

General toxicology: experimental observations

It is useful to discuss experimental toxicity studies in terms of both the nature of adverse effects and the duration of exposure necessary to produce responses. The following sections discuss effects in terms of the length of time over which the chemical was administered. Terminology of time periods is almost arbitrary. The terms, "acute", "subacute", "subchronic" and "chronic" refer to periods from a single exposure to a life time intake, but the boundaries between periods are not specific. Durations of experiments are specified in the discussion of each study.

The studies discussed in this section are typical assays based on laboratory animal treatment and observation. Many similar tests have been conducted on wildlife species. While the latter work is definitely applicable in the general assessment of MSMA toxicity, as a matter of convention it is collected in a separate section on environmental toxicity. It should be noted that because of differences in metabolism, storage and excretion of arsenicals, the rat does not usually provide a good model for predicting human toxicity. Cullen and Reimer (1989) have summarized these peculiarities.

Effects observed after single doses and administration over periods up to a few weeks (acute and subacute toxicity)

As a generalization, organic arsenicals such as MSMA, cacodylic acid and DSMA are much less toxic than inorganic arsenic species such as the arsenic oxides, acids and arsine gas or the organic methyl arsines. Stevens *et* al. (1979) found median lethal doses (LD_{50}) of cacodylic acid and DSMA in rats and mice to be between 520 and 720 mg/kg, following intraperitoneal administration. An oral LD_{50} for MSMA administered to mice has been reported to be 1800 mg/kg, and 700 mg/kg for rats. MAA Task Force Three (1993) describes studies of various formulations which indicate oral LD_{50}S for rats of 760-920 mg/kg, based on active ingredient, and about 380 mg/kg based on elemental arsenic.

Some other species are suggested to be more sensitive, however. Dickinson *et al.* (1972) administered 10 mg MSNIA/kg/day to cattle for ten days, which resulted in death of four of the five animals in the experiment. The primary injury was in the kidneys, particularly in the renal tubules. The apparent high toxicity of MSMA in this study should be questioned, because Lakso and Peoples (1975) fed cattle the much more toxic sodium arsenate at 2.75 mg/kg/day and potassium arsenite at 1.57 mg/kg/day, although for only five days, without apparent ill effects. The rapid clearance of MSMA observed by Shaiatpanahi and Anderson (1984) in sheep and goats suggests that ruminants do not have an unusual retention of MSMA that might lead to greater sensitivity. The description of protocol in Dickinson (1972) is also confusing.

A determination of LD.50 for MSMA in snowshoe hares of 173 mg/kg has been attributed by other authors to Exon *et al.*, (1974), who were quoting unpublished work that cannot now be found for this review. Jaghabir *et al.* (1988) estimated a figure of 102 mg/kg for domestic rabbits. This report does not adequately describe the research protocol or the product used, however.

Dermal toxicity of the formulations is markedly lower that observed after oral intake.

Standard eye and skin irritancy tests described in the MAA Task Force Three (1993) document indicate minimal to mild irritation by the various formulations, with exception of one older formulation that was highly irritating. It was found that the effect was due to a dye used as a marker, which is no longer used.

In the case of other herbicides, surfactants have been found responsible for some of the topical irritation; whether this is the case with MSMA formulations is not known. In any case irritancy is limited and controllable by ordinary handling precautions.

For a general comparison of the acute toxicity of MSMA with inorganic arsenicals, the acute LD_{50} for arsenic acid administered intravenously is reported to be 6 mg/kg and the intraperitoneal LD_{50} for sodium arsenate is 14-18 mg/kg. On the basis of MSMA as such, the difference is 50 to 100 fold, and on the basis of arsenic content about 20 fold.

Lethality is no more than a crude index of toxicity, and it is not useful for judging the potential effects of chemicals in humans, unless the substance is exceedingly toxic. It is necessary in any case to seek evidence of effects that might appear long before an animal is seriously affected, particularly after extended periods of exposure.

One case of peripheral neuropathy (altered nerve function in the extremities) lasting several months has been reported (Hessl and Berman, 1982) in a farm worker who was sprayed repeatedly with MSMA while operating a tractor. Inorganic arsenic intoxication has been reported to cause peripheral neuropathy. Other such episodes with MSMA have not been reported.

Effects of administration over periods of several weeks (subchronic toxicity)

Long-term studies for pesticide registration employ several dose rates, the highest of which should produce some kind of adverse effect. The reason for this is to learn the maximum level that can be tolerated without significant effect. For example, a well designed cancer study that produces no increase in tumor incidence at a dose rate that causes significant weight loss or other injury is usually considered to represent reasonable assurance that the substance is not carcinogenic in that species. If a higher dose could have been tolerated, it is possible that an increase in tumor formation might have occurred, and current regulatory practices would require additional study at higher doses. If tumor incidence is increased only in an organ that is also seriously affected by non-tumor pathological change, the cancer-causing potential of the chemical is questionable.

Before long-term experiments can be done it is necessary to conduct range-finding tests to learn the maximum tolerated dose (MTD) in the species to be studied. While these studies are not directly used in evaluating registration, they are part of the record and do have some value in the broader effort to evaluate risk in the workplace or the environment. Several such tests are described in MAA Task Force Three (1993).

A 14 week experiment with mice, using 12 animals of each sex, on a diet containing 0, 10, 100, 500 and 1250 parts MMAA per million parts diet (ppm) produced no significant toxicologic response, and did not reach high enough levels to indicate an MTD. The dose rates resulting from consumption of these feeds were 0, 2.4,24, 120 and 300 mg/kg/day. A follow-up study for 24 days, at dietary concentrations of 3000, 6000 and 9000 ppm caused no mortality, but there was weight loss at all dose rates, and evidence of irritation of the upper intestine at the highest rate. A concentration of 4000 ppm (1200 mg/kg/day) was judged to provide an MTD.

The administration of MNIAA to animals is identical to administration of MSNIA. These different forms of the same substance are in equilibrium depending on the pH of the solution. This relationship was described in more detail in the section on chemistry.

Rats were found to be more sensitive. Thirteen weeks on diets at dose rates of 0, 0.8, 8, 40 and 100 mg/kg/day caused no mortality, but there was considerable injury to the intestine, resulting in failure to absorb fluid, with dehydration at the two highest dose rates. The two higher dose rates also caused changes in the thyroid which suggested that an increased requirement for thyroid hormone had occurred. The no effect level was considered to be 8 mg/kg/day, and the report suggested 100 mg/kg/day as an MTD. The reasoning behind this MTD may be questionable, because the effects seen at that level were apparently greater than the marginal responses considered to be tolerable (MAA Task Force Three, 1993).

Exon *et al.* (1974) examined the relation between tissue pathology and concurrent total arsenic levels after feeding one series of rabbits MSMA for 2,4, 7,12, and 17 weeks, and feeding another set for 12 weeks followed by an additional 5 or 13 weeks on a control diet. The diet contained 50 ppm MSMA and the initial daily dose of MSMA in the diet was estimated to be 1.5 mg/kg as arsenic, or 2.92 mg MSMA/kg. At ten weeks the ration was reduced to prevent obesity, which reduced the daily dose to half the initial level. It is not clear why the initial dose rate was not maintained by adjusting the dietary concentration.

Two animals of each sex were examined at each time period. Females from the first group were bred at the twelfth week and offspring sampled at 1 and 20 days of age. Liver and kidney concentrations of total arsenic were at a constant level of roughly 0.5 ppm from 2 to 12 weeks, then rose sharply at the week 17 sampling to 0.78 ppm in liver and 1.4 ppm in kidney. Unfortunately arsenic analyses were not carried out on later samples, and it is not known whether the increase noted at 17 weeks was sustained or was an artifact. Arsenic was not detectable in bone until 17 weeks. Tissues of offspring did not contain detectable residues of arsenic.

Liver inflammation was evident after 12 weeks, which reversed when the intake rate was reduced, even though tissue levels remained high. In animals treated for 12 weeks, then maintained for 5 weeks on a control diet, liver, hair and urine arsenic levels were not different from control values. The authors suggested that liver inflammation was related to the rate of intake, not residue levels in the liver.

Another study of organ pathology in rabbits by Jaghabir *et al.* (1989) provided somewhat similar information. Animals were maintained over 40 days on 5, 10 and 20 mg MSMA/kg, administered daily by stomach tube. The digestive tract, liver and kidney were severely inflamed at all doses. The severity of lesions, based on a subjective scale of observation, did not appear dose related. The authors comment that the most severe lesions were in the mid-dose group. This information is somewhat difficult to interpret, but may relate to the suggestion of Exon *et al.* (1974), that the rate of intake is more important than tissue levels. Jaghabir *et al.* (1989) remark that the lesions in liver and kidney appeared reversible, although no animals were maintained after exposure for later examination. As remarked earlier, information on purity of product and methodology in their report is not adequate.

Prukop and Savage (1986) treated mice three times weekly for 10 weeks with a commercial formulation of MSMA diluted to provide doses of 11.9 and 119 mg/kg/dose, which were intended to be 0.01 and 0.1 LD_{50} respectively. Erythrocyte and leucocyte counts were unaffected at either dose, as were serum albuman and globulin fractions.

Judd (1979) maintained whitefooted mice that had been trapped in the wild or were offspring of trapped animals on drinking water containing 1000, 3000, 5000 or 10,000 ppm MSMA formulation. This experiment was described as a study of acute toxicity, but it appears that MSMA intake was maintained for 21 days. Water intake by the animals drinking water at 1000 ppm was normal, but animals given higher concentrations lowered their consumption sharply, which compromised findings with respect to effects of the arsenical. There were no appreciable differences in hemoglobin concentration, packed red blood cell volume, or blood glucose levels between animals exposed to 1000 ppm MSMA formulation and those given tapwater. (There is confusion in this paper about the concentration of MSMA, because in the text it is stated that the concentration at 1000 ppm herbicide is 477 ppm MSMA, and in Table 1, the MSMA concentration is stated to be 0.719 mg/ml, which is 719 ppm. The difference is close to that which might occur if the specific gravity of 1.55 had been somehow factored in.) Daily water consumption is noted in the paper. The daily dose of MSMA would have been 124 mg/kg/day if the concentration was 719 ppm and 82 mg/kg/day if the concentration was 477 ppm. In either case, these are high sustained doses, with no adverse response in the systems measured.

Continuation of intake at 1000 ppm to a total of 60 days caused no change in body weight, but appeared to slightly decrease hemoglobin concentration, packed cell volume and blood glucose from control levels.

Judd points out that the total MSMA consumed was highest at the lowest concentration, because of the drastic decrease in water consumption at the higher levels. The effects observed at the high dose rates is not surprising when water consumption is calculated as a fraction of that consumed by control animals: 1000 ppm, 107% of control; 3000 ppm, 27.2%; 5000 ppm, 5.8%; 10,000 ppm, 2.75%. It is likely that the water was unpalatable and that the animals suffered from severe dehydration. Data from the animals confronted with concentrations above 1000 ppm has no value for judging systemic toxicity of MSMA as such; it is surprising that the experiment was even continued.

Effects observed after long term administration (chronic toxicity)

Dogs are frequently used as representatives of larger, non-rodent species, and presumably provide a further link in predicting potential harm to humans. Beagles were given MMAA by capsule at daily doses of 0, 2, 8 and 35 mg/kg/day over a 52 week period (MAA Task Force Three, 1993). The two higher dose rates caused gastrointestinal irritation, beginning at about week 13, with frequent vomiting and diarrhea. By the end of the study period, at the highest dose the blood chemistry indicated decreased liver function. These effects, as well as other pathology at termination, were suggested in the report to be secondary to poor physical condition rather than specific organ damage. There was no detectable effect at a dose of 2 mg/kg/day over the 52 weeks of the study.

Studies to determine whether a chemical can cause cancer require treatment with the chemical over the lifetime of test animals. Modern cancer studies take advantage of this opportunity to search for other more subtle general effects that might appear over long terms of exposure. It is generally expected that non cancer effects will have appeared by six weeks of administration of a chemical if they are going to appear at all, but exceptions occasionally appear, and it is essential that observations be made over the entire period of treatment.

A two year study of mice fed diets containing 0, 10, 50, 200, or 400 ppm MMAA (approximately 0, 2.4, 12, 48 or 96 mg MSMA/kg/day) did not detect any treatment related mortality. There were 52 animals of each sex at each dose level (MAA Task Force Three, 1993). Weight gain was decreased at 400 ppm, and many of these animals exhibited loose, mucoid stools. Water consumption increased in the two highest dosage groups of both sexes, and females at these levels consumed more food than controls.

Water consumption changes in this case contrast with the drastic decrease in water consumption reported by Judd (1979), who administered the chemical in the water. In the mice of the cancer study discussed here, MMAA was introduced in the food at considerably lower doses, and the effect on the bowel corresponds to the more aggressive irritation seen in many shorter term studies. In fact, in this study, the large intestine was considered to be the primary target organ.

Blood characteristics (cell numbers and integrity, and blood chemistry) were not changed by any treatment level. Organ weights did not change, except a decrease in spleen weight relative to body weight at the two highest doses. This has questionable significance because there was no evidence of pathological change in the spleen. It is likely that the apparent difference between spleen and other organs is not real but is an anomaly produced in the overlap of statistical ranges.

Not surprisingly, gross and cellular pathology related to treatment was found in the large intestine. Particularly, there was cellular change related to irritation and a more rapid rate of cell loss and replacement than is normal. There was an apparent increase in changes in the kidney that also occur normally with aging in lifetime cancer studies.

A similar study of rats (MAA Task Force Three, 1993) involved groups of 60 animals of each sex, at dietary concentrations of 0, 50, 400, and 1300 ppm, about 4, 32 and 104 mg/kg/day. The higher levels resulted in increased mortality after about 40 weeks, and the maximum concentration was reduced to 1000 ppm at 53 weeks. At 60 weeks it was further reduced in males to 800 ppm. At the two year termination of the work, mortality was 160% of control for high dose males and 200% of control for high dose females. There was a significant sex difference; 18% of control females failed to survive the study period compared to 42% of males.

As with mice the predominant lesions were in the large intestine, causing diarrhea. Water and food intake increased but weight gain was lowered. The large intestines of many animals at the intermediate and high dose rate were ulcerated and perforated, with secondary effects on adjacent organs. These findings indicate that the study employed doses much higher than the maximum tolerated dose.

Blood chemistry reflected the high dose rates. At the highest dose, total plasma protein, albumin and cholesterol were reduced, beginning at 3 months in females and 12 months in males. Blood glucose was also reduced. These and other changes suggested that

some impairment of liver function occurred, although the findings suggested that the integrity of liver cells appeared to remain intact. The observed changes appear consistent with effects seen in other studies. None of the effects appeared in the low dose groups.

Gross and microscopic pathology was not remarkable, except for increased thickness of thyroid follicular epithelium in the high and middle dose groups. This finding has also been seen in other experiments, and is the kind of change that can result from stimulation of cells that produce thyroid hormone. Whether the effect is due to direct impact on the thyroid or high demands from other parts of the body cannot be determined with present information. The latter alternative seems most likely.

Reproductive effects

Prukop and Savage (1986) treated mice with 11.9 and 119 mg MSMA/kg three times weekly for ten weeks during reproductive activity. Groups of one male and five females were caged together, with males removed at 19 days and females removed when found to be pregnant. At the high dose, all females in the group failed to produce litters, and one died. A following experiment in which only males were treated, at the higher dose rate, resulted in a failure rate of almost 50%. It was stated that in the latter experiment, litters that were produced were normal in size, weight and frequency of still birth. There was no information as to the mechanisms involved, but given that the effects appeared to fall on both sexes, it is likely that the effect may be non-specific, related to general toxicity rather than a specific reproductive influence.

Cacodylic acid, which is closely related to MSMA, was found by Kavlock *et al.* (1985) to produce fetal toxicity and birth defects, but only at maternally toxic doses. (This was a study of several chemicals, and in each case the doses expected to cause 10% and 40% lethality were used. The estimates were derived from the dose response curve for lethality.) An earlier study from the same group (Rogers *et al.,* 1981) used a more detailed dose response schedule in rats and mice. Doses of cacodylic acid in rats were 0, 7.5, 15, 30, 40, 50, or 60 mg/kg/day, and 0, 200, 400, or 600 mg/kg/day in mice. The dosage pattern reflects the greater sensitivity of the rat, and is probably due to differences in the metabolic disposition of the organic arsenicals.

In both studies treatment was through days 7-16 of gestation, which is the period of organ differentiation and development. All doses in the mouse produced obvious maternal toxicity, and the only teratogenic (birth defect) response was cleft palate at the two highest doses. Fetal death was elevated only at the highest dose level, and at 400 mg/kg/day there was a significant increase in malformations and developmental delays. At 200 mg cacodylic acid/kg/day, the only effect was a lower maternal weight gain. In rats there was little effect at 30 mg/kg other than an alteration in the regular pattern of the ridges of the palate. The significance of this response is not known. At 40 mg/kg/day there were a variety of defects, as well as obvious maternal toxicity.

A screen of a large number of chemicals, including cacodylic acid but not MSMA, evaluated postnatal effects in mice (Gray and Kavlock, 1984). Only a single dose rate was used; in the case of cacodylic acid it was 600 mg/kg/day, on days 8 through 12, which is within the period of primary organ formation in the mouse. The effects included some decrease in pregnancy rates and a slight decrease in litter size. Some resorption of whole litters occurred. Organ and whole body weights of offspring were decreased through 60 days of age. Postnatal death was 24% greater than the assigned control group, but survival at 30 and 60 days was higher than that of the controls. Harrison *et al.* (1979), found that high doses of DSMA and sodium cacodylate increased fetal death and resorption, and caused skeletal deformities. No dose response data was obtained. Hood *et al.* (1982) treated hamsters with 1000 mg cacodylic acid/kg at various days of gestation. It is not surprising that such a dose devastated the offspring. Most of the few that survived were malformed. Unfortunately, the experiment provided no useful information about dose response or the no-effect dose that should be expected for these kinds of effects.

A teratogenicity (birth defects) study was conducted on female New Zealand rabbits at oral doses of 0, 1, 3, 7, and 12 mg/kg/day, through days 7-19 of gestation (M.A.A. Task Force Three, 1993). In the rabbit, this is the period when organs and limbs are forming, and is the period during which birth defects may be induced by sufficient doses of chemicals or other agents. Earlier treatment may result in loss of the embryo, but is not likely to cause birth defects. Intoxication after this period may result in delayed development or other toxic effects similar to those that may affect the mother, but is also not likely to cause teratogenicity.

The animals were killed on day 29 for examination of the reproductive tract and fetuses. Two abortions occurred in the highest dose group, which also experienced significant body weight loss. The report states that preimplantation losses increased in groups dosed at 1, 7 and 12 mg/kg/day, which is difficult to understand because implantation occurred before treatment began. The entire litter of one animal at 7 mg/kg/day died, but other than that individual, post implantation (after the embryo attaches to the wall of the uterus and begins to develop) loss was not in excess of controls, and in the two lowest dose groups losses were less than control rates.

Some fetal anomalies were seen in both treated and control animals, but they did not appear to reflect an effect of treatment on fetuses at doses that were maternally tolerated. The report indicated a no effect level for maternal and fetal toxicity of 3 mg/kg/day through the period of fetal development.

MMAA was given to pregnant rats on days 6-15 of gestation at oral doses of 0, 10, 100, or 500 mg/kg/day (MAA Task Force Three, 1993). Each group included 25 animals, which were examined on day 20 of gestation. Food consumption and body weights were decreased in the two high dose groups, and at the high dose there was evidence of intestinal effects. There was no apparent maternal effect at 10 mg/kg/day. Fetal body weight was lowered in the high dose group but there was no evidence of fetal toxicity at 10 or 100 mg/kg/day. There was no evidence of a teratogenic effect in any group.

A three generation reproduction study of rats also showed no significant effect (MAA Task Force Three, 1993). This assay is intended to reflect any influence that could disrupt reproductive performance, and includes both males and females. If an effect occurs, the mechanism may not be identified, but because of its sensitivity, when no effect is seen there can be confidence that the chemical is not likely to affect any reproductive or related function, such as the nervous system.

In the first generation (F_0), 40 animals of each sex were placed on diets containing 0, 25, 50, 100, and 200 ppm (approximately 2, 4, 8, and 16 mg/ kg body weight/day. Although not stated in the report, such studies usually include an extended feeding period on test diets prior to mating, and the diet is continued through weaning of the offspring. In this case, two litters were obtained from each pair. The second litters from F_0 are designated F_{lb}, and 20 animals of each sex from F_{1b} were selected randomly and fed the same diets from weaning through reproduction and weaning of their offspring, which are the F_2 generation. F_2 males and females were taken through the same cycle. There were no significant effects observed on any reproductive index, but the lack of any observable toxicity in either males or females indicates that the maximum tolerated dose was not achieved.

The data on MSMA and related compounds that are presently available suggest that reproductive and fetal developmental effects of methyl arsenicals only occur as a result of severe general maternal toxicity at very high doses, rather than as a specific reproductive response.

Carcinogenicity and genetic effects

There are few published investigation that provide useful information about genetic or carcinogenic effects of MSMA. The study of genetic toxicity (mutations and other effects on chromosomes and DNA) is important for two reasons. The potential of a chemical to induce genetic injury or mutation is in itself of obvious public health importance, and chemicals that are strong mutagens are much more likely to be able to cause cancer unless demonstrated not to do so.

Genetic toxicity (mutations and DNA damage)

There are numerous in vitro methods for determining whether a chemical has the capability to cause mutation or genetic damage. Perhaps the most widely known is the Ames assay, in which mutant bacterial strains may mutate back to their original nature when exposed to a chemical mutagen. It is possible to use cultured animal cells, yeasts, insects and whole animals to do short term, relatively inexpensive tests that indicate genetic effects. They do not necessarily indicate that the same effects will occur in higher organisms, but the tests will show whether concern about these effects is warranted.

Most genetically active chemicals are inactive as they enter the body and may be transformed to the active form by the liver and other organs. This process is part of the normal metabolism that detoxifies chemicals for excretion. When detoxifying enzymes are overloaded, intermediate products that normally would be converted to innocuous end products may escape to react where they should not. In mutation studies, the chemicals are treated with cell preparations from liver, which will "activate" them in a manner somewhat similar to the sequence occurring in intact animals.

In primary cultures of rat liver cells, MMAA at concentrations up to one mg/litre did not cause unscheduled DNA synthesis (UDS) (MAA Task Force Three, 1993). UDS is not indicative of mutation as such but is an index of damaged DNA which must be replaced or repaired. In the Ames Salmonella reverse mutation assay, using several tester strains, MMAA did not cause base pair or frameshift mutations, with or without metabolic activation, at levels up to 10 mg per culture plate (MAA Task Force Three, 1993).

The L5178Y mouse lymphoma cell line is a widely used standard mutagenicity testing system. MMAA at concentrations up to 6 mg/litre produced no increase in mutation frequency. The concentrations in the metabolic activation tests were lower, but showed an equivocal positive outcome. The results were slightly greater than in concurrent control preparations, but within the range observed for solvent controls in other studies. Under the circumstances the test may conservatively be considered to indicate a weak mutagenic

response (MAA Task Force Three, 1993). It is surprising that this finding has not been challenged. The use of a metabolic activation system is standard in mutagenicity assays, but MSMA is not acted upon by the enzymes that are induced in such a system. One must wonder why even a questionable response would be seen; it may be that factors unrelated to the test chemical were involved.

The tests discussed above are intended to assess interaction between a chemical and specific sites on the DNA molecule. Other assays are designed to learn whether a chemical can interfere with the overall structure of chromosomes. Cultures of Chinese hamster ovary cells exposed to MMAA did not indicate a tendency to disrupt chromosomes (MAA Task Force Three, 1993). The concentrations used were not stated, but it appears that the maximum doses were at the limit of tolerance by the cells. If the concentration is high enough to cause significant non-genetic cell damage, the genetic effects have little meaning.

Some assays of DMAA (cacodylic acid) have been done and are mentioned here because DMAA is a metabolic product of MSMA. DMAA was negative in the Ames assays, but showed a weak effect in the mouse lymphoma cell test, and was positive in yeast (MAA Task Force Three, 1993).

There has been other research into interactions between organic arsenicals and genetic material. A possible mechanism by which a methylated arsenical might cause genetic injury has been proposed by Yamanaka *et al.* (1989). DMAA (cacodylic acid) at a dose of 1500 mg/kg body weight induced breaks in DNA strands in cells of various organs in mice. Yamanaka *et al.* speculate that some DMAA may be further changed to dimethyl arsine (DMA), which is gaseous and would eventually be liberated through the lung. They further inquired into the idea by exposing cell nuclei from lung tissue to DMA in *vitro.* The biochemical evidence suggested to them that in intact animals DMA is responsible for DNA strand breaks through production of active oxygen species in the cells. The effect of DMA was at maximum 12 hours after administration and almost fully repaired at 24 hours. Effects in other organs were limited.

In further work, the same group (Nakano *et al.* 1992) found that in pulmonary endothelial cells (cells lining the capillaries that supply blood to the alveoli of the lung) chromatin protein associated with DNA tended to migrate to the membrane surrounding the cell nucleus. The change was seen only with electron microscopy and was not observed in the endothelium of the liver. The authors speculate about the apparent tissue specificity of these observations, and the apparent lung carcinogenicity of inorganic arsenic in humans.

Whether these findings have a relation to possible human cancer initiation is questionable. It must be remembered that the dose was massive compared to any possible dose in the field. Such a high dose is also likely to behave quite differently from the amounts of methylated arsenical arising from relatively slow conversion of the small amounts of inorganic arsenic to be found in the diet. The concentrations employed in the cellular experiments was also very high relative to that which might be expected from field exposure. The rapid recovery suggests that repair processes are effective, minimizing the possibility that nuclear damage would be locked into genetic information.

Furthermore, oxidizing reactions of the kind that are referred to above occur at a high rate in normal cells, and the role of the additional burden of this study is not easily measured. It is doubtful that differences in conversion to DMA are responsible for a difference in carcinogenicity between humans and laboratory animals, because humans, mice and hamsters excrete DMA at about the same rate and to about the same extent (Marafante *et al.,* 1987).

Carcinogenicity

The arsenicals represent another paradox at this point. Epidemiological evidence in human populations has suggested very strongly that chronic exposure to excessive amounts of inorganic arsenic can cause skin and lung cancer.

Thus far, attempts to induce cancer of any kind by administration of inorganic arsenic to experimental animals have not been successful. Arsenic is the only substance for which there is reasonable evidence of carcinogenicity in humans that has not produced the disease in animals. Inorganic arsenic is not the subject of this analysis, however, because extensive research on the metabolic fate of arsenicals shows that intake of MSMA will not result in exposure to inorganic arsenic.

The nature of MSMA metabolism together with its very limited genetic effect indicate that it should not cause cancer. That reasoning is supported by direct carcinogenicity assays that were described in the section above on chronic toxicity. The subjects of those studies showed no evidence of a carcinogenic response (MAA Task Force Three, 1993). It is essentially impossible to *prove* that a chemical cannot cause cancer, because of the large natural background. However, there is good direct and indirect evidence presently available that indicates that it is highly unlikely that MSMA is carcinogenic, even at high doses.

Environmental toxicity

Terrestrial species

Other than the studies described in this report which used test animals to predict impacts on humans, there are few reports in the literature of studies conducted to assess the effects of MSMA use on wild animals. Observations by operational foresters and biologists have not identified any apparent toxicological concerns to wildlife in British Columbia. However, no formal assessments have been attempted.

Concern has been expressed by wildlife management agencies that browsing animals, such as deer, or insectivorous birds, such as woodpeckers, could be affected by MSMA use. An investigation of the possible impact of MSMA use on selected wildlife species should be considered.

An example of a human toxicology study that can be used to infer the toxicity of MSMA to wildlife is the field mice study conducted by Judd (1979), discussed in the section on general toxicity. The report by Mathews and Porter (1989) on a presumed accidental poisoning of one deer by MSMA was discussed in the section on environmental fate, as a question about the consequences of distribution and availability after inappropriate handling in forestry. While the authors suggested that the animal acquired the chemical from frills on treated trees, it is much more likely that the source was a spill that was not reported or detected.

Classical laboratory toxicity studies usually do not include birds, because such data are not clearly applicable to questions of human risk. For wildlife risk prediction, the most common representative bird species are the northern bobwhite and the mallard, both reared for testing programs, not captured in the wild.

The acute LD_{50} for MSMA administered to 17 week old bobwhite was found to be 834 mg/kg; no mortality occurred at a single dose of 292 mg/kg. When administered in the diet to 10 day old bobwhite at concentrations ranging from 562 up to 5620 ppm the LC_{50} (median lethal concentration) was calculated to be 3269 ppm. (The duration of the feeding period was not stated but presumably the test was of standard eight day duration.) A conversion ratio of feed concentration to actual dosage in mg/kg is not available, but on the basis of comparison with data from chicks, the LD_{50} was estimated to be about 650 mg/kg/day. Nine day old mallards were tested on the same dosage schedule and suffered no mortality or other effects at any concentration. The highest concentration, 5620 ppm, was estimated to provide a dose of 1100 mg/kg/day (MAA Task Force Three, 1993).

Populations of amphibians may occur in treated forests. Effects on adults are unlikely; the 96 hour LC_{50} for Xenopus adults is about 1100 ppm. Study of embryonic effects indicates a dose response for teratogenic and fetotoxic responses of embryos to be about 20 ppm. This figure represents aquatic exposure, in which the chemical is continually available in the medium in which the organisms reside, and where potential for uptake is vastly greater than in a dry medium.

Apparently the only terrestrial insect to be evaluated is the honey bee. When applied directly to the thorax, the contact LD_{50} was found to be 68 micrograms per bee, and the no observed effect level was considered to be 36 micrograms per bee (MAA Task Force Three, 1993). In evaluating the effect of broadcast spraying of various herbicides, Moffett *et al.* (1972) placed bees in cages and sprayed MSMA in water, with 0.1% X 77 surfactant, at a rate of 4 lb ai per acre, from a height of 18 inches. They estimated that about 25% of the application was deposited on bees or the floors of cages. Mortality was 10% at the end of day one, 40% after two days and about 70% in three days. DSMA was only slightly less toxic. The same group (Morton *et al.*, 1972) fed 60% sucrose solutions containing 10, 100, and 1000 ppm MSMA, MMAA or DSMA. The lowest concentration sharply reduced bee half-life and the higher levels devastated the test groups.

While these findings suggest a possible impact from broadcast spraying, direct applications of MSMA to tree stems for bark beetle control cannot result in exposures that could affect bee populations. The presumed toxicity of MSMA for bark beetles results from high exposures induced by the trap tree approach, which does not draw other species of insect to the insecticide. There appears to be no other work directed specifically at possible impacts of MSMA on invertebrates in soil or on the forest floor. The question with respect to uses of MSMA for bark beetle control may be addressed in two ways. The simplest answer arises from the known distribution of the applications and movement on the forest floor. A small fraction of trees in a stand are treated, which means that MSMA is present only in infrequent "spots" in the forest floor. If the invertebrate and microbial populations are considered as populations, only a small fraction of the area population is subject to exposure, whether or not the exposure is significant to individual organisms. The studies of Norris et al. (1983) show that movement away from the stem into soil is not great, usually not distinguishable from pretreatment levels.

Accumulations in litter under ponderosa pine canopies were quite high, probably from needle fall, but movement downward to soil appeared limited.

It is curious that western larch treatment resulted in only detectable but not large deposition in litter, given the annual loss of all foliage.

The behaviour of chemicals in soil also suggests that risk to soil organisms at any biological level from MSMA application should be minimal. Few pesticides other than fumigants are useful in controlling invertebrate soil pests in agriculture, because binding to soil particles effectively isolates the chemical from absorption by the organisms. The solution is injection of substances with high vapour pressure that do not bind easily to soil, using techniques that permit a sufficient residence time to kill nematodes and other pests before the pesticide dissipates or breaks down. Soil binding is particularly effective in the case of arsenicals and is responsible for the limited transport away from sites of application.

Adverse impact on bacterial and fungal populations are highly unlikely. Cullen and Reimer (1989) review the large literature on the reactions of inorganic arsenic by such organisms, and it is clear that they are able to carry out reactions in the presence of concentrations ranging up to the hundreds of parts per million of inorganic arsenic, as well as tolerating the concentrations of reaction products, particularly methyl arsines.

Bollen et at (1974,1977) evaluated microbial growth rates and carbon dioxide production from cultures of organisms from the forest floor and found no effects of MSMA at concentrations as high as 1000 mg As/kg (ppm). Ammonia formation increased and nitrite and nitrate formation decreased with increased MSMA concentration, but the changes were modest through concentrations up to 1000 mg/kg.

Aquatic species

There have been a variety of assays of toxicity of MSMA to fish and other aquatic animals. Because of the variety of conditions into which a pesticide might be introduced, when assessing potential hazards to aquatic species, it is necessary to assume the maximum sensitivity indicated in toxicity studies, regardless of details of water temperature, hardness and pH, all of which influence aquatic toxicity. If such a worst case suggests a potential problem, details of environmental conditions are then important in both risk assessment and risk management. If a substance is of sufficiently limited toxicity under the most sensitive circumstances, no further analysis is needed. In terms of impact on aquatic species, MSMA appears to have little potential unless spilled directly into a water course. The highly constrained use of MSMA for bark beetle control is not likely to result in effects on aquatic organisms.

Effects stated in terms of concentrations in water are difficult to visualize in terms of events that might happen in the forest environment. First, recall the work of Norris (1983), in which no increase in arsenic concentration could be detected (detection limit 0.01 ppm) in a stream running through an MSMA thinning operation conducted on both sides of the stream. Then consider that the theoretical concentration that might result from a broadcast spray of one kg/ha directly over water 10 cm deep, is 0.1 ppm. For 4 kg/ha the concentration would be 0.4 ppm, and if the water is 30 cm 0 foot) deep, the concentration would be 0.133 ppm. This assumes no degradation or other removal. This is a useful comparison when reading literature that seeks effects at 10, 100 or 1000 times as concentrated.

Mayer and Ellersiek (1986) summarized several thousand static toxicity tests on 410 chemicals done by US Fish and Wildlife Service laboratories. The lowest LC_{50} found for fish exposed to MSMA was 13 ppm for small bluegill after 24 hour exposure to MSMA as diluted 34.8% liquid concentrate, and 12 ppm after 48 hours. Some other values for fish exposed to the concentrate were in excess of 100 ppm. It is possible that the high toxicity of the formulation is due to the surfactant, which is present in the formulation at a concentration of 37.8%. Surfactants are considerably more toxic to fish than most active herbicides. For example, Wan *et al.* (1987) and Folmar *et al.* (1979) showed that the surfactant used in formulations of glyphosate exhibited a similar order of toxicity to fish as the 13 ppm value noted above. Whether the surfactants are similar is not important because effects on gills will be similar.

Anderson *et al.* (1975) found black bass and channel catfish to be highly tolerant to MSMA, apparently without surfactant. The 48 hour LC_{50} (called median lethal threshold by Anderson *et al.)* for fingerling bass was estimated at 1660 ppm and the 96 hour figure was 900 ppm. For channel catfish the values were 4700 and 3050 ppm.

MAA Task Force Three (1993) quotes a thesis by Skelley (1986) reporting studies of exposure of channel catfish and fathead minnows to technical MSMA and the formulation Daconate. For channel catfish the 96 hour LC_{50} for Daconate containing 35% MSMA was 385 ppm, for Daconate containing 48% MSMA it was 675 ppm, for 51 % technical MSMA 2460 ppm and for Bueno 6 with 48% MSMA, 2460 ppm. A similar pattern was evident with fathead minnows. Corresponding values were 448, 550, 1210 and 1290 ppm. The

less toxic preparations lack surfactants often used in herbicide formulations, which, like the very similar household detergents, are known to be relatively toxic to fish.

Most aquatic toxicity studies are based on concentrations of the test material in water. Cockell and Hilton (1988) included various arsenicals in the diet of juvenile rainbow trout over an eight week trial. The only compound in that work of interest here was DMAA, which was added to the diet at concentrations expressed arsenic, of 200, 400, 800, and 1600 ppm. The no effect level for DMAA approached the highest concentration, which would be about 3000 ppm MSMA. Weight gain at the highest dose rate was slightly impaired, corresponding to a slightly increased ratio of feed intake to weight gain. Carcass total arsenic accumulation at the end of the exposure was almost linearly related to DMAA concentration in water.

In the summary of Fish and Wildlife Service data, Mayer and Ellersiek (1986) report an LC_{50} for Gammarus, a crustacean, in excess of 100 ppm. Anderson *et al.* (1975) reported 48 and 96 hour LC_{50}s of 5100 and 1100 ppm for crayfish. Naqvi *et al.* (1985) collected several species of microcrustaceans for testing against MSMA. The LC_{50}s found for organisms of the genera Cladocera, Calanoida, Cyclopoida, and Ostracoda were 40, 40, 100, and 100 ppm. Concentrations that were 99% lethal for the same groups were 150, 130, 470, and 780 ppm. This kind of information is useful in cases where a risk/benefit decision must be made, which is not a factor with MSMA, but it might occur with use of an insecticide where the need for treatment might be balanced against impact on biota.

Naqvi *et al.* (1987) also studied the effect of MSMA on crayfish, finding 96 hour LC_{50}s of 100 ppm for juveniles and 1000 ppm for adults. The same laboratory (Naqvi and Flagge, 1990) then studied the effect of sustained concentrations of MSMA on crayfish reproduction. Males and females were exposed to 100 ppm MSMA for 12 weeks, then mated. The females were exposed for an additional 12 weeks. 20 hatchlings; from treated females were then exposed to 15 ppm MSMA for one week. The treatment of adults resulted in a sharp reduction of hatching success. Unfortunately, no dose response information was obtained.

There appears to be only one investigation of effects of MSMA or related compounds on amphibians. Shultz and Dumont (1984) found the 96 hour LC_{50} for Xenopus adults to be about 1100 ppm. They exposed toad embryos to concentrations of 0, 25, 50, 75 and 100 mg MSMA/litre (ppm) for 96 hours, observing mortality, general fetal toxicity and incidence of developmental defects. The dose response for incidence of abnormal embryos suggests a no-effect level of about 18 ppm, and for survival the NOEL appears to be in a similar range.

In summary, the available data indicate that concentrations of MSMA that might arise as a result of use in bark beetle control, or for that matter, other forestry uses, are far below levels that might elicit even the most sensitive responses in aquatic species. Even if the relatively low concentrations stated in Mayer and Ellersiek (1986) are considered as guidance, it is clear that impact of MSMA in these uses will be negligible. Similarly, the likelihood that terrestrial species will be affected by MSMA as applied is very small.

Nevertheless, as with any substance, mishandling and spillage have the potential for harm in the immediate area and require careful attention to proper procedures and work discipline.

Exposure to MSMA

The toxicology of a chemical has no meaning in evaluation of risks to workers or the public (or lower species) unless there is information about potential exposure to the chemical. It is necessary to know how much of the material has come into contact with an individual in such a way that it can be absorbed into the body, whether through the skin, the digestive tract or the lungs. Almost all chemical exposure is by way of the skin, but an applicator with poor personal habits could ingest small amounts when eating or smoking when the hands are contaminated.

There are only two significant potential sources of exposure to MSMA in the context of its use in bark beetle control. The most important is obviously the process of handling and applying the insecticide, in which the skin is the most important route of entry. The other possible source is derived from the treated trees. Logging and milling could result in skin exposure or inhiliation of contaminated wood dust. Burning of treated trees as slash, waste or fuel might result in inhalation of inorganic species formed in combustion. Inhalation is not a significant route of exposure to MSMA as used in insect control.

The most accurate measurement of exposure and subsequent absorption is the quantitative measurement of excretion of the various forms of arsenic in the urine. There is a small background of arsenic excretion in both inorganic and organic forms by virtually everyone which decreases the accuracy of low level measurements.

Measurement of applicator exposure

There have been direct determinations of exposure of workers applying organic arsenicals in forestry thinning operations. In such use the application method is the same as is used for insect control, except that far more trees are treated in a given period by an applicator. The findings are directly applicable to the concerns of this report, even though they probably over-estimated exposure in insect control because of the large number of trees treated. A cooperative study sponsored by the US Forest Service, Bureau of Land Management, Bureau of Sport Fisheries and Wildlife, the states of Oregon and Washington, and chemical producers was reported by Norris (1974a). One segment by Tarrant and Allard (1972) was also published in the open literature. They monitored urinary total three six-man crews during and after application of MSMA and cacodylic acid, by injection hatchet and "hack and squirt" methods. Clean garments were provided each day, including cotton gloves (now recognized as inappropriate because they increase absorption from the hands).

Urine samples were collected Monday morning and Friday evening for nine weeks. Total arsenic in Monday samples ranged from 0.03 to 0.1 ppm (control 0.04) and Friday samples contained 0.26 to 0.5 ppm arsenic. There was no clear exposure advantage with either application method. Over the nine-week study period there did not appear to be an appreciable increase in successive urine concentrations of arsenic on either Monday or Friday. In other words the exposures did not lead to increasing arsenic levels in the workers.

In related work that provides the best information on which to base daily applicator exposure estimates, Wagner and Weswig (1974) collected 24-hour urine samples from Thursday afternoon to Friday afternoon weekly during the application season. The average amount of DMAA applied was 817 grams per man per week. Prior to exposure, blood arsenic levels were 0.03 to 0.08 ppm, which rose to 0.03-0.27 ppm on the second week and 0.2-0.27 in week three. Concentrations then declined through the next eight weeks, in some cases to levels below those prior to initial exposure. Unexposed controls also had lower levels at the end of the season, suggesting an influence of weather or general physical conditioning. Total urinary arsenic was variable, ranging from 104 to 256 micrograms per 24 hours in week four, to 8-212 micrograms per 24 hours in week 11. Workers noted the garlic-like odor of arsine in the treated area for several days, which probably arose from soil microbial activity, but would not make a measurable contribution to exposure.

For purposes of risk prediction, the highest daily figure will be considered as a representative exposure. Assuming a 50 kg worker, the daily dose while working is estimated to be 0.0051 mg/kg.

Norris (1985) reviewed the various studies of worker exposure to arsenical herbicides and associated high urinary arsenic levels with poorly trained, careless applicators. He also noted that simple protection and proper work practices brought exposures down to very low levels.

Concentration of arsenic in MSMA treated trees

The potential health impact of handling or burning wood that has been treated with MSMA can only be estimated if the concentration of MSMA or its degradation products in the wood is known. Even then the problem is complicated by the fact that distribution of the

pesticide after treatment is quite variable through the tree. Although in bark beetle suppression only about one percent of trees in a given stand are treated, it is necessary to assume a worst case in which the wood supply consists entirely of treated trees and that the arsenic present is in an inorganic form. If such a conservative estimate indicates that exposures do not approach levels of concern, no further assessment is required.

The first measurements of arsenic in trees following MSMA treatment were apparently those of R.S. Hodgkinson (1983a) of the British Columbia Ministry of Forests, reported internally. After injecting MSMA into spruce in mid-May at 100 g/L As, the total arsenic level in phloem averaged 24 ± 7.3 ppm at 20 m from the injection site. In a further test, injection of MSMA at 80 g/L a.i. (the normal dosage for spruce beetle control) resulted in 9.6 ± 4.8 ppm of arsenic at the 20 m level (Hodgkinson 1983b). Other analyses were reported to the Ministry soon afterward by Tom Maher (1984) of Northwood Pulp and Paper Ltd. After injecting MSMA at 160 g/L, Maher found a range of 17.2 to 41 ppm total arsenic in phloem of spruce trees 15 metres from the stump. (One sample containing only 5.5 ppm is ignored in this discussion.) Sapwood at the same level contained 6.2 ppm; the range was 2.3-10.3 ppm. (Presumably, the cut-off was at about the level of the injection.)

Newton (1986) measured total arsenic levels in lodgepole pine and a mixed stand after "hack and squirt" application, and in ponderosa pine and Douglas-fir after injector application of MSMA. The treatment rate for ponderosa pine and Douglas-fir was about 370 mg/5 cm diameter. Lodgepole pine and the mixed stand were treated at about twice that rate. Average application rates were slightly below one kg/hectare. The major purpose of the study was to estimate arsenic contribution to litter and soil with leaf-fall. Concentrations in foliage averaged 40 ppm after fall application and 52 ppm after spring application. It is not clear how much time elapsed between treatment and sampling. The woody xylem was stated to contain concentrations that were usually less than 3 ppm but the data was not included. Bark was apparently not examined. A single larch that had been treated five years earlier was found to have 670 ppm in the phloem and about 20 ppm in the woody portion of the trunk. A lodgepole pine had similar levels in the stem but in the phloem the arsenic concentration was much lower than in the larch, slightly above 120 ppm.

In a study by MacLauchlan *et al.* (1988a), treatment of lodgepole pine with quarter-strength MSMA resulted in substantial accumulation of arsenic in the stump below the frill, and extensive transport to foliage, but there was relatively little in sapwood and phloem of the stem. Trees averaged 72 cm circumference, and each was treated with about 11.5 gm. MSMA (5.32 gm arsenic) in late August (several seeks later than the normal operational treatment period) and felled about 10 weeks later. Sapwood sampled every two metres above the frill did not differ significantly in total arsenic concentration from control trees 0.8 vs. 1.2 ppm), and arsenic in phloem was only slightly higher than in untreated trees (2.4 vs. 0.9 ppm). In stumps below the frill sapwood averaged about 28 ppm and phloem averaged about 60 ppm. Foliage concentrations were on the order of 35 ppm.

The same group conducted a similar study with 1/8,1/4, and 1/2 strength MSMA (MacLauchlan *et. al.,* 1988b). The 1/8 strength treatment was late summer, felled 10 weeks later, the 1/4 strength treatment was late April, felled 10 weeks later, and in the 1/2 strength experiment, treatment was late April with falling about six weeks later. Average concentrations in phloem were 5.2, 4.1 and 5.3 ppm, respectively, and in sapwood 4.6, 2.2 and 3.4 ppm. Application rate was 2 ml / cm circumference and mean circumferences were 45.2, 49 and 57.8 cm. The concentrations of MSMA were 40, 80, and 160 mg/ml, therefore the applied doses per tree were 3,600, 7,840 and 18,560 mg MSMA, or 1,667, 3,630 and 8,593 mg arsenic. It is curious that the sapwood and phloem concentrations did not reflect the differences in dose.

Distribution of MMAA and inorganic arsenic in the cross section of a treated Douglas-fir tree was measured by Manville et al. (1988), apparently two weeks after application of MSMA. (MMAA is the acid form of MSMA). At the pH in the tree the equilibrium between MSMA and MMAA will favor the latter.) Concentration of MMAA in phloem was 99 ppm 1.5 metres above the frill, and decreased to 9 ppm at 16.5 metres. Inorganic arsenic was relatively constant at 4-5 ppm except for a concentration of 10.8 ppm at 4.5 metres and another of 1.5 ppm at 13.5 metres. At all heights, concentration decreased with distance away from the phloem. In the xylem sample closest to the phloem radially and closest to the frill along the axis of the stem, concentration was 42 ppm and at the center of the tree at the same level the concentration was 4.2 ppm. The average of all samples throughout the tree, including phloem, was 15 ppm MMAA and 1.6 ppm inorganic arsenic. A concentration of 15 ppm MMAA is equivalent to 7.5 ppm arsenic. For purposes of evaluating exposure the higher figure will be used. This average is not inconsistent with other work. (In averaging arsenic concentrations in various parts of a tree, it must remembered that the parts of the stem where concentrations are relatively high constitute a small part of the total volume. Therefore, any average other than a composite of the whole tree will be biased upward.)

Buffam *et al.,* (1973) and Lister *et al.* (1976) injected and measured various dosages of Silvisar 510@ (cacodylic acid-up to 340 g/L a.i.) in spruce. Buffam *et al.* found residues as high as 50 ppm 4.6 m above the butt; Lister *et al.* found average levels less than 10 ppm. Whether the differences relate to MSMA vs. cacodylic acid, or location is unclear.

Exposure to sawdust from treated trees

The studies of MSMA indicate that sapwood arsenic concentrations should not exceed 20 ppm and will probably be much less. The higher concentrations of arsenic in phloem make a minor contribution to the burden of the whole tree. Expressed as percentage, 20 ppm is 0.002% arsenic. The chemical form of the measured arsenic is not known, so it is assumed in the interest of health conservative assessment that it is in the form of inorganic arsenic, which is much more toxic than MSMA.

British Columbia Industrial Health and Safety Regulations (Workers Compensation Board, 1980) set an 8 hour workplace air quality standard for arsenic and its compounds of 0.5 mg/cubic metre. To make a comparison between the maximum expected workplace exposures and the limits set by regulations, we will make certain assumptions. The first is clearly the worst conceivable case; it is an assumption that all sawdust in a mill contains 20 ppm arsenic and is all of respirable particle size. In other words, all of the sawdust produced is so fine that it can be inhaled into the lungs.

The other assumption is somewhat more reasonable, that a person doing hard physical work ventilates the lungs at 20 cubic metres of air per workday. At the allowable concentration of 0.5 mg arsenic/cubic metre the daily intake of arsenic would be 10 mg. If wood dust contained 20 ppm (20 mg arsenic/kg wood), a worker would have to inhale 500 grams of wood per shift to reach the allowable maximum. The regulations stipulate a maximum average wood dust concentration of 5 mg/cubic metre of air, or a daily total of 100 mg, under our assumption of a 20 cubic metre ventilation per shift. 100 mg of wood dust at 20 ppm contains 0.0020 mg arsenic, which is about 5,000 fold less than the regulations pen-nit. The dose to a 50 kg worker would be 0.00004 mg/kg/day. If the arsenic content in wood were as high as 50 ppm, arsenic in airborne wood dust would be 1/2000 of the maximum allowable air concentration.

Yarding, loading and sorting treated logs is not likely to be a source of exposure. Arsenic in the wood is tightly bound and should be difficult to displace with surface contact. No specific studies of arsenic dislodgement from wood have been made, but the large margins of safety associated with fine particulate wood dusts support the idea that uncut logs are not a significant source of arsenic for workers even if it is argued that the air quality standard is not stringent enough.

Exposure to smoke from burning of wood or slash from treated trees: household firewood, disposition of treated trees and prescribed fire, mill wastes

MSMA or arsenic exposure associated with combustion of MSMA-treated wood has not been examined specifically, but it is possible to make reasonable estimates. There are three scenarios to consider: use of treated wood for domestic fuel, open burning of treated trees for disposition or prescribed burning for either vegetation management or site preparation, and burning of bark wastes at the n-till. The approach in each case will be to use information about the atmospheric concentration of other wood combustion products to estimate distribution of smoke, and to use known relationships between amount of fuel burned and amount of particulates and other combustion products formed.

Domestic fuel

Burning of treated wood for domestic fuel requires two exposure assessments, one for short-term exposure that may result in systemic, reversible effects, and a different approach for long term exposure that governs cancer risk.

For domestic fuel burning, a useful surrogate marker is benzo(a)pyrene (BaP), which is a polycyclic aromatic hydrocarbon that is produced in any combustion process. It is better known as a major carcinogenic product in automotive exhausts. Combustion of seasoned pine in a fireplace has been found to produce about 0.05 mg BaP/kg fuel (Dasch, 1982). A similar figure has been determined for spruce in the presence of adequate oxygen (Ramsdahl *et al.,* 1982).

If the arsenic level in wood is 20 ppm (20 mg/kg) and if it is assumed that all of the arsenic will be volatilized or otherwise carried in the combustion gases, the gases from one kg of wood will contain 20 mg of arsenic. It may be in any form, including arsenic trioxide, which is likely to be formed in combustion. Although this assessment provisionally assumes that all MSMA-derived arsenic in a treated tree is converted to trivalent inorganic forms, actual conversion is likely to be much less. McMahon *et al.* (1985) have shown that combustion of wood treated with copper chromated arsenate (CCA) converts less than 30% of residual arsenic to volatile forms at temperatures of 800 C or less. Prolonged heating of ash releases much higher amounts.

The relation between BaP and arsenic in smoke may be taken as constant in this example, at 20 mg arsenic/kg wood burned and 0.05 mg BaP/kg wood burned. BaP concentrations in fuel burning homes are usually below 0.000005 but may reach 0.00002 mg/cubic metre (Hornig *et al.,* 1981; Engel, 1985; Imhoff and Manning, 1983; Moschandreas *et al.,* 1981).

If the air of a home heated with such MSMA treated wood contains 0.00002 mg BaP/cubic metre, estimated arsenic concentration in air would be:

0.05 mg BaP per kg wood /0.00002 mg BaP per cubic metre air 20 mg arsenic per kg wood/0.008 mg arsenic per cubic metre.

Air arsenic concentration in this case would be 0.008 mg/cubic metre. In the more likely case of 0.000005 mg BaP per cubic metre the concentration of arsenic in air would be correspondingly lower, 0.002 mg per cubic metre or less.

If a resident is assumed to respire at a rate of 20 cubic metres/24 hours of light to moderate activity, and output from the stove continues 24 hours, the daily intake of airborne arsenic would be between 0.04 and 0.160 mg. For a 50 kg person the dose would be between 0.0008 and 0.0032 mg/kg, for a day on which treated wood is used as fuel.

The exposure scenario above is based on the assumption that the entire wood supply for a given period is derived from treated sources. Such exposure will not be sustained for long periods and for the purpose of estimating cancer risk, an estimate of average daily exposure over a lifetime is necessary.

Trees that are treated with MSMA and felled are widely scattered and left in place, not gathered in a pile, so there is no practical prospect that a firewood supply can be drawn only from treated trees. Relatively few of the treated trees are easily accessible from roadways for use as firewood. In forested areas, firewood is drawn from sources no more than a few miles from the home because access to wood is relatively easy. The likelihood of access to any treated wood for more than a season is slight.

It is estimated that no more than one percent of trees are treated in a given stand, and no more than five percent of those are accessible in a season. The movement of treatments from region to region, out of reach of a given wood gatherer can be expected to diminish access over a lifetime by at least ten fold.

The consequence of the lifetime dilution of exposure will be to bring average daily exposure down to a range of 0.0000001 to 0.0000004 mg/cubic metre.

The above estimates do not include a factor for actual time spent in the home, or the finding (McMahon *et al.*, 1985) that more than half of the arsenic in wood does not enter the air space. Inclusion of these factors would result in additional lowering of the average daily dose by about four fold.

Exposure from open burning of treated wood or slash

Exposure resulting from open burning of wood can be evaluated on the basis of smoke density as described in Dost (1986). Particulate emissions (smoke) range from 8.5 to 40 grams/kg fuel (Imhoff and Manning, 1983; Dasch, 1982, Sandberg and Martin, 1975; Radke, 1978; Lim and Lips, 1981). Most values are at the low end of the range.

The light extinction for smoke is about 0.5 grams per square metre. In other words a square column one metre on a side containing 0.5 grams of smoke would block all light, regardless of the length of the column. If the column is 100 metres long, a total of 0.5 grams would give a concentration of 5 mg (0.005 gm) per cubic metre. At that concentration an object 100 metres away would not be visible. This can be the basis of the comparison with airborne arsenic levels.

A kg of wood (which is assumed to contain 20 milligrams of arsenic whether in organic or inorganic form) produces 8.5 grams of smoke under the conditions set above. At a visibility limit of 100 metres, or 5 mg/cubic metre, the volume of air occupied by 8.5 grams of smoke would be 1700 cubic metres, which would contain 20 mg arsenic. The arsenic concentration would then be 0.012 mg/cubic metre. Smoke at 100 metres visibility is difficult to tolerate, and exposure for more than a short time is unlikely. If the amount of smoke per kg wood is assumed to be 40 grams, which is the highest published value, at the same smoke density the arsenic concentration becomes less, or 0.0025 mg/cubic metre. A worker exposed to this concentration for a full work day, at a fairly high rate of activity would respire about 20 cubic metres/day. Total daily dose would then be 0.05 mg, or of a 50 kg worker 0.001 mg/kg for a work day.

The same approach can be used to estimate exposure to smoke emitted during slash burning. Particulate emission from slash is stated to range from 18 to 50 pounds per ton, averaging about 34 pounds/ton or 17 grams /kg (Sandberg and Dost, 1990). The somewhat higher emission for slash compared to wood is probably related to the high concentration of volatile organic molecules in foliage, smaller fuel size and incomplete combustion due to vortex mixing, cooling and transport. At 17 grams particulate per kg burned, the volume of distribution at a visibility limit of 100 metres will be just twice that estimated for the example used for wood combustion.

This means that any substance distributed from wood in the smoke will be half as concentrated. However, concentration of arsenic in foliage of treated trees is higher than in wood. If twice as high (40 ppm) the air arsenic level would be about the same, providing an exposure and daily dose of 0.001 mg/kg. At a foliar concentration of 100 ppm, arsenic concentrations in smoke could be 2 1/2 times higher; the dose would be 0.0025 mg/kg.

Combustion of mill wastes

In some cases, bark is disposed of by burning. Spruce and pine both have thin bark, with phloem constituting a large fraction of the bark. Because concentrations of arsenic are usually higher in phloem of trees treated with MSMA than in sapwood, it is necessary to evaluate the potential for exposure through inhalation of smoke from waste burners.

Manville *et al*. (1988) with Douglas-fir and MacLauchlan *et al*. (1988a, 1988b) with lodgepole pine, showed that arsenic concentration in all parts of the stem decreases with distance from the frill. Manville *et al.*, using a dosage rate of 44 g of As/tree, found levels approaching 100 ppm in phloem just above the injection site, and Maclauchlan *et al.*, using a dosage rate of 12g of As/tree, measured residues of about 60 ppm. Progressing upward through the useable part of the stem, concentrations diminished to less than 10 ppm. Hodgkinson (1983a,b) with spruce, found about 25 and 10 ppm respectively, 20 m above the frill after injecting 160 and 80 g/L respectively. Maher (1984) found a similar level but did not specify the height above application.

From these data, it seems conservative to assume an average whole bark concentration of 40 ppm arsenic. At that level, under smoke exposure conditions of 100 metre visibility described above and continual burning of treated wastes, the air concentration would be 0.0025 mg/cubic metre, resulting in an intake of 0.001 mg/kg/day. In reality, the amount of bark burned as waste is likely to be a small fraction of total waste burned, even if the entire input to the mill is from treated stems. If the input to the mill is run-of-the woods in a treated area, where perhaps one tree in a hundred is treated, the average concentration will be vanishingly small. If mixed from both treated and untreated forests the average will drop still further. Furthermore, a waste burner producing smoke so dense as to restrict visibility to 100 metres would not be tolerated. A reasonable estimate of actual exposure is on the order of 0.1 % of the above worst case, or 0.0000025 mg arsenic/cubic metre and 0.000001 mg/kg/day for a worker on the site.

Summary of dosage estimates, based on exposure estimates

These estimates are based on assumption of MSMA plus any derived arsenic as a total of 20 ppm arsenic in the entire wood supply. It is assumed that the entire exposure is absorbed and represents the effective dose, and that the exposed individual weighs 50 kg. Dosage in mg/kg would be proportionally greater for a smaller person and less as body weight increases.

Source of exposure	Max. conc. in air mg As/cubic M	Max. dose, in mg As/kg/day
Application of MSMA	NA	0.005
Wood dust in mill*	0.00002	0.00004
Domestic stove emission, one day	0.008	0.0032
Domestic stove emission aver/day, lifetime	0.0000004	0.00000014
Slash or waste, single day	0.0025 (100 m visibility in smoke)	0.001
Burning of mill waste (bark)	0.0000025	0.000001

*Assumes wood dust levels at allowable 5mg per cubic metre.

Assessment of health risk associated with use of MSMA

Graded or consistent effects (non-genetic/non-carcinogenic)

Analysis of all the available data convincingly indicate that for non-cancer endpoints, there is little likelihood of adverse human health effects or environmental impact associated with application of MSMA in bark beetle control. This conclusion applies to potential exposures to both MSMA and any inorganic arsenic that might arise as a result of biological action on MSMA_ It is based on the well established detoxication pathways for inorganic arsenic, and on risk estimation under an assumption that all MSMA is converted to inorganic arsenic. Exposure to inorganic arsenic arising from burning of treated wood is considered separately.

For general or non-cancer effects, which are subject to a threshold or no-observed-effect level (NOEL), assessment of risk is a comparison between the dose resulting from some means of exposure, and the most sensitive NOEL in the most sensitive species found experimentally. The ratio between the two figures is called the safety factor, or margin of safety. Typically, with data of good quality, a safety factor of 100 is considered to assure that there is a practical certainty that such exposure will not result in harm.

For the purpose of this assessment, the NOEL of 2 mg/kg/day for the beagle dog in a 52 week study is the lowest of any study. In contrast to the chronic beagle study, the exposures of humans are almost always short term, possibly excepting the low level exposure that might occur from residential woodburning under unusual conditions. The use of a chronic study as a standard for short exposures adds considerably more conservatism to the assessment.

The dose rate in the animal study is relative to administered MMAA. Because of difficulty in determining the chemical species in urine samples from workers, wood specimens or environmental samples, the concentrations are expressed as total arsenic. MSMA is about 54% arsenic, and on that basis the daily dosage to the beagle dog represented 1.1 mg arsenic/kg.

For workers applying MSMA, the highest daily excretion measured (as arsenic) by Wagner and Weswig (1974) indicated a daily dose of 0.005 mg MSMA/kg. Based on a NOEL of 2 mg MSMA/kg. (1.1 mg arsenic/kg) the safety factor for a 50 kg worker for that dose is about 400. This is a level that is on the order of that suggested by Valentine et al. 1979 as the threshold for methylation of inorganic arsenic, where the arsenic level in blood may begin to rise. Because methylation has already been accomplished, in the case of MSMA that figure does not represent a threshold for application.

Exposure to wood or wood dust containing arsenic has been discussed in detail, above. Even by making assumptions in the realm of absurdity about the fineness of saw dust and dust levels in the workplace, and assuming that all MSMA arsenic has been converted to the more toxic inorganic arsenic form, exposures to arsenic by inhalation in a mill operation will be 2000-5000 fold lower than industrial health standards allow. The estimated daily dose is 0.00004 mg arsenic/kg/day, with a safety factor of 27,000 based on the no observed effect level for MSMA.

Graded or consistent effects of organic or inorganic arsenic (non-genetic/ non-carcinogenic) possibly arising from combustion of MSMA treated wood

Assessment of non-carcinogenic risk associated with exposure to inorganic arsenic resulting from combustion of treated wood is complicated by several factors. Because inorganic arsenic is not a pesticide, there is not a systematic body of registration data that provides threshold information for the various possible graded responses. Most of the interest in arsenic arises from exposures either in smelters and related industrial settings, or to ambient arsenic in water supplies. Arsenic is also ubiquitous in the atmosphere, although exposures are low. Marcus and Rispin (1988) estimated an average daily public intake of respirable arsenic on the order of 0.00009 mg/day (0.0000018 mg/kg/day). Because of strong binding of arsenic in the lung, it appears that the systemic responses to similar doses to the lung and digestive tracts are not similar.

For residential wood combustion, assuming that the entire supply comes from treated wood over a given period, the estimated exposure for a 50 kg person will be 0.0032 mg/kg/day, (see exposure estimate above) with a safety factor of over 300, if the airborne arsenic is in the form of MSMA. In this case, comparison with the long term study of dogs is not as conservative, because residential exposure under these assumptions is also long term.

Slash or waste wood burning was estimated to produce a maximum concentration in air of 0.0025 mg per cubic metre in smoke at visibility limit of 100 metres. A respiratory turnover of 20 cubic metres per day is assumed for a given work day under exertion. The daily intake for a 50 kg person would be 0.050 mg, or 0.001 mg/kg. The safety factor if airborne arsenic is MSMA will be 1100.

If consumption of treated wood were to increase for an extended period, there would seem to be a possibility that the arsenic burden could become significant. However, a mitigating factor is the poor availability of small amounts of respired arsenic. It is interesting that arsenic associated with larger particles is more readily absorbed than smaller particles (Smith et al., 1977), presumably because the larger particles are moved out by the mucociliary apparatus and swallowed.

The same considerations apply in this case as were discussed with respect to domestic fuel consumption. In this case exposure is occupational, however, and management of burning and personnel can control exposure. The assumption of 100 metre visibility in smoke is extreme, and while possible for short periods, should not be sustained. It should not be expected that slash or waste wood burning will result in significant exposures to arsenic; a greater hazard is exposure to combustion products of the wood itself.

Combustion of bark only in a waste burner would produce higher concentrations of arsenic in smoke, because of the higher levels found in the inner bark after MSMA injection. Concentration in bark is assumed to be 40 ppm, twice that of whole stems, but the supply to the burner is highly diluted and smoke exposure would not approach that based on the assumptions for slash burning. The air levels are estimated at 0.0000025 mg/cubic metre and daily dose is estimated at 0.000001 mg/kg/day, during days in which burning occurs. The safety factor relating to MSMA accordingly would be in excess of one million.

For inorganic arsenic, intake is on the order of the average daily respiratory intake for the population at large, during periods when contaminated material is burned. It seems clear that short term use of such wood represents no problem, and it is likely that the limited availability is completely protective.

As a matter of risk management, it would be a simple matter to post any treated trees as a warning not to use the wood or fuel.

Risk of systemic toxicity from use of MSMA in bark beetle control

Source of exposure	Safety factor
Applicator exposure to MSMA	400
Inhalation of wood dust containing MSMA	27,000
Domestic stove emission if MSMA	340
if inorg. As	see text
Open burning of slash or waste if MSMA	1,000
if inorg. As	see text
Burning of mill waste if MSMA	1,000,000
if inorg. As	see text

Cancer risk associated with MSMA use in bark beetle control: intact MSMA

Standard carcinogenicity assays have shown that MMAA and therefore MSMA do not have discernible potential to cause cancer. The primarily negative results of mutagenicity assays are consistent with a lack of potential for carcinogenicity by some genetic impact. Furthermore, the metabolism of MSNLA, and related substances in the body indicate that there should be no intermediate products that can react with genetic material to begin the carcinogenic process.

Most or all genotoxic carcinogens (cancer causing agents that react directly with DNA, the genetic material in the cells) are relatively insoluble substances that must be made more soluble for excretion. The reactions to accomplish this have many steps, and intermediates in the sequence may be highly reactive. If they escape the sequence they can react with and damage large molecules such as DNA and some proteins if not trapped by defense mechanisms. Arsenicals are changed in the body, but by a different process, and all of the chemical forms appear to be relatively unreactive in the cells.

Other pathology observed at very high doses of MSMA, such as hyperplasia of the thyroid or excessive turnover of cells in the large intestine might be suggested to cause tumors by non-genetic mechanisms if sustained over long periods. These are threshold-based effects, and at lower doses have no impact on tissues and no potential for neoplastic activity.

Because of the failure to induce cancer experimentally with treatment by MMAA, and the absence of other indication of carcinogenic potential, it is not appropriate to prepare a quantitative estimate of cancer risk for MSMA as such. The data indicate that

the probability that MSMA itself, as used in bark beetle control may cause cancer (cancer risk) is low enough to be considered in practical terms as equivalent to zero.

MSMA as used to control bark beetles has virtually no prospect of leaving the treated tree to injure non-target vegetation, game or water supplies, or to expose members of the public directly. There seems to be no utility in setting up hypothetical public exposure scenarios for this use of MSMA, since there is no evidence of transport on which to base such estimates. Similarly, there is little probability of exposure of aquatic populations unless a spill occurs in or near a water body.

Movement into adjacent plants edible by humans, livestock or game is not a significant source of exposure. Uptake of arsenic in any form by edible fungi has apparently not been studied, and it would be useful to know if mushrooms have some peculiar tendency to concentrate arsenic.

Cancer risk associated with MSMA use in bark beetle control: inorganic arsenic potentially derived from MSMA

While MSMA itself poses no cancer risk, it is necessary to examine the possibility that inorganic arsenic may be formed by some process, resulting in human exposure. It is known that arsenic is associated with cases of human cancer, even though attempts to find experimental evidence for carcinogenicity in animals have failed. Other exposure routes derived from MSMA use are inconsequential. Combustion is the one process by which MSMA may form significant amounts of inorganic arsenic, a large portion fraction of which will probably be arsenic trioxide.

Estimates of exposure to smoke-borne arsenic in circumstances associated with MSMA use have been discussed earlier. There is also data (Woolson, 1986) showing that when oak treated with cacodylic acid is burned, most of the arsenic is found in the ash as arsenate, with small amounts in particulate material. It is reasonable to expect MSMA to behave in the same way, and McMahon *et al.* (1985) has shown that less than 30% of arsenic from copper chromated arsenic emerges from combustion as inorganic arsenic unless subjected to temperature over 800 C for extended periods. For conservatism, it will be assumed that all of the combustion product is available in air.

The epidemiological data of Enterline *et al.* (1987) suggest that cancer risk associated with smelter atmospheres may be proportionally greater at lower long term doses that at higher dose rates. Enterline *et al.* (1987) have tabulated in condensed form respiratory cancer mortality for Tacoma smelter workers and standardized mortality ratios (SMR) based on background rates of respiratory cancer deaths in white males in the state of Washington. The data indicate that exposures up to 10 years to concentrations up to 0.4 mg/cubic metre do not significantly increase the SMR. Plotting of data on average exposures of 0.213 (<0.400), 0.564 (0.400-0.799) and 1,487 (>0.800) mg/cubic metre indicate threshold SMRs between 0.045 and 0.100 mg/cubic metre through working histories up to 29 years.

The maximum exposures from burning wood from trees treated with MSMA, discussed above, are on the order of 0.008 mg/cubic metre or less, over much shorter periods. Comparison with the findings of Enterline *et al.* (1987) suggest that it is unlikely that even complete conversion to inorganic arsenic in combustion will increase cancer risk, judged on the basis of a non-threshold, linear mechanism.

Conventional risk assessment depends on use of a unit risk derived mathematically from either animal data or epidemiological analysis. The US Environmental Protection Agency has set a unit risk for airborne arsenic of 0.0043 per microgram per cubic metre. This means that a continuous lifetime exposure to one microgram arsenic per cubic metre is estimated to confer an added risk over background of 4.3 chances of cancer in 1000 lifetimes.

For cancer risk estimation, intermittent exposure is averaged over a typically 70 year life span. In the exposure estimate for residential wood burning, above, the availability of treated wood and frequency of treatment have been incorporated.

On the basis of the U.S. EPA unit risk of 0.0043 per microgram per kg/day the estimated cancer risk at an average concentration of 0.0000004 mg (0.0004 micrograms) /cubic metre is 0.0000017 or 1.7 chances in a million lifetimes. If the home is occupied less that 100% of the time, and the finding of McMahon et at (1985) that less than 30% of arsenic in treated wood emerges in smoke, the estimated risk decreases substantially, and may be considered the practical equivalent of zero risk.

Estimates of carcinogenic risks associated with combustion of treated wood as slash or waste are lower than those arising from residential wood combustion.

Burning of wood waste or slash will result in intermittent, infrequent exposure that, in terms of average lifetime exposure, will represent insignificant cancer risk.

There is evidence that the carcinogenic response to arsenic in humans is epigenetic, or indirect. In other words, arsenic may not cause direct genetic damage that initiates the carcinogenic process. Stohrer (1991) has presented a most convincing argument to support such a mechanism, showing that arsenic induced cancer in humans is a threshold-based phenomenon, just as are the non-carcinogenic effects. Marcus and Rispin (1988) have also indicated that arsenic carcinogenesis must be a threshold based effect.

There appears to be no carcinogenic risk associated with MSMA use, in terms of either MSMA itself, or inorganic arsenic that may arise from it. That conclusion is supported by the assays of MSMA itself, conventional assessment of carcinogenic risk from airborne arsenic, the apparent threshold SMR shown by Enterline, and the strong arguments in favour of a threshold based mechanism.

Even though there is apparently minimum risk associated with use of MSMA, adequate training, discipline and supervision should be emphasized for all control operations. These measures would further increase the conservative safety factors used in this report. Personal protection is easily achieved without compromising worker comfort or productivity, and the relative safety of the pesticide should not be an excuse for poor work practices.

Glossary

Absorption. The movement of a chemical from an exposed surface (skin, respiratory or digestive tract) into the circulation to be distributed throughout the body. In most cases, a small fraction of material deposited on the skin and a high fraction of that taken into the digestive or respiratory tracts is absorbed.

Acute. Very short term. An acute intoxication is one that occurs with a single dose or a very short (acute) period of exposure. The intoxication may last only a short time, or if the injury is severe a long recovery period may be necessary. (See also **Subacute**)

Background. Existing natural levels of a chemical in a given area, or the natural frequency of a disease condition in a population.

Cambium. The actively dividing layer of cells which produces a vascular plant's conducting tissues, thus increasing the girth of a branch, trunk or stem.

Chronic. Long term, referring to either the period of exposure or intake of a chemical, or the duration of an effect. Exposures of from six months to a lifetime are usually considered chronic. (See also **Subchronic**)

Dose. The amount of a chemical that is absorbed into the body, usually expressed as milligrams of chemical per kilogram body weight (mg/kg). The dose resulting from skin exposure is usually a small fraction of the amount that reaches the skin, and usually a large part of exposure in the digestive or respiratory tracts is absorbed.

Dose response. The change in effect as dosage changes. As the dose increases so does the response and the response lessens with lower dose. Every interaction between a chemical and a biological system is dose-responsive.

Epidemiology. Epidemiology is the study of associations between disease and environmental factors. The connection between lung cancer and smoking was identified through epidemiological investigation. It is possible to show association through this kind of study, but causal relationship cannot be proven.

Exposure. Contact of a chemical with a body surface (skin, respiratory tract, digestive tract) from which it can be absorbed into the body.

Inorganic arsenic. Arsenic compounds that do not contain carbon, such as sodium arsenate and potassium arsenite.

Margin of Safety. See **Safety factor**

Metabolism. Alteration of chemicals in biological systems. Inorganic arsenic is metabolized by addition of a methyl (CH_3) group to form monomethyl arsonic acid (MMAA), then addition of another methyl group to form dimethyl arsinic acid. (See Figure 1)

NOEL, NOAEL. See **No-observed-effect level; threshold**

No-observed-effect level (NOEL). Also called no-observed-adverse-effect level. On a dose-response curve, the dose below which no effect can be seen, or the highest dose that produces no response. The NOEL will be different for each kind of effect, in each species. For judging safety factors, the lowest NOEL is usually compared with the dose measured or estimated in the field. The NOEL is in practical terms the same as a threshold, but there is a conceptual difference. (See **Threshold**)

Organic arsenic. Organic molecules are those made up primarily of carbon. Organic arsenic is a general term referring to carbon containing molecules which also contain arsenic. MSMA and cacodylic acid are examples.

Pathology, cellular. Microscopic or electron microscopic changes observed at the cellular level.

Pathology, gross. Changes due to injury, toxicity or other effects observable to the trained eye.

Phloem. One of the conducting tissues in vascular plants, through which products of photosynthesis are transported. In trees phloem is found immediately inside the bark.

Risk. The probability that an activity will result in harm to humans or other organisms. In the context of chemicals, risk is the probability that use or misuse of a chemical will result in adverse health effects.

Safety factor. Referring to systemic and reproductive effects, The difference between the NOEL and the dose acquired in the field. If the NOEL for an effect is one mg/kg, and the dose to an applicator is determined to be 0.001 mg/kg, the safety factor is 1000. Also called margin of safety.

Semiochemicals. A chemical substance that mediates one or more interactions between organisms (i.e., a message-bearing chemical).

Subacute. Relatively short term. There is no defined specific time period, but the ten-n usually refers to exposures lasting more than a day and up to two weeks.

Subchronic. Periods of medium duration. There is no defined specific time period, but the term usually refers to exposures up to six months.

Systemic exposure. Exposure that is likely to result in absorption of a chemical followed by distribution throughout the body, as distinguished from contact that results in effects only at the site, such as skin or eye irritation.

Systemic toxicity. General effects of a chemical in some or most organs of the body. The term usually refers to responses other than cancer, genetic effects or reproductive effects.

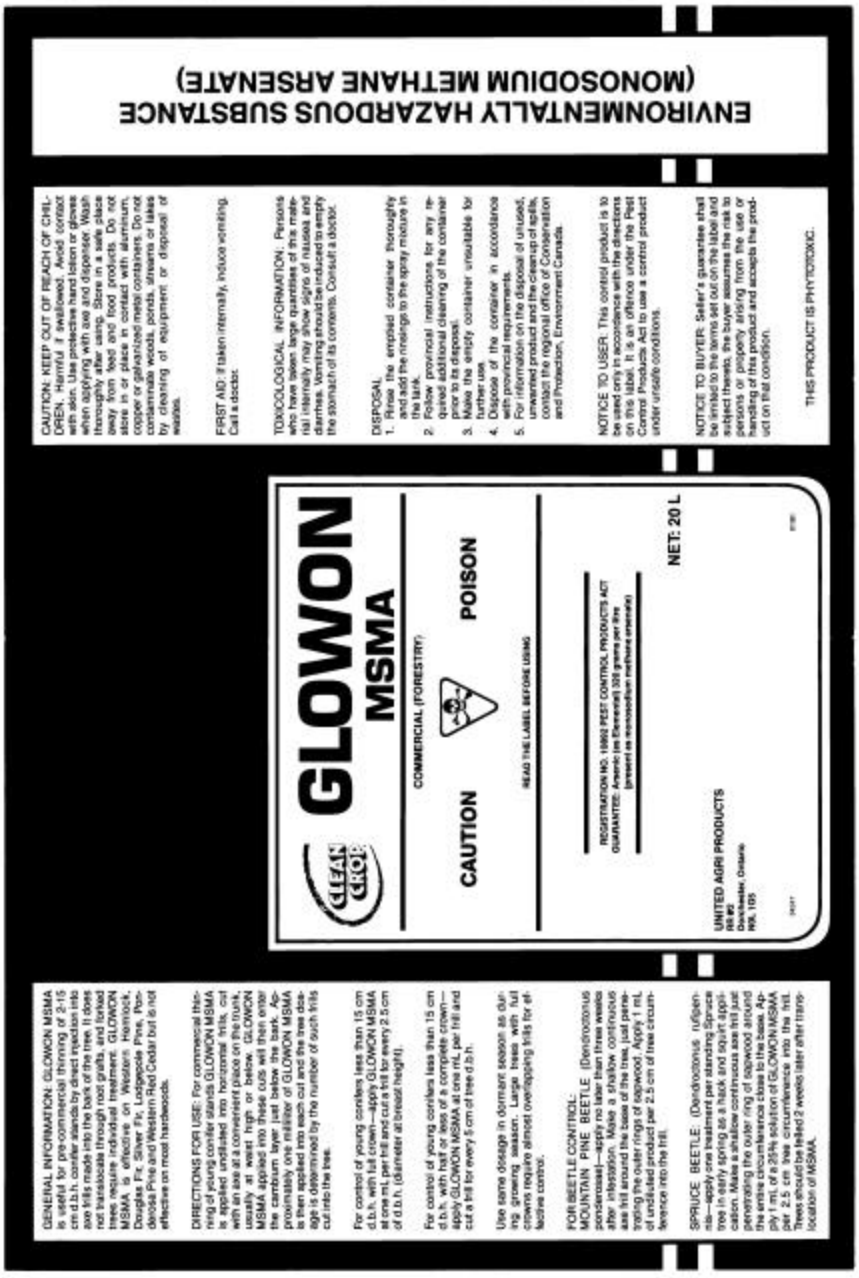
Threshold. The lowest dose that produces a response in a given system. Threshold is not practically different from the NOEL, the highest dose that does not produce a response. Because of biological variation it is not possible to differentiate the two terms.

Total arsenic. All forms of arsenic in a system measured together, without differentiating the various inorganic and organic forms of arsenic. In older research, methods were not usually available for measuring the different arsenic compounds separately; after administering an organic arsenical such as MSMA, it was only possible to identify changes in total arsenic, without knowing whether it was still as MSMA or changed to another form.

Toxicity. The whole pattern of adverse effects that can be produced by a chemical. Toxicity is a property of a chemical and is consistent at a given dose in a given species and frequently similar among species.

Xylem. The principal strengthening and water conducting tissue of stems, leaves and roots. In trees live xylem is found immediately inside of the phloem and dead xylem, inside of the live tissue, is the structural wood.

Appendix A – GlowonÒ formulation specimen label



Appendix B - MSMA material safety data sheet

GLOWON®

SECTION I - PRODUCT IDENTIFICATION

Manufacturers' Name:
United Agri Products
Box 22116
London, Ontario
N6C4NO
Trade Name: Glowon® Liquid Tree Killer

Emergency Telephone Numbers:
519-659-9111

CANUTEC 613-996-6660

Synonyms: Monosodium Acid Methanearsonate (MSMA)

Shipping Name: DOT - not restricted

Data: not restricted

SECTION II - HAZARDOUS INGREDIENTS

Material or Components %:
Monosodium Acid Methanearsonate, CAS NO> 2163806 - 51.19%

SECTION III - PHYSICAL DATA

Boiling Point, 700 mm Hg: CA 234 degrees
Specific Gravity (H_20 = 1): at 20 degrees C. 1.550

Vapour Density (Air - 1):
Percentage Volatile by Volume: 1,580
Appearance and Odor: Clear, colorless, odorless
Melting Point:
Vapour Pressure:
Solubility in H_20 % by Wt.: Miscible

pH: 6.6 as is

SECTION IV - FIRE AND EXPLOSION HAZARD DATA

Flash Point (Test Method): Not Flammable >200 degrees F.
Autoignition Temperature:
Flammable Limits in Air, % by Volume: N/A
Lower - N/A Upper - N/A
Extinguishing Media: N/A
Special Fire Fighting Procedures: None.
Unusual Fire and Explosion Hazards: None.

SECTION V - REACTIVITY DATA

Conditions Resulting to Instability: Very stable.
Incompatibility: Strong reducing agents. Hazardous Decomposition Products: Methyl arsines.
Conditions Contributing to Hazardous Polymerization: Will not occur.

SECTION VI - DISPOSAL, SPILL, OR LEAK PROCEDURES

Aquatic Toxicity (E.G. C6 HR. TLM): 96 hour TLM of MSMA for fingering black base, mixed red swap and white river crayfish and channel catfish of 900, 1100 and 3050 mg per litre respectively.

Waste Disposal Method: Bury in an approved landfill area away from water supplies.

Steps to be Taken if Material is Released or Spilled: Absorb on clay or vermiculture.

Neutralizing Chemicals:

SECTION VII - SPECIAL PROTECTION INFORMATION

Ventilation Requirements: Not necessary

Specific Personal Protective Equipment: Not necessary

Respiratory (Specify in Detail):

Eye: Not normally necessary

Gloves: Not necessary

Other Clothing and Equipment: None

SECTION VIII - SPECIAL PRECAUTIONS

Precautionary Statements: Keep out of reach of children. Harmful if swallowed. Avoid skin contact or the breathing of spray mist. Wash hands after using. Keep children and domestic animals off treated areas until washed into soil. Do not graze treated areas.

Other Handling and Storage Requirements: Avoid storage near feed or food products. Do not contaminate waters used by wildlife, aquatic life, domestic animals or waters used for irrigation.

Additional Regulatory Concerns: Tolerances have been established for MAA under CFR 40 part 180.289 and apply to both MSMA and DSMA. Current tolerances are 0.35 ppm. in or on citrus fruits, 0.7 ppm in or on cotton seed, and 0.9 ppm in cottonseed hulls. Tolerances in or on grapes and sugarcane are currently pending.

Is this product, or all its ingredients being certified for inclusion on the *Toxic Substances Control Act* inventory of chemical substances? YES

References

Allard, J. (1974) Arsenical silvicide effects on human health. See Norris, L.A. (1974a). p 4.

Anderson, A.C., Abdelghani, A.A., Smith, P.M., Mason, J.W. and Englande, A.J. Jr. (1975) The acute toxicity of MSMA to Black Bass (*Micropterus dolomieu*), Crayfish (*Procambarua* sp.) and Channel Catfish (*Ictalurus lacustris*) Bull. Envir. Contam. Toxicol. 14: 330-333.

Anderson, A.C., Abdelghani, A.A., Hughes, J. and Mason, J.W. (1980) Accumulation of MSMA in the fruit of the blackberry (*Rubus* sp.) Jour. Envir. Sci. Health B 15:247-258.

Anderson, L.W.J., Pringle, J.C. and Raines, R.W. (1978) Arsenic levels in crops irrigated with water containing MSMA. Weed Sci. 26:370-373.

Bollen, W.B., Norris, L.A. and Stowers, K.L. (1974) Effect of Cacodylic Acid and MSMA on microbes in forest floor and soil. Weed Sci. 22:557-62.

Bollen, W.B., Norris, L.A. and Stowers, K.L. (1977) Effect of Cacodylic Acid and MSMA on nitrogen transformation in forest floor and soil. Jour. Envir. Qual. 6:1-3.

Buchet, J-P, Geubel, A., Pauwels, S., Mahieu, P. and Lauwerys, R. (1984) The influence of liver disease on the methylation of arsenite in humans. Arch. Toxicol. 55:151-154.

Buchet, J-P. and Lauwerys, R. (1985) Study of inorganic arsenic methylation by rat liver in vitro: Relevance for the interpretation of observations in man. Arch. Toxicol. 57:125-129.

-----.(1987) Study of factors influencing the in vivo methylation of inorganic arsenic in rats. Toxicol. Appl. Pharmacol. 91:65-74.

-----.(1988) Role of thiols in the in vitro methylation of inorganic arsenic by rat liver cytosol. Biochem. Pharmacol. 37:3149-3153.

Buffam, P.E., Lister, C.K., Stevens, R.E. and Frye, R.H. (1973) Fall cacodylic acid treatments to produce lethal traps for spruce beetles. Envir. Entomol. 2:259-262.

Charbonneau, S.M., Tam, G.K.H., Bryce, F., Zawidska, Z. and Sandi, E. (1979) Metabolism of orally administered inorganic arsenic in the dog. Tox. Lett. 3:107-113.

Charbonneau, S.M., Hollins, J.G., Tam, G.K.H., Bryce, F. Ridgeway, J.M. and Willes, R.F. (1980) Whole-body retention, excretion, and metabolism of [74As] arsenic acid in the hamster. Tox. Lett. 5:175-182.

Cockell, K.A. and Hilton, J.W. (1988) Preliminary investigations on the comparative chronic toxicity of four dietary arsenicals to juvenile rainbow trout (*Salmo gairdneri* R.) Aquatic Toxicol. 12:73-82.

Crecelius, E.A. (1977) Changes in the chemical speciation of arsenic following ingestion by man. Envir. Health Perspec. 19:147-150.

Cullen. W.R. and Reimer, K.J. (1989) Arsenic speciation in the environment. Chemical Reviews 89:713-764.

Dasch, J.M. (1982) Particulate and gaseous emissions from wood burning fireplaces. Envir. Sci. Technol. 16:638-645.

Dickinson, J.0. (1972) Toxicity of the arsenical herbicide monosodium. acid methanearsonate in cattle. Am. Jour. Vet. Res. 33:1889-1892.

Domir, S.C., Woolson, E.A., Kearney, P.C. and Isensee, A.R. (1976) Translocation and metabolic fate of monosodium methanearsonic acid in wheat (*Triticum aestivum* L.)

Dost, F.N. (1986) An estimate of carcinogenic risk associated with polyaromatic hydrocarbons in smoke from prescribed burning in forestry. Report prepared for US Dept. of Interior, Bureau of Land Management, Washington, D.C.

Edmonds, J.S. and Francesconi K.A. (1977) Methylated arsenic from marine fauna. Nature 265:436.

Engel, P.R. (1985) Ambient air monitoring study of residential woodburning in Mio, Michigan. Proc. Air Poll. Cont. Assoc. 85:43.2.13 pp.

Enterline, P.E., Henderson, V.E. and Marsh, G.M. (1987) Exposure to arsenic and respiratory cancer. Amer. Jour. Epidem. 125:929-938.

Exon, J.H., Harr, J.R. and Claeys, R.R. (1974) The effects of long term feeding of monosodium methanearsonate (MSMA) to rabbits. Nutr. Repts. Internat. 9:351-357.

Fischer, A.B., Buchet, J-P and Lauwerys, R.R. (1985) Arsenic uptake, cytotoxicity and detoxification studied in mammalian cells in culture. Arch. Toxicol. 57:168-172.

Folmar, L.C., Sanders, H.O. and Julin, A.M. (1977) Toxicity of the herbicide glyphosate and several of its formulations to fish and aquatic vertebrates. Arch. Environ. Contam. Toxicol. 8:269-278

Freeman, H.C., Uthe, J.F., Fleming, R.B., Odense, P.H., Ackman, R.G., Landry, G. and Musial, C. (1979) Clearance of arsenic ingested by man from arsenic contaminated fish. Bull. Envir. Contam Toxicol. 22:224-22

Georis, B., Cardenas, A., Buchet, J-P. and R. Lauwerys. (1990) Inorganic arsenic methylation by rat tissue slices. Toxicology 63:73-84.

Gray, L.E. and Kavlock, R. (1984) An extended evaluation of an in vivo teratology screen utilizing postnatal growth and viability in the mouse. Terat. Carcino. Mutag. 4:403-426.

Harrison, W.P., Frazier, J.C., Mazzanti, E.M. and Hood, R.D. (1979) Teratogenicity of disodium methanearsonate and sodium dimethylarsinate (sodium cacodylate) in mice. Teratology 21:43A.

Hessl, S.M. and Berman, E. (1982) Severe peripheral neuropathy after exposure to monosodium methanearsonate. Jour. Toxicol.: Clinical Toxicol. 19:281-287.

Hiltbold, A.E., Hajek, B.F. and Buchanan, G.A. (1974) Distribution of arsenic in soil profiles after repeated application of MSMA. Weed Sci. 22:272-275.

Hiltbold, A.E. (1975) Behavior of organoarsenicals in plants and soils. In: ACS Symposium Series 7, Arsenical Pesticides, Ed, E.A. Woolson. American Chemical Society.

Hodgkinson, R.S. (1983a) Spruce beetle suppression with felled lethal trap trees in central British Columbia in 198 1. British Columbia Forest Service Internal Report PM-PG-2, 36 p.

-----. (1983b) Spruce beetle suppression with lethal trap trees in central British Columbia in 1982. British Columbia Forest Service Internal Report PM-PG-4, 32 p.

Hood, R.D., Harrison, W.P. and Vedel, G.C. (1982) Evaluation of arsenic metabolites for prenatal effects in the hamster. Bull. Envir. Contam. Toxicol. 29:679-687

Hornig, J.F., Soderberg, R.H. and Larsen, D. (1981) Ambient air assessment in a rural New England village where wood is the dominant fuel. Proceedings, Conference on wood combustion environmental assessment. US EPA-600/9-81-029 PB 81-248155. pp 55-68.

Imhoff, R.E. and Manning, J.A. (1983) Comparison of measured and modeled ambient concentrations of residential wood combustion emissions. Proc. Air Poll, Cont. Assoc. 83:54.10.16p.

Jaghabir, M.T.W., Abdelghani, A. and Anderson, A.C. (1988) Oral and dermal toxicity of MSMA to New Zealand white rabbits, *Oryctalagus cuniculus.* Bull. Envir. Contam. Toxicol. 40:119-122.

Jaghabir, M.T.W., Abdelghani, A. and Anderson, A.C. (1989) Histopathological effects of monosodium methanearsonate on New Zealand white rabbits (*Oryctalagus cuniculus*). Bull. Envir. Contam. Toxicol. 42:289-293.

Johnson, L.R. and Hiltbold, A.E. (1969) Arsenic content of soil and crops following use of methane arsonate herbicides. Soil Sci. Soc. Amer. Proc. 33:279-282.

Johnson, L.R. and Farmer, J.G. (1991) Use of human metabolic studies and urinary arsenic speciation in assessing arsenic exposure. Bull. Envir. Contam. Toxicol. 46:53-61.

Judd, F. (1979) Acute toxicity and effects of sublethal dietary exposure of monosodium methanearsonate herbicide to *Perotnyscus leucopus* (Rodentia: Cricetidae)

Kavlock, R.J., Chernoff, N. and Rogers, E.H. (1985) The effect of acute maternal toxicity on fetal development in the mouse. Terat. Carcino. Mutag. 5:3-13.

Lakso, J.U. and Peoples, S.A. (1975) Methylation of inorganic arsenic by mammals. Jour. Agric. Food Chem. 23:674-676.

Lim, K.J. and Lips, H.I. (1981) Overview of emissions from wood combustion. Proc.: Conference on Wood Combustion Environmental Assessment. US EPA 600/9-81-029. PB81-248155 pp 39-54.

Lister, C.K., Schmid, J.M., Minnerneyer, C.D. and Frye, R.H. (1976) Refinement of the lethal trap tree method for spruce beetle control. Jour. Econ. Entomol. 69:415-418.

MAA Task Force Three. (1993) SARA Title III Section 313 Delisting petition for monosodium methanearsonate (MSMA) and disodium methanearsoneate (DSMA). Prepared by OHM Corporation, Walnut Creek CA, for ISK Biotech Corporation, Mentor, OH.

MacLauchlan, L.E., Borden, J.H., D'Auria, J.M. and Wheeler, L.A. (1988a) Distribution of arsenic in MSMA-treated lodgepole pines infested by the mountain pine beetle, *Dendroctanus ponderosae* (Coleoptera: Scolytidae), and its relation to beetle mortality. Jour. Econ Entomol. 81:274-280.

------. (1988b) Distribution of arsenic in lodgepole pines treated with MSMA. West. Jour. Appl. For. 3:37-40

Maher, T. (1984) Report on arsenic residues in MSMA-treated spruce trees. Internal report, Northwood Pulp and Timber, Limited, Prince George, BC.

Manville, J.F., McMullen, L.H. and Reimer, K.J. (1988) Impact and role of monosodium methanearsonate on attack and progeny production by the Douglas-fir Beetle (Coleoptera: Scolytidae) in lethal trap trees. J. Econ. Entomol 81: 1691-1697

Marafante, E., Vahter, M., Norin, H., Envall, J., Sandstrom, M., Christakopoulos, A. and Ryhage, R. (1987) Biotransformation of Dimethyl arsinic acid in mouse, hamster and man. Jour. Appl. Toxicol. 7:111-117.

Marcus, W.L. and A.S. Rispin (1988) Threshold carcinogenicity using arsenic as an example. In: Advances in Modem Environmental Toxicology, Vol. XV., pp 133-158. Risk Assessment and Risk Management of Industrial and Environmental Chemicals. Cothern, C.R., Mehlman, M.A. and Marcus, W.L. Eds. Princeton University Publishing Company, Princeton N.J.

Marcus-Wyner, L. and Rains, D.W. (1982) Uptake, accumulation, and translocation of arsenical compounds by cotton. Jour. Envir. Qual. 11: 715-719.

Mathews, N.E. and Porter, W.F. (1989) Acute arsenic intoxication of a free-ranging white-tailed deer in New York. Jour. Wildlife Dis. 25:132-135.

Mayer, F.L. and Ellersiek, M.R. (1986) Manual of acute toxicity: Interpretations and data base for 410 chemicals and 66 species of freshwater animals. United States Department of the Interior, Fish and Wildlife Service. Resource publication 160, Washington, D.C.

McMahon, C.K., Bush, P.B. and Woolson, E.A. (1985) Release of copper, chromium, and arsenic from burning wood treated with preservatives. Proc. Air Poll. Cont. Assoc. 85:56.3.

Moffett, J.O., Morton, H.L. and MacDonald, R.H. (1972) Toxicity of some herbicidal sprays to honey bees. Jour. Econ. Entom. 65:32-36.

Morton, H.L., Moffett, J.0. and MacDonald, R.H. (1972) Toxicity of herbicides to newly emerged honey bees. Environ. Entomol. 1:102-104.

Moschandreas, D.J., Buchan, R.M. and Fox, D.G. (1981) Residential indoor air quality and wood combustion. Proc. Conference on wood combustion environmental assessment. US EPA 600/9-81-029 P1381-248155.
pp 99-108.

Nakano, M., Yamanaka, K., Hasegawa, A., Sawamura, R. and Okada, S. (1992) Preferential increase in heterochromatin in venular endothelium of lung in mice after administration of dimethylarsinic acid, a major metabolite of inorganic arsenics. Carcinogenesis 13:391-393.

Naqvi, S.M., Davis, V.0. and Hawkins, R.M. (1985) Percent mortalities amd LC_{50} values for selected microcrustaceans exposed to Treflan, Cutrine-Plus and MSMA herbicides. Bull. Envir. Contam. Toxicol. 35:127-132.

Naqvi, S.M., Hawkins, R.M. and Naqvi, N.H. (1987) Mortality response and LC50 values for juvenile and adult crayfish, *Procamarus clarkii* exposed to Thiodan (insecticide), Treflan, MSMA, Oust (herbicides) and Cutrine-Plus (algicide) Envir. Pollution 48:275-283.

Naqvi, S.M. and Flagge, C.T. (1990) Chronic effects of arsenic on American Red Crayfish, *Procambarus clarkii*, exposed to monosodium methanearsonate (MSMA herbicide. Bull. Envir. Contam. Toxicol. 45:101-106.

Newton, M. (1986) Residues from organic arsenical herbicides in chemically thinned forests. Jour. Envir. Qual. 15:388-394

Norris, L.A. (1974a) The behavior and impact of organic arsenical herbicides in the forest: Final report on cooperative studies. USDA Forest Service PNW Forest and Range Experiment Station, Corvallis, OR.

-----. (1974b) Studies of exposure of applicators and animals to arsenicals. See Norris, L.A. (1974a) p 75.

-----. (1977) Arsenic in cattle hair after forests are precommercially thinned with organic arsenical herbicides. USDA Forest Service Research Note PNW-296.

-----. (1985) Exposure of applicators to monosodium methane arsenate and cacodylic acid in forestry. ACS Symposium Series 273:109-121.

Norris, L.A., Canutt, P.R. and Neuman, J.F. (1983) Arsenic in the forest environment afterthinning with MSMA and cacodylic acid. Bull. Envir. Contam. Toxicol. 30:309-316.

Odanaka, Y., Matano, 0. and Goto, S. (1980) Biomethylation of inorganic arsenic by the rat and some laboratory animals. Bull. Envir. Contam. Toxicol. 24:452-459.

Peoples, S.A., Maddy, K.T., Peifer, W.R. and Edmiston, S. (1979) Occupational exposures to pesticides containing organoarsenicals in California. Vet. Human Toxicol. 21:417421.

Prukop, J.A. and Savage, N.L. (1986) Some effects of multiple sublethal doses of monosodium methanearsonate (MSMA) on hematology, growth and reproduction of laboratory mice. Bull. Envir. Contam. Toxicol. 36:337341.

Radke, L.F., Stith, J.L., Hegg, D.A. and Hobbs, P.V. (1978) Airborne studies of particles and gases from forest fires. Jour. Air Poll. Cont. Assoc. 28:30-34.

Ramsdahl, T., Alfheim, I., Rustad, S. and Olsen, T. (1982) Chemical and biological characterization of emissions from small residential stoves burning wood and charcoal. Chemosphere 11:601-611.

Robinson, E.L. (1975) Arsenic in soil with five annual applications of MSMA. Weed Science 23:341-343.

Rogers, E.H., Chernoff, N. and Kavlock, R.J. (1981) The teratogenic potential of cacodylic acid in the rat and mouse. Drug and Chem. Toxicol. 4:49-61.

Sandberg, D.V. and Martin, R.E. (1975) Particle sizes in slash fire smoke. USDA Forest Service Research Paper PNW 199.7p.

Sandberg, D.V. and Dost, F.N. (1990) Effects of prescribed fire on air quality and human health. In: Natural and prescribed fire in Pacific Northwest forests; Walstad, J.D, Radosevich, S.R. and Sandberg, D.V., Eds. Oregon State University Press, Corvallis.

Schultz, T.W. and Dumont, J.N. (1984) Teratogenicity and embryotoxicity of monosodium methanearsonate herbicide. Trans. Am. Microscop. Soc. 103:263-274.

Shariatpanahi, M. and Anderson, A.C. (1984) Distribution and toxicity of monosodium methanearsonate following oral administration of the herbicide to dairy sheep and goats. Jour. Envir. Sci. Health B19:427-439.

Smith, T.J., Crecelius, E.A. and Reading, J.C. (1977) Airborne arsenic exposure and excretion of methylated arsenic compounds. Envir. Health Perspec. 19:89-93.

Stevens, J.T., Halle, L.L., Farmer, J.D., DiPasquale, L.C., Chernoff, N. and Durham, W.F. (1977) Disposition of 14C and/or Z4-As-cacodylic acid in rats after intravenous, intratracheal or peroral administration. Envir. Health Persp. 19:151-157.

Stevens, J.T., DiPasquale, L.C. and Farmer, J.D. (1979) The acute inhalation toxicology of the technical grade organoarsenical herbicides, cacodylic acid and disodium methanearsonic acid; a route comparison. Bull. Envir. Contam. Toxicol. 21:304-311.

Stohrer, G. (1991) Arsenic: Opportunity for risk assessment. Arch. Toxicol. 65:525-531.

Tam, G.K.H., Charbonneau, S.M., Bryce, F., Pomroy, C and Sandi, E. (1979) Metabolism of inorganic arsenic (74As) in humans following oral ingestion. Toxicol. Appl. Pharmacol. 50:319-322.

Tam, G.K.H., Charboneau, S.M., Bryce, F. and Sandi, E. (1982) Excretion of a single dose of fish-arsenic in man. Bull. Envir. Contam. Toxicol. 28:669-673.

Tamaki, S. and Frankenberger, W.T. (1992) Environmental biochemistry of arsenic. Rev. Envir. Contam. Toxicol. 124:79-110.

Tarrant, R.F. and Allard, J. (1972) Arsenic levels in urine of forest workers applying silvicides. Arch. Envir. Health 24:277-280.

Tseng, W.P. (1977) Effects and dose-response relationships of skin cancer and blackfoot disease with arsenic. Envir. Health. Persp. 19:109-119.

Vahter, M. (1981) Biotransformation of trivalent and pentavalent inorganic arsenic in mice and rats. Envir. Res. 25:286-293.

Vahter, M., Marafante, E., Lindgren, A. and Decker, L. (1982) Tissue distribution and subcellular binding of arsenic in marmoset monkeys after injection of 74As-arsenite. Arch. Toxicol. 51:65-77.

Vahter, M. and Envall, J. (1983) In vivo reduction of arsenate in mice and rabbits. Envir. Research 32:14-24.

Vahter, M., Marafante, E. and Dencker, L. (1984) Metabolism of 74As Dimethyl arsonic acid in mice and rats. Arch. Envir. Contam. Toxicol. 13:259-264.

Valentine, J.L., Reisbord, L.S., Kang, H.K. and Schluchter, M.D. (1987) Arsenic effects on population health histories. In: Trace Elements in Man and Animals 5. Mills, C.F., Bremner, 1. and Chesters, J.K., Eds. Commonwealth Agricultural Bureaux, Aberdeen, Scotland.

Von Endt, D.W., Kearney, P.C. and Kaufman, D.D. (1968) Degradation of monosodium methanarsonic acid by soil microorganisms. Jour. Agric. Food Chem. 16:17-20.

Wagner, S. and Weswig, P. (1974) Arsenic in blood and urine of forest workers applying dimethylarsinic acid. See Norris, L.A. (1974a) Appendix 3

Wan, M.T., Watts, R.G. and Moul, D.J. (1987) Toxicity to salmonids of the herbicide glyphosate (Roundup®) and its surfactant (MON 0818) Regional Program Report 86-18, Environment Canada, Pacific and Yukon Region.

Warren, H.V., Delavault, R.E. and Barakso, J. (1968) The arsenic content of Douglas-fir as a guide to some gold, silver and base metal deposits. Canadian Min. and Metal. Bull. July, 1968:860-866.

Woolson, E.A. (1977a) Fate of arsenicals in different environmental substrates. Envir. Health Persp. 19:73-81 (1977b) Generation of alkylarsines from soil. Weed Science 25:412-416. (1986) Burning cacodylic acid-treated oak trees: How safe? Forest Prod. Jour. 36:49-52.

Workers' Compensation Board of British Columbia (1980) Industrial Health and Safety Regulations.

Yamanaka, K., Hasegawa, A., Sawamura, R. and Okada, S. (1989) Dimethylated arsenics induce DNA strand breaks in lung via the production of active oxygen in mice. Biochem. Biophys. Res. Commun. 165:43-50.

Yamauchi, H. and Yamamura, Y. (1983) Concentration and chemical species of arsenic in human tissue. Bull. Envir. Contam. Toxicol. 31:267-277.

Yamauchi, H. and Yamamura, Y. (1984) Metabolism and excretion of orally administered dimethylarsinic acid in the hamster. Toxicol. Appl. Pharmacol. 74:134-140.

Yamauchi, H., Yamato, N. and Yamamura, Y. (1988). Metabolism and excretion of orally and intraperitoneally administered methylarsonic acid in the hamster. Bull. Envir. Contam. Toxicol. 40:280-286.

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