Toxicology and Potential Health Risk of Chemicals that May Be Encountered by Workers Using Forest Vegetation Management Options

PART V: RISKS TO WORKERS USING HEXAZINONE FORMULATIONS (PRONONE® AND VELPAR®)

Forest Practices Branch
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7

Abstract

Hexazinone is a broad-spectrum soil active herbicide used for site preparation, conifer release and in nurseries. The acute toxicity of hexazinone is low. Dermal toxicity is also very low, indicating poor absorption across the skin. It is irritant to the eyes, but does not produce skin sensitization. In a standard 90-day subchronic assay, rats consuming a diet containing 5000 ppm hexazinone (about 250 mg/kg/day) were unaffected except for slightly decreased weight gain. There was no effect at 1000 ppm. Dogs given 200 mg hexazinone/kg/day were unaffected except for modest weight loss.

Two-year cancer studies of rats and mice indicated no detectable carcinogenic response, and there were no pathological changes other than benign adenomas (harmless tumours) found in the livers of mice maintained on a diet containing 10,000 ppm hexazinone. Lifetime systemic no-effect levels were 10 mg/kg/day for rats and 35 mg/kg/day for mice. Some liver effects were detectable at higher dose rates. Hexazinone was found to have no effect on reproduction and did not cause birth defects at doses that can be tolerated by the dams. It was shown to have limited mutagenic potential.

Risks associated with use of hexazinone in forestry are slight, limited to eye and skin irritation. If daily intake is on the order of 0.03 mg/kg, which is to be expected of a worker who is moderately careful, the safety factor based on the no-observable-effect level (NOEL) of 10 mg/kg/day will be over 300. Hexazinone and its metabolites are excreted rapidly, without accumulating in any species. Small quantities of hexazinone can be found in milk of heavily exposed mammals but the use pattern precludes significant exposure of lactating animals. There is no calculable carcinogenic or reproductive risk for hexazinone exposure to trained applicators using safety gear, and following the label instructions and proper application standards.

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Foreword

Vegetation management is an important reforestation activity for controlling competing vegetation or brush encroachment of young tree seedlings. The activity is necessary to get tree seedlings to free-growing status in most new forest sites established in areas that have been harvested or denuded by wildfire, insects and disease.

There are a number of options for managing forest vegetation. The treatment options include prescribed fire, herbicides, manual removal with hand and power tools (e.g., girdling and slashing tools, chain saws and brush saws), placement of mulch mats, mechanical techniques with heavy machinery, and biological methods. The use of livestock (e.g., sheep) is currently the common biological control technique employed in reforestation areas in British Columbia. Biological methods with insects or specific pathogens is used on forest rangelands for noxious weed control but not commonly used for vegetation control in young forest stands.

The selection of a treatment option involves a decision-making process based on integrated vegetation management concepts that include evaluation of the need for treatment, consideration of all the approved treatment methods and choosing the most appropriate treatment method, monitoring and evaluation. Factors considered in selecting a particular method are the ability of the method to meet the required reforestation objectives, the impact of the treatment at the specific site on human safety and the environment (e.g., recreational resources, fish and wildlife and their habitat, range resources and water supply), as well as the economics of the treatment.

This publication is one of a series of papers that evaluates the potential health effects on forest workers using the commonly employed methods of vegetation control. Other papers in the series are listed at the end of this paper. The emphasis is on risks associated with exposure to chemicals during the use of two most important methods for controlling competing vegetation in regenerated (natural or planted) forest areas. These methods are the use of herbicides and manual removal or control with handheld-motorized (power) equipment.

The herbicides discussed are those that have been commonly used in forestry in Canada. The database on health effects of herbicides is extensive and permits reliable estimates of risk. For components of chain saw exhaust and fuels, there is also voluminous background of toxicological information, but exposure data in forestry is limited. Nonetheless, there is enough information to develop preliminary assessments of potential health effects. While there appears to be a high incidence of physical injury associated with manual methods of brush control, there is virtually no validated data on which to base estimates of risk. The existing data are those of workers compensation boards and insurance companies but such data are generally difficult to obtain or are not specifically enough to characterize the kind of activity that leads to injury.

The information in these reports should provide the basis for important decisions about the way vegetation management in forestry should be carried out, and the use of some forestry activities as a source of assisted employment.

Contents

Introduction

Hexazinone is a broad spectrum, soil active herbicide available for forestry uses in nurseries, in site preparation and for conifer release. Most other uses are on rights of way and industrial facilities. It has relatively few uses on food crops. Hexazinone is available in granular and liquid formulations. In the formulations Pronone 5® and Pronone 10®, hexazinone is coated over montmorillonite clay granules, and coated with water-soluble binders. Net concentrations of active ingredient are 5 and 10 percent.

Hexazinone has attracted little toxicological interest beyond the data needed for registration because of its inherent low toxicity and limited potential for exposure. As a result, published literature on hexazinone toxicology is relatively modest. Most of the pertinent detailed information is in the registration documentation provided to Canadian and US regulatory agencies. However, the toxicology data developed for registration of hexazinone has been reviewed in the open literature by Kennedy (1984) and Kennedy and Kaplan (1984). There are no more recent publications on mammalian toxicology of hexazinone as such in the refereed literature. The environmental behaviour of hexazinone and its effects on lower organisms continues to receive attention because of the variety of environmental characteristics any pesticide might encounter. Most aspects of behaviour of hexazinone in the environment are of limited direct interest in considering worker safety.

The US Forest Service "Pesticide Background Statements, Volume I. Herbicides" (1984) reviews all available sources to that time, including proprietary registration data. The information is also incorporated in the USDA-Forest Service (1988) Pacific Southwest Region (Region Five) Environmental Impact Statement (EIS) as well as that of the Southern Region (Region Eight) (USDA-Forest Service, 1989) for reforestation vegetation management.

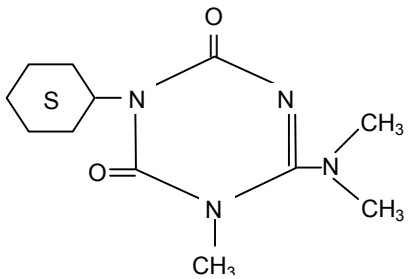
In 1994, the United States Environmental Protection Agency (USEPA) published the Reregistration Eligibility Decision (RED) for hexazinone, based on data in the above documents and that requested in the 1988 Registration Standard issued by the agency. Because all of the available data is collected in the above reviews, citations for specific findings are not referenced.

Absorption, Distribution, Metabolism and Excretion of Hexazinone

There is no direct data on absorption of hexazinone across human skin. Absorption of the granular or powder (water dispersible) formulations is slight because particulate material has little opportunity to become soluble in the fats of skin cells, a process that expedites absorption across those cells. Some liquid formulations include 40-45% ethanol to bring the poorly soluble hexazinone into solution, and the ethanol may increase penetration to some extent. Dermal toxicity studies indicate that very high doses are necessary to produce a response, indicating poor absorption across the skin.

Hexazinone is excreted quite rapidly, but unlike most of the common forestry herbicides, it is subject to minor changes (metabolism) in the body. The hexazinone molecule is illustrated here to provide a sense of the slight changes the molecule undergoes.

Structural Formula of Hexazinone



As many as eight different, similar products may be formed, all resulting from changes at the several side groups and atoms around the basic triazine ring. Both the triazine and cyclohexyl rings remain intact. Such a pattern is typical of the triazine herbicides, and renders them more soluble and more easily excreted. None of these alterations appears to change the toxicological profile appreciably, other than producing products with lower toxicity, primarily because excretion rate is increased.

Experiments with radiolabeled hexazinone administered to rats indicated that most of the administered material was excreted in urine and faeces in 24 hours, and elimination approached completion in 72 hours. If the animals were pretreated with unlabeled hexazinone before administration of labelled material, metabolism was accelerated, probably due to induction of liver enzymes acting on the molecule. (Induction is a normal process in which synthesis of enzymes that act on foreign molecules or endogenous hormones is stimulated by presence of the target chemical.) Tissue residues were not detectable.

Studies of goats indicate that hexazinone can move into milk in low concentrations. In cows fed 25 ppm for 30 days, only small amounts of one metabolite were found in milk. Because hexazinone has some fat solubility it is not remarkable that traces are found in milk. However, the main use of hexazinone is in forestry, and milking animals are not likely to be exposed to this herbicide. It is possible that nursing animals in the wild may be exposed, but movement into their milk would be so limited that there should be no impact. The three generation reproduction assays discussed below show that high concentrations in the diet of nursing mother rats did not have an adverse effect on pups.

While all of the products of hexazinone metabolism have been identified, the proportions of each product and the remaining parent molecule probably vary with species and the dose rate. These differences have not been fully defined. The metabolites formed by microbial and chemical processes in the environment are similar to those formed in the body; intake of environmental breakdown products is not likely to produce responses different from those of the parent compound.

Acute and Subacute Toxicity

The short-term toxicity of hexazinone has been reviewed by Kennedy (1984). Evaluation in various species of mammals uniformly shows hexazinone to have slight to moderate acute toxicity (toxicity resulting from single dose or very short term treatment). Oral median lethal doses (LD_{50}) range upward from 800 mg/kg body weight in guinea pigs to 1700 mg/kg in rats to an unknown level in excess of 3400 mg/kg in dogs. (Higher doses cannot be given to dogs because hexazinone at such levels induces vomiting.) The LD_{50} of hexazinone injected intraperitoneally in rats is over 500 mg/kg. The

low toxicity even when potential impact is maximized by such treatment indicates that hexazinone has little ability to interfere with normal cellular function.

Systemic toxicity of hexazinone applied to the skin is very low. In rabbits the maximum dose that could physically be applied was almost 5300 mg/kg, which did not cause lethality. This very high dose indicates poor skin absorption. The rabbit is used because its skin is perhaps the most permeable among laboratory species, and it is often intrinsically more sensitive to chemicals than other species. Hexazinone is a skin and eye irritant but did not produce dermal sensitization (development of allergy) in guinea pigs, the usual test species for such reactions.

USEPA characterizes the acute toxicity of hexazinone as group III for oral intake, and IV for dermal and inhalation effect. In other words, acute toxicity is very low. It is a severe eye irritant, however (USEPA, 1994).

Metabolites of hexazinone (products of alteration by the body) that have been tested for acute toxicity in rats are several folds less toxic than the parent compound. Acute assays do not define longer term potential toxicity, but on a comparative basis, such tests are an indication that there would be little difference from the parent in long term effects.

More persuasive is the fact that because of rapid metabolism, animals on long term study were continually exposed to all of the metabolites at levels much higher than can be acquired from products of degradation of hexazinone in the external environment.

In a range-finding study done to determine appropriate dose rates for long term study, oral doses of 300 mg hexazinone/kg/day were given to six rats for five days, with a two day rest, then given for five additional days. Total dose over 12 days was 3000 mg/kg. Half the animals and their controls were examined at four hours after the last dose and the rest were observed for 14 days. A slight weight loss was observed, but there was no evidence of pathologic or clinical change.

Subchronic and Chronic Systemic Toxicity

Kennedy and Kaplan (1984) have reported on the effects of hexazinone administered over periods up to two years in rats and mice. Over a 90-day trial, rats fed diets containing 5000 ppm hexazinone (approximately 250 mg/kg/day) grew slightly less rapidly than controls, but at 1000 ppm (50 mg/kg) there were no observable effects. No other effects were evident in any treated group.

A 90-day study of dogs was also conducted to obtain information from a non-rodent species. Hexazinone concentrations in feed were 200, 1000 and 5000 ppm (approximately 8, 40 and 200 mg/kg/day). The larger size of dogs also provides the ability to study of diagnostic blood chemistry in more detail. At the highest dose rate there was a modest weight loss, and limited alterations in clinical chemistry measurements, but generally there were no discernable effects. At lower dose rates there was no change in any determination. At all dose rates there was no evidence of tissue pathology due to the treatment.

The two year cancer studies in rats and mice were also designed as a source of information about other general toxic responses to hexazinone under conditions of long term exposure. Clinical evaluations started at the end of the first year, when some animals were removed for pathological examination. Interim observations provide two kinds of important information. The rate of development of effects over time may be judged, and early changes that might have been repaired and not visible at the end of the test period may be seen.

Male rats fed 2500 ppm (approximately 125 mg/kg/day) and females fed 1000 and 2500 ppm weighed less at the end of the study than those in other groups. There were also minor alterations

in some parts of the clinical chemistry profile at the highest doses. Organ weight changes were found in animals at the higher dose levels, but there were no pathological alterations at any dose rate other than increased numbers of white blood cells. Survival was normal at all levels. No other evidence of intoxication was found. The no-effect level was considered to be 200 ppm, which translates to a lifetime daily dose of about 10 mg/kg.

In a similar investigation, mice were fed diets containing 200, 2500 and 10,000 ppm hexazinone for two years. The two highest dose rates caused decreased weight gain; liver weight was increased in animals at the highest dose rate. Pathological change in the form of liver hypertrophy, focal necrosis and liver adenomas and carcinomas was increased over historical and concurrent controls at the highest dose rates. (See discussion of carcinogenicity below.) No other changes were found. The no-effect dose rate was considered to be 200 ppm, which in mice is about 35 mg/kg/day.

The difference in estimated dose rates between mice and rats at the same dietary concentration results from the higher consumption of feed per unit weight as animals decrease in size. Weights of rats in the study reported were about 100 grams at the beginning of the study and increased to about 700 grams for males and about 500 grams for females by the end of the two-year period. (These weights are consistent with unrestricted access to feed.) Male mice began at 28 grams and finished at about 40 grams, and females began at 22 grams and weighed about 35 grams at termination of the study.

A 12-month feeding study of Beagle dogs was conducted at dietary intakes of 0, 200, 1500 and 6000 ppm. At the highest dose rate various blood chemistry, haematology and non-neoplastic pathology findings indicated significant effects on the liver. The no-effect level was 200 ppm, which is equivalent to 28 mg/kg/day for males and 34 mg/kg/day for females.

Reproductive and Developmental Toxicity

After 90 days, in the long term test discussed in the preceding paragraphs, six rats of each sex at each dose rate were selected for a range-finding one generation reproduction study, with diets containing 1000 and 5000 ppm hexazinone. (Range-finding studies are designed to aid in determining dose rates for larger and longer-term studies.) Each female was mated with three males from the same dose group. There was no effect on fertility, litter size or survival in either treated group. Pups from the parents receiving the highest concentration weighed less than those of the 1000 ppm and control groups, however.

A more detailed three-generation reproduction assay was conducted in rats in parallel with the two-year study of carcinogenicity and long term toxicity. The program included five groups of 30 animals of each sex. Concentrations of hexazinone in the diets of the respective treated groups were 200, 1000, and 2500 ppm hexazinone in the diet (approximately 10, 50 and 125 mg/kg/day). There were two control groups.

After 90 days on the diets, 20 males and 20 females from each group except one control group were selected for the reproduction study. Each female was mated with each of three males from the same group, and represented the parent generation. At weaning the offspring were placed on the same diet as the parents and were maintained on that diet through weaning of their offspring. At about 110 days of age, one male and one female were picked from each litter to be the parents of the second generation and the same process was followed to produce the third generation. Each generation of offspring was examined for any effects of the treatment. The original parents were then maintained as part of the carcinogenicity study.

All reproductive indicators were normal, except that in the second and third generation, pups at the 2500 ppm dietary concentration grew slower than did controls.

The USEPA RED (1994) does not discuss the above work, published by Kennedy and Kaplan (1984). Why the latter study was not evaluated in the RED is not known. The RED discusses a two generation reproduction study in rats as being "the one study available," with no comment as to the acceptability or lack thereof of the work described by Kennedy and Kaplan.

In the two-generation study, the continuous dietary concentrations were at 0, 200, 2000 or 5000 ppm, approximately 10, 100 and 250 mg/kg/day. The middle and high dose rates caused decreased maternal weight and decreased pup weight, and the highest dose caused decreased pup survival in the second litter. The no-observed effect level for both maternal systemic and reproductive effects was 200 ppm.

Teratogenicity of hexazinone (ability to cause birth defects) has been evaluated in rats and rabbits. In the rat study, pregnant females were fed diets containing 200, 1000 and 5000 ppm hexazinone from the sixth to the fifteenth day of gestation and placed back on the normal diet on day 15. (The sensitive period of organ development when birth defects can be caused in rats is between days six and 15 of gestation.) Pups were surgically removed on day 21 and examined in detail. In this study only the controls and the pups coming from the 5000 ppm group were examined, with the expectation that if any abnormalities were found, the animals in groups receiving lower doses would be examined. There was no evidence of birth defects in rats at a maternal dietary intake of 5000 ppm (approximately 250 mg/kg/day) during the period of organ formation, although there was some evidence of maternal toxicity at an intake of 1000 ppm.

A later study in rats utilized doses of 0, 40, 100, 400 and 900 mg/kg/day, administered by stomach tube. There were maternal systemic effects, including increased liver weight, at the two highest doses. At those doses foetal weights were decreased, and an increased incidence of kidney defects and delayed ossification of some bones. No-effect doses for maternal and foetal effects were 100 mg/kg/day.

In the rabbit study, females were artificially inseminated and given the test material by stomach tube from day 6 to day 19, at doses of 20, 50 and 125 mg/kg. The lower dose rate for rabbits reflects the somewhat greater general sensitivity of this species. The highest dose rate produced no teratogenic response, but did cause some maternal toxicity. At 50 mg/kg there was no detectable effect.

Hexazinone does not cause reproductive or developmental effects at any dose that can be tolerated by the parents.

Mutagenicity of Hexazinone

Mutagenicity or genetic toxicity of a pesticide is evaluated for two reasons. There is a normal background of genetic disease in the human population, and use of chemicals should not add to the burden. Possibly more important, the first steps in development of cancer are mutations. Chemicals that do not cause genetic damage in tests such as those discussed below are not likely to initiate the carcinogenic process.

The single positive finding was evidence of chromosome damage in cultures of Chinese hamster ovary cells. The effect was seen at concentrations of 4 to 5 mg hexazinone and its metabolites per millilitre of culture medium (4000-5000 parts per million), but not at 2 mg/ml.It is not possible to directly relate concentrations used in such a test to dosage in a mammal, but some perspective can be gained by comparing the concentration in the culture dish to hypothetical tissue concentrations. It may be assumed that both the culture medium and the animal body are about 70% water. It is also assumed for the purpose of this comparison that all administered hexazinone stays in the body with no excretion. A concentration of 5 mg/ml in the test would then be similar to that produced in the animal by a dose of 5000 mg/kg. This comparison ignores the fact that 5000 mg/kg is

more than a lethal dose, and ignores the rapid excretion of hexazinone from the intact animal.

Other mutagenicity assays were negative. Ames tests were negative, with five different tester strains of Salmonella, with and without reaction by liver enzymes involved in drug metabolism and activation. (Most chemicals, including direct carcinogens, are reactive with genetic material only after metabolism in the body by such enzymes.) Chinese hamster ovary cells in culture were used in a system to detect point mutations; the results were negative. Doses to rats of up to 1000 mg/kg did not produce chromosomal alterations in bone marrow cells, even though there was visible intoxication at doses of 300 mg/kg and above. Hexazinone also failed to induce unscheduled deoxyribonucleic acid (DNA) synthesis in isolated liver cells, indicating that there was no DNA damage. It is reasonable to conclude that the existing data is sufficient to indicate that hexazinone does not represent a mutagenic threat.

Carcinogenicity of Hexazinone

Two-year feeding studies utilized dietary concentrations of 200, 2,500 and 10,000 ppm for mice (approximately 35, 440 and 1,100 mg/kg/day) and 200, 1,000 and 2,500 ppm for rats (approximately 10, 50 and 125 mg/kg/day). In the assays on rats there was no evidence of carcinogenicity, but there was evidence of non-neoplastic change, consisting of hyperplasia and benign adenomas in the high-dose mice.

USEPA (1995) has classified hexazinone in group "D," not classifiable as to human carcinogenicity. This means essentially that the data are adequate and do not indicate carcinogenicity, but neither is the data sufficiently conclusive that it can be stated that hexazinone cannot cause tumors. This status apparently results from the findings of liver hyperplasia and benign adenomas at high doses in mice, and a positive assay for chromosome aberrations. For comparison, Group "E" in the USEPA classification indicates that a chemical is considered to be "not carcinogenic in humans," and Group "C" refers to chemicals that are possible human carcinogens.

The data do not show evidence of carcinogenicity, so it is not possible to estimate a potency slope from which to make a quantitative risk estimate (USEPA, 1993). The seemingly ambiguous classification is best explained by quoting the RED document (USEPA, 1994):

"Peer Review: The carcinogenic potential of hexazinone was evaluated by OPP's Carcinogenicity Peer Review Committee (CPRC) on July 27, 1994. The Committee concluded that hexazinone should be classified as a Group D chemical. It was also recommended that, for the purpose of Risk Characterization, the Reference Dose (RfD) approach should be used for quantification of human risk." (OPP is the Office of Pesticide Programs of EPA.)

"The CPRC decision to re-categorize hexazinone as Group D was based on the registrant's submission of a re-evaluation of mouse liver sections (based on the latest diagnostic criteria for mouse liver neoplasms). Based on these new data, there was only a statistically significant increasing trend in combined adenoma/carcinoma tumors in female CD-1 mice. It was noted though, that combined adenoma/carcinoma hepatocellular tumors in female CD-1 mice occur at a low rate (<5% in historical controls, and the incidence of these concurrent controls was only 1-2%) whereas the incidence for combined liver tumors at the HDT was 9%." (HDT is Highest Dose Tested.)

"Overall it was felt that the animal evidence was equivocal (not entirely negative, but yet not convincing) based on the new readings. Based on these data, the only statistically significant increase was in the female mice (by trend test, not by pairwise comparison with controls). Additional testing would not provide any clarification, therefore hexazinone was re-categorized as a Group D; not classifiable as to human carcinogenicity."

Estimation of risk associated with hexazinone exposure is therefore to be based on systemic or general toxicity, not potential for genetic toxicity or carcinogenesis.

Exposure to Hexazinone

In the US Forest Service Environmental Impact Statement (EIS), Vegetation Management for Reforestation in the Pacific Southwest Region (USDA-Forest Service, 1988) exposure estimates for hexazinone based on data for other chemicals, are 0.065 mg/kg/day for typical backpack application and about 0.02 mg/kg/day for mixer/loaders in aerial application. In the Forest Service EIS for the Southeastern Region (USDA-Forest Service, 1989), the estimate of typical doses resulting from exposure to hexazinone in backpack application is stated to be 0.01 mg/kg/day and about 1.0 mg/kg/day at maximum. The latter figure appears to be incorrect by an order of magnitude, possibly because the number of days in the unusually long application season for hexazinone appears to have been somehow factored into the daily dose estimate. Comparison with exposure and dose measurements for 2,4-D and estimates for other herbicides based on 2,4-D also indicates at least a ten-fold error. Typical spot treatment was estimated to lead to doses of 0.01 mg/kg/day and maximum doses were estimated to be 0.035 mg/kg/day, which are more realistic figures.

A study of worker exposure to hexazinone has been conducted by the Centre de Toxicologie de Quebec for the Quebec Ministry of Forests (Bertrand and Dugal, 1988). It includes a limited examination of hexazinone metabolism in two human volunteers. Only the summary of the study is available. It appears that the intent of the study was to determine which application methods would keep human exposure below certain predetermined levels. In this case, a standard of 5000 micrograms per litre in urine was used, based on review of toxicological data and scaling factors to account for differences in size. If a body weight of 60 kg and daily urine volume of 1.4 litres are assumed, this standard translates to a daily dose of about 0.12 mg/kg/day. That level is not likely to have effects, but it is higher than even the US Forest Service estimates, which include very conservative assumptions about rate of absorption across the skin. Actual measures of contact with skin and other surfaces were apparently not made. A number of useful observations were made in this work, however. Spot gun application resulted in high exposures beyond those considered acceptable. This is an interesting finding, because spot gun use is usually considered to result in low exposure. There may have been equipment characteristics that resulted in unusual exposure. Use of granules and a technique of applying a band of hexazinone around the base of a stem resulted in very low contact.

Other findings were consistent with numerous studies of other herbicides. There was no correlation between duration of exposure and urinary output. Protective equipment and its proper use were very important in decreasing exposure, as were availability of clean eating and rest sites. The status of equipment also played a significant role in exposure.

Other work is in progress to quantify hexazinone exposure more directly. It would appear that studies of exposures as measured by urinary excretion of hexazinone and its metabolites should be undertaken as well as skin absorption studies.

The existing data suggests that some applicators may receive doses of 0.03 mg/kg/day, or more, but there is no way to confirm this estimate. This exposure will be used provisionally to estimate risks associated with hexazinone use.

Assessment of Health Risks Associated With Use of Hexazinone

As discussed earlier, hexazinone is placed in group "D" in USEPA rankings of substances for carcinogenicity. The animal studies do not indicate a carcinogenic response.

The exposures that may be experienced by applicators over a lifetime work history are expected to produce no carcinogenic risk. The no-observed-adverse-effect level (NOAEL) for systemic toxicity is considered to be 10 mg/kg/day, based on lifetime exposure of rats. Worker exposure to hexazinone will occur only a limited number of times, but the lifetime NOAEL is used as a conservative comparison nonetheless. The reproductive NOAEL is set at 50 mg/kg/day. USEPA (1993) quotes a reference dose (RfD) of 0.033 mg/kg/day. The reference dose is the daily dose calculated to have virtually no probability of effect when taken in over a lifetime. It is derived from the lowest NOAEL, with an automatic safety factor of 100, and additional factors based on quality and amount of data. In this case an additional factor of three was included as a recommendation to raise the safety factor to 300.

The margin of safety for systemic effects is estimated by United States Forest Service (USFS) at 970 for backpack applicators in typical operations. The safety factor for maximum exposure should be about 100, taking into account the apparent error in their document. For reproductive effects the safety factors are five times higher.

The typical intake is estimated by USFS to be about one-third of the RfD, and the maximum is about three times greater than the RfD. This does not imply that an effect will occur at such exposure, even with long term exposure. It does mean that a recommended certainly safe dose rate has been exceeded. The USFS exposure estimates are conservative, in part because the authors expect poor practices by some applicators. Also, it must be remembered that short-term exposure criteria are based on data from lifetime treatment.

If the daily dose is taken to be 0.03 mg/kg/day, the safety factor for systemic effects will be about 333. This dose is also equivalent to the RfD of 0.033 mg/kg/day.

If concentrated hexazinone is spilled on the body and not cleaned up at once, the exposure and dose could be relatively high. USDA-Forest Service (1989) estimates a dose of 120 mg/kg based on hypothetical volumes and concentrations. Obviously there is no standard spill, and any large number is as good as any other; the estimate is largely an exercise. 120 mg/kg is 12 times the NOAEL. Effects can only be speculated upon, but if clothing is removed and the worker washes immediately, the actual absorbed dose will be close to zero. Some skin and eye irritation is likely, however.

Overall, risks associated with use of hexazinone are not significant. Workers are likely to remain within a 100-fold safety factor for systemic effects or reproductive responses. Workers can reduce exposure to hexazinone (or any herbicide) by proper use and care of protective equipment and clothing, use of clean eating and rest areas, and having good wash facilities available for spill cleanup and hygiene.

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Glossary

Active Transport – Molecules within cells or in fluids outside the cells may move across membranes passively by diffusion**,** just as a drop of dye might spread in water, or by an energy consuming process where the molecule is moved across a membrane into another compartment where the concentration may be higher. Without this "pumping" mechanism molecules would move the wrong way. The best examples of this active transport process with respect to herbicides is the movement of organic acids like 2,4-D and triclopyr from the brain to the blood and from the blood into the kidney tubules for excretion. Glyphosate, on the other hand, moves out by diffusion without help from active transport.

Acute toxicity – (Short term toxicity) –Acute toxicity is the quality or potential of a substance to cause injury or illness from a single dose or short period of exposure. See **subacute, subchronic and chronic.**

Adjuvant – Any additive to a pesticide formulation that is not active itself, but is intended make the active ingredient work better.

Cancer – A malignant growth of potentially unlimited size that invades local tissues, and may spread to other parts of the body

Carcinogen – A chemical capable of inducing cancer.

Carcinogenic – Capable of causing cancer.

Chronic toxicity – (Long-term toxicity) – Chronic toxicity is the quality or potential of A substance to cause injury or illness after repeated exposure for a long period of time. Chronic toxicity tests run for a year or more; for rodents the period may extend through the entire life span. A chronic effect persists for months or years and may arise from acute or long term exposure. See **acute, subacute, subchronic.**

Contaminant – In a formulation, usually residues or impurities from the manufacturing process present in small quantities. Contaminants must be identified to the regulatory agency, which judges whether they are of concern.

Deoxyribonucleic Acid – See **DNA.**

Degradation – Breakdown of a compound by physical, chemical or biochemical processes into basic components with properties different from those of the original compound.

Dose – The amount of a chemical that actually enters the body to be distributed to all of the organs and cells. Distribution to tissues and cells is selective, and depends on the nature of the chemical and characteristics of each kind of cell.

Dose-response relationship – The central idea in toxicology and in pharmacology (which is the science dealing with beneficial effects of therapeutic drugs). As the dose (or concentration) of a chemical increases, the effect increases, and as the dose is lowered, the effect becomes less. This response pattern applies to every interaction between a chemical and a biological system, whether human, fish, bacteria or any other kind of organism or tissue. The dose-response relationship is absolutely essential to judgement of the effect of any chemical.

DNA (Deoxyribonucleic Acid) – The genetic library in each cell that contains all of the instructions for building and operating the body. Each kind of cell contains all of the information for the whole body. Only the information needed for each kind of cell is used by that cell; the rest is repressed. Liver cells do not try to be muscles, and muscles do not try to become brain cells, but they contain all of the information**.**

Enzymes – Complex proteins that catalyze (expedite) biochemical reactions. See Metabolism.

Epidemiology – The scientific study of the cause, distribution, and control of epidemics or other disease in a region. In the context of these reports, epidemiology is the study of possible associations between environmental and occupational chemicals and occurrence of diseases. The term "associations" is used in its statistical sense, which means that the relationship cannot demonstrate cause and effect.

Exposure – Amount of a chemical that reaches a surface from which it might be absorbed. The dose is some fraction of the exposure. Exposure does not include material that is on nearby foliage or other surfaces. It is only the material that reaches the skin (by contact), respiratory tract (by inhalation) or digestive tract (by ingestion).

Foetus – The later stage of mammalian development in the womb. In human, this refers to the unborn child during the period of uterine life from the end of the second month until birth.

Foetal toxicity – Direct effects of a toxicant on the foetus, independent of effects on the mother.

Formulation – A complete pesticide preparation as sold by a manufacturer for practical use. It includes the active ingredient and any necessary adjuvants and solvents. For use, it may or may not require further dilution or mixing with other substances. Formulation can also be defined as the process used by manufacturers in preparing a pesticide for practical use.

Half-life – The length of time required for disappearance of half of the material present in an organism or in environmental media. It is a more useful idea than "persistence" because it allows prediction of the time required to reach low target levels with out making measurements over exceedingly long periods. A better term is "Half-time," because the information only relates to a given location, and says nothing about the processes that deplete the chemical. If it evaporates or is carried away intact by water it may still exist in its original form. The term "half-life" originated with description of radioactive decay, in which elements become a totally different substance. The English language sometimes loses precision as it evolves.

Hazard – The kind of effect that a chemical can cause. Cancer, liver disease, skin irritation, reproductive problems, or some other more or less specific response that can be defined and measured. The term is also used non-specifically to signify any dangerous situation.

Herbicide – A chemical substance or cultured biological organism, used to kill or suppress the growth of plants.

Hormone – A substance secreted by specialized endocrine cells and transported by the blood stream throughout the body to regulate biochemical activity of other cells. Insulin and testosterone are hormones.

Immune system – All of the structures and cells and their products that protect against infectious organisms and against cells of the body that have become altered in the very early development of cancer.

Irritation – A purely local or topical reaction which may include redness, blistering, swelling, burning or itching.

Lethal – Causing death.

LD_{50} – Acronymn for Median lethal dose.

Lethal concentration (LC_{50}) – Rate at which 50 percent of test animals will be killed.

LOAEL – Acronym for lowest-observed-adverse-effect level.

Lowest-observed-adverse-effect level (LOAEL) – The lowest measured amount of a chemical that produces significant increases in frequency or severity of adverse effects in exposed subjects. in the general sense it includes all biochemical, pathological, behavioral, reproductive, genetic and other measurable changes. the

term may also be applied to any specific parameter under observation.

Malignant – Deadly or very injurious. As applied to cancer, invasive of local tissues and metastatic (migration of cancer cells to other tissues).

Margin of Safety (MOS) – The difference between the estimated dose of a pesticide and the NOAEL. A **MOS** of 100 (estimated dose 100 fold less than the NOAEL) is usually considered to assure that no adverse effects will occur.

Median effective dose (ED_{50}) – The dose or dose rate that causes 50% of subjects to respond. The nature of response must be specified, i.e., sedation, elevated blood pressure, death. The ED_{10} is the dose effective in 10% of animals.

Median lethal dose (LD_{50}) – The dose of a chemical, biological agent, or other substances that causes death in 50% of defined test animals.

Metabolism – the sum total of the biochemical reactions that a chemical undergoes in an organism. The processes include biochemical (enzymatic) reactions in the cells of the body that convert nutrients to energy and structural materials of the body; reactions that change wastes so they can be removed; and reactions that convert foreign substances, such as some pesticides to forms that can be excreted.

MOS – Acronym for margin of safety.

Mutagenic – Capable of producing genetic changes.

Mutagens – Chemicals that are able to induce gene or chromosome damage that is stable and survives cell division to reach the next generation of cells. See **mutation.**

Mutation – Genetic change in DNA of a cell that can be transmitted to the next generation of cells. If in sperm or egg cells, a mutation may be transmitted to offspring. If in somatic (body) cells such as liver, muscle or other organs, a mutation may pass to daughter cells in the organ. The change may have no effect on cell function or it may damage the cell, or even imaginably improve it.

NOAEL – Acronym for **no-observed-adverse-effect level.**

No-observed-adverse-effect level (NOAEL) – The dose rate or concentration at and below which no adverse effects can be detected. (See **threshold; SEE LOAEL)** If the estimated dose of a herbicide to a worker is very low compared to the **NOAEL** for the most sensitive effect found in the laboratory, no harmful effect is to be expected.

NOEL – Acronymn for **no-observed-effect level.**

No-observed-effect-level – (NOEL)-Dose of a chemical or biological agent at which there are no biologically or statistically significant effects attributable to treatment. The term can refer to adverse, beneficial or meaningless effects and is falling out of use in toxicology.

Persistence – The duration of measurable concentrations of a pesticide in soil, foliage or other media. (See Half-life.)

Pesticide – Any chemical (or biological product) intended to control or kill pests. Herbicides, insecticides, fungicides are all pesticides. The term is sometimes incorrectly used to mean only insecticide, for example “pesticides and herbicides.”

Reference dose (RfD) – Any oral dose below the RfD is considered unlikely to be associated with an adverse health effect and is therefore acceptable. The RfD is usually based on the most sensitive oral NOAEL, with all appropriate safety factors included.

Registration – The process by which government (e.g., Canadian federal government) authorities determine that a pesticide is suitable for use. Standards of public and worker safety, environmental impact, and usefulness must all be met.

RfD – Acronym for reference dose.

Risk – The probability (likelihood) that some adverse or undesirable effect will take place in the future, as a result of some specified activity. Risk may relate to health, finances or any other kind of undesirable impact. Real risk may be so small that it cannot be distinguished from zero, or so great that it is a certainty. In the context of pesticides, risk is the probability that use of the pesticide will result in some specified harmful effect on workers or the public. Risk assessment is the process of estimating that probability.

Safety Factor – See **Margin of Safety.**

Sensitization – The initial exposure of an organism to specific antigen (foreign protein or chemically altered body protein) resulting in a response of the immune system such that subsequent exposure induces an allergic reaction.

Subacute – Extending over a few days to perhaps a month. This and related terms do not carry defined time periods; consequently there is overlap in the way they are used. See **Acute, subchronic and chronic.**

Subchronic – For experimental studies, relatively long term, but not as long as a chronic study. Typically three to six months. See **acute, subacute, and chronic.**

Teratogen – A chemical that can cause birth defects.

Teratogenic – Relating to or able to produce birth defects.

Threshold – The lowest dose that will produce a given effect. As a practical matter, the threshold is little different from the **NOAEL.**

Tolerance – Lesser than normal sensitivity of an individual to the adverse effect of a chemical. also, the allowable residue of a pesticide on a food or feed crop.

Toxicant – A toxic agent; a poison.

Toxicity – The whole pattern of harmful effects (illness and other undesirable effects) that a chemical can cause. It is a property of the chemical; it does not change.

Toxicology – The group of scientific disciplines that identifies and studies the adverse effects of chemicals on biological systems, whether in the laboratory or in the field.

Toxin – A poisonous substance produced by a living organism. The term is sometimes incorrectly used in reference to non-biological chemicals.

Tumour – a new growth of cells multiplying progressively and without control. Classically, the term means a swelling.

Titles in this Series

1 Principles of health effects evaluation and risk estimation for chemicals that may be encountered in forest vegetation management

2 Pesticide testing for registration: toxicity, environmental behaviour, and epidemiology

3 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part I: Risk to workers associated with exposure to emissions from power saws

4 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part II: Exposure to and absorption of herbicides used in forestry

5 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part III: Risk to workers using 2,4-D formulations

6 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part IV: Risk to workers using glyphosate formulations (e.g., Vision®, Roundup®, Vantage Forestry® and Forza®)

7 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options. Part V: Risk to workers using hexazinone formulations (Pronone®, Velpar® L)

8 Toxicology and potential health risk of chemicals that may be encountered by forest vegetation management workers. Part VI: Risk to workers using triclopyr formulations (Release®, or Garlon 4®)

9 Toxicology and potential health risk of chemicals that may be encountered by workers using forest vegetation management options: Summary

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