

Human Health Assessment: Atrazine

Report for the Minnesota Department of Agriculture's Pesticide Registration Review



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Glossary of Terms and Abbreviations

AHS	Agricultural Health Study
AM	Atrazine mercapturate
aPAD	acute population adjusted dose
ATSDR	Agency for Toxic Substances and Disease Registry
CARC	Cancer Assessment Review Committee (EPA OPP)
CDC	Centers for Disease Control and Prevention
CMG	Common mechanism group
cPAD	Chronic population adjusted dose
CRP	Conservation Reserve Program (USDA)
CWS	Community water system
DACT	Diaminochlorotriazine
DDA	Didealkylatrazine
DEA	Desethylatrazine
DEHA	Deethylhydroxyatrazine
DIA	Desisopropylatrazine
DIHA	Deisopropylhydroxyatrazine
EPA	United States Environmental Protection Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act (EPA)
FFDCA	Federal Food, Drug, and Cosmetic Act (EPA and FDA)
FQPA	Food Quality Protection Act (EPA)
FSH	Follicle stimulation hormone
GDM	Gestational diabetes mellitus
GnRH	Gonadotropin-releasing hormone
GW	Groundwater
HA	Hydroxyatrazine
HRL	Health Risk Limit (MDH)
IUGR	Intrauterine growth retardation
LBW	Low birth weight
LH	Luteinizing hormone
LOD	Limit of detection
LOQ	Limit of quantitation
MCL	Maximum contaminant level (EPA)
MDA	Minnesota Department of Agriculture
MDH	Minnesota Department of Health
MNCPPES	Minnesota Children's Pesticide Exposure Study
MOA	Mode of action
MOE	Margin of exposure
MPCA	Minnesota Pollution Control Agency
MRL	Method reporting limit
NASS	National Agricultural Statistics Service (USDA)
NHL	Non-Hodgkin lymphoma
NTNC	Non-transient non-community water system
OPP	Office of Pesticide Programs (EPA)
PAD	Population adjusted dose
PDP	Pesticide Data Program (USDA)
PMR	Pesticide management region
ppb	Parts per billion (equivalent to micrograms chemical per liter of water sample or ug/L)
PPE	Personal protective equipment
PWS	Public water system
RED	Reregistration Eligibility Decision (EPA)
RfD	Reference dose
SAP	Science Advisory Panel (EPA)
SDWA	Safe Drinking Water Act (EPA)
SGA	Small-for-gestational-age
SOC	Synthetic organic compounds
SW	Surface water
TNC	Transient non-community water system
USDA	United States Department of Agriculture
USGS	United States Geological Survey

Introduction

This report was produced by the Minnesota Department of Health (MDH) and submitted to the Minnesota Department of Agriculture (MDA) to support MDA's special registration review for the herbicide atrazine. Atrazine and its chlorinated metabolites, deethylatrazine (DEA), deisopropylatrazine (DIA), and diaminochlorotriazine (DACT) are the primary focus of this review. In this document, MDH considered human health risks from potential dietary (food and drinking water), occupational, and aggregate exposures, taking into consideration the health of infants, children and adults. In conducting its evaluation, MDH relied upon information available in the published scientific literature, Minnesota-specific drinking water and groundwater data from a variety of sources, and United States Environmental Protection Agency (EPA) reports. Based on currently available information, MDH did not find unacceptable human health risks resulting from currently registered uses of atrazine. However, based on its review, MDH has identified data gaps which require additional information and has provided recommendations to MDA on ways to reduce potential exposures associated with the current use of atrazine. This document consists of six sections. Section I provides background on MDH's responsibility to promulgate rules that establish health-protective limits for atrazine in groundwater. Section II gives an overview of atrazine toxicity and epidemiology. Section III summarizes the exposure assessment. Section IV presents the risk characterization for atrazine and Section V describes recommended actions for MDA to undertake as an outcome of the registration review process for atrazine. Section VI lists report references.

I. Background

The goal of The Minnesota Groundwater Protection Act (Act) is to maintain groundwater "free from degradation caused by human activities." The Act, however, recognizes that this goal is aspirational and not always possible (Minnesota Statutes, section 103H.001). Therefore, the Act authorizes MDH to promulgate health-based guidance values known as Health Risk Limits ("HRLs") for those situations where the goal has not been achieved; that is, where groundwater quality monitoring results show that there is a "degradation of groundwater" (Minnesota Statutes, section 103H.201, subd. (1)).

A HRL is the concentration of a chemical in drinking water that, based on the current level of scientific understanding, is likely to pose little or no health risk to humans, including vulnerable subpopulations. This concentration is a function of how toxic a chemical is (that is, the minimum quantity that will cause health effects), the duration of exposure, and the amount of water individuals drink during the exposure period. In addition, HRLs may incorporate adjustment factors to account for uncertainty in our understanding of a chemical's health risks; chemicals with fewer studies will tend to have a higher degree of conservatism built into the guidance value to compensate for the higher degree of uncertainty.

HRLs are applicable to the use of groundwater as drinking water (Minnesota Statutes, section 103H.005, subd. (3)). The Legislature has declared elsewhere that the "actual or potential use of

the waters of the state for potable water supply is the highest priority use” for the state’s waters (Minnesota Statutes, section 115.063(2)). Thus, HRLs are not intended to be used as standards appropriate for the environment generally, but as conservative, human health-protective upper limits for contaminants in groundwater that may serve as drinking water.

At the federal level, EPA established a Maximum Contaminant Level (MCL) of 3 ppb (as a running-annual average) for atrazine in public water supplies that went into effect in 1992¹. EPA also established a one-day Health Advisory Level (HAL) of 100 ppb. MDH began testing for atrazine in public water supplies in 1993. In 1994, MDH used EPA’s 1991 Integrated Risk Information System (IRIS) Reference Dose (RfD)² value for atrazine to derive a state standard Health Risk Limit (HRL) of 20 ppb for private wells. In 2007, the Water Level Standards Legislation (MN Session Laws 2007, Ch 147, Art 17, sec 2) required HRLs for contaminants in private domestic wells to be the more stringent of either the HRLs or the EPA-derived MCL. As a result, the atrazine MCL value of 3 ppb was adopted as the HRL. This value will remain in effect until such time that MDH derives and promulgates revised values for atrazine.

Current Evaluations:

Within and outside MDH, atrazine and its metabolites remain chemicals of active research and assessment. The EPA Office of Pesticide Programs (OPP) Reregistration Eligibility Decision (RED) document for atrazine was finalized in 2006. EPA recently announced that it will conduct a comprehensive new human health assessment of atrazine in 2010. During this re-evaluation, EPA will consider the potential for atrazine cancer and non-cancer effects, and will incorporate data generated since 2003 from laboratory and population-based studies, including the most recent studies on atrazine and its potential association with birth defects, low birth weight, and premature births. At the end of this process, EPA will decide whether to revise its current risk assessment and whether new restrictions are necessary to better protect public health. MDH is also following the progress of on-going atrazine assessments in EPA’s Office of Water and California EPA.

MDH is actively working to derive updated HRL values for atrazine and its chlorinated metabolites using recently revised methodology (adopted in 2009 health risk limit rules). This revised methodology explicitly incorporates children’s exposure and toxicological sensitivity as well as consideration of multi-duration exposures. Toxicity information relevant for acute, short-term, subchronic and chronic oral exposures is being reviewed. In conducting this review of atrazine and its chlorinated metabolites, MDH is relying on peer reviewed studies and toxicity assessments conducted by EPA OPP and the Agency for Toxic Substance Disease Registry (ATSDR). Based on the information available for this assessment, MDH has found sufficient data to conduct a separate review for the atrazine metabolite diaminochlorotriazine (DACT). The information available for desethylatrazine (DEA) and desisopropylatrazine (DIA) is much more limited. Based on information that is available for DEA and DIA, MDH considers it more appropriate to group these metabolites with DACT, rather than with atrazine.

¹ The atrazine MCL of 3 ppb only considers “parent” atrazine and does not include specific metabolites or degradation products of atrazine.

² A reference dose (RfD) is an estimate of the amount of a chemical that a person can be exposed to on a daily basis that is not anticipated to cause adverse systemic health effects over the person's lifetime.

II. Health Effects

This section summarizes MDH's comprehensive review of the current toxicological and epidemiological data for atrazine. These data come from peer reviewed studies and assessments conducted by EPA OPP and ATSDR.

A. Toxicity

Atrazine is metabolized to four hydroxyl metabolites and three chlorinated metabolites. For some health endpoints (e.g. effects on the hypothalamic pituitary gonadal axis) atrazine and its chlorinated metabolites (DEA, DIA, and DACT) have a similar mode of action (MOA). However, for other related endpoints (e.g. effects on the hypothalamic pituitary adrenal axis) recent studies show that atrazine, and DIA have a different mode of action compared to DACT. Atrazine and its chlorinated metabolites are the primary focus of this review. The hydroxyl metabolites have a different mechanism and are evaluated separately. In deriving toxicity values, it is standard practice to focus on the effect or effects from a single study (the "critical study") that occurred at the lowest observed adverse effect level (LOAEL).

1. Atrazine and its chlorinated metabolites

a. Acute and short-term effects

For atrazine, the critical study and selected endpoints for the acute and short-term durations are based on developmental and reproductive effects as a result of adverse effects on the endocrine system. Developmental, reproductive and multigenerational studies in animals show that exposure to atrazine leads to decreased fetal body weight, decreased litter size, and increased incidence of incomplete ossification. Rats showed the greatest sensitivity to atrazine in a multigenerational study, with a critical effect of decreased body weight in two generations. In an additional study of lactating rats, atrazine given to the dams resulted in a decrease in suckling induced prolactin release and increased incidences of prostatitis in the male offspring. This effect on male offspring was not due to exposure of the pups to atrazine but rather atrazine's endocrine effect on the dams. The exposures in this study also caused adverse effects in male and female reproductive tissue development.

DACT is the predominant metabolite resulting from mammalian exposure to atrazine. Experimental evidence suggests that the other chlorinated metabolites, DEA and DIA, are the initial metabolites of atrazine which are then rapidly further metabolized to DACT. For DACT, the critical study and selected endpoints for the acute and short-term durations are based on developmental effects. In a developmental study in rats, exposure to DACT caused decreased fetal body weight and increased incidence of incomplete ossification.

In addition to the 10x uncertainty factor applied to address extrapolation of animal data to humans and the 10x factor applied to address human variability, other uncertainty factor considerations include concerns that potential adverse neurodevelopmental and neuroendocrine

effects have not been adequately evaluated in the current toxicity databases for atrazine and DACT. Also, no multigenerational study is available for DACT. For atrazine, the multigenerational study appears to be the most sensitive and appropriate for evaluating potential early-life effects. However, the potential for atrazine and DACT to cause additional effects (e.g. altered mammary gland development) at even lower doses is also being investigated.

b. Subchronic effects

For atrazine, the critical study and selected endpoints for the subchronic duration are based on female reproductive system toxicity, the most sensitive endpoint, as a result of endocrine mediated effects. In rats, atrazine alters estrus cycle and suppresses the luteinizing hormone (LH) surge. Atrazine disrupts endocrine function and the estrus cycle mainly through action on the central nervous system. This leads to anovulation, high plasma levels of estrogen, and the possibility of prolonged or permanent estrus. Effects on the endocrine-hypothalamic axis also lead to effects on prolactin levels in rats. LH and prolactin are released by the pituitary gland in response to gonadotropin-releasing hormone (GnRH) from the hypothalamus. LH surge, which occurs in puberty and infancy, differs in rats versus primates. In humans and other primates, LH surge occurs in the third trimester of pregnancy up to three months after birth. Studies in nonhuman primates have shown GnRH pulse, LH and follicle stimulation hormone (FSH) surge vary in timing and magnitude according to sex. In addition to these female reproductive effects, a reproductive study in rats has shown that atrazine significantly decreases intratesticular levels of the male hormone testosterone. Apparent decreases in serum testosterone were not statistically significant. In rat prostate tissue, conversion of testosterone to its primary metabolite was suppressed leading to decreased production of the metabolite. Recent studies have also shown that atrazine and DIA (but not DACT) can affect the hypothalamic pituitary adrenal axis resulting in elevation of adrenocorticotrophic hormone, corticosterone and progesterone levels in male and female rats.

For DACT, the critical study and selected endpoints for the subchronic duration are also based on female reproductive system toxicity. In a subchronic study in rats, DACT caused a lengthening of the estrus cycle leading to persistent estrus and/or diestrus. In this same study, there were no reported biologically significant effects on gross histopathology, clinical chemistry, hematology, or urinalysis, and no effects on serum hormone levels including corticosterone, prolactin, progesterone, and estradiol. The effects on the estrus cycle attributed to DACT are reported at a dose level lower than the dose of atrazine eliciting the same effects. This difference between DACT and atrazine in LOAELs may be due in part to experimental study design (i.e., dose selection), differences noted in the toxicokinetics between atrazine and DACT (i.e., chlorinated metabolites appear to be more readily absorbed than atrazine), or a combination of the two reasons. The same uncertainty factor issues outlined above for the acute and short-term durations will need to be considered for the subchronic duration of exposure to atrazine and DACT.

c. Chronic effects

The database for atrazine includes chronic studies conducted in rats, mice, and dogs. Of note in these studies were observations of cardiac effects in the mouse and dog studies. However, the

most sensitive endpoint is female reproductive system toxicity, which occurs as a result of endocrine mediated effects. Therefore, the subchronic rat study for atrazine noted above will be used as the critical study for the chronic duration evaluation.

Similarly for DACT, there is a one year dog study in which tremors, cardiac effects, and mortality were observed. However, as with atrazine, the critical endpoint is female reproductive system toxicity as a result of endocrine mediated effects. Therefore, the subchronic rat study for DACT noted above will be used as the critical study for the chronic duration evaluation.

In addition to the uncertainty factors taken into account for the acute, short-term, and subchronic time periods listed above, the uncertainty associated with using less-than-chronic studies to evaluate chronic exposures to atrazine and DACT must be considered. MDH will consider the data available for each compound as well as EPA observations that in other studies the changes in estrus cycle between treated animals and controls do not continue to widen as part of the normal aging process, indicating that longer exposures may not lead to a progression of this effect.

d. Cancer

MDH concurs with the current EPA Scientific Advisory Panel's (SAP) analysis and classification of atrazine as "Not Likely to Be Carcinogenic to Humans".

The EPA Cancer Assessment Review Committee (CARC) in 2000 concluded that:

- Although atrazine has been shown to cause hypothalamic-pituitary disruption, the hormonal environment conducive to tumor development in the Sprague-Dawley (SD) rat, increased levels of prolactin and estrogen, is unlikely to occur in humans.
- Prostate glands of laboratory animals do not appear to be a direct target of atrazine toxicity. Atrazine has been shown to result in prostatic inflammation in the adult male rat offspring of treated dams, supporting a neuroendocrine mode of action rather than one that would explain prostate cancer in adult male workers (see Epidemiology section below). Further, the type of hormonal changes caused by atrazine (i.e., decreased prolactin) would not be expected to result in the development of prostate cancer.
- A dose-related increase in ovarian tumor incidence is not seen in any atrazine study. Additionally, the key events in the mode of action established for atrazine, (i.e., decreased serum LH levels and a decreased number of ovulations over a lifetime), are not events hypothesized to be associated with ovarian carcinogenesis in humans.
- There was no increase in any dose group for a lymphoma of any type, including non-Hodgkin's lymphomas (NHL) in atrazine treated SD or F344 rats. The alterations in reproductive hormones with which atrazine exposure is associated have not been linked to increased risk of NHL.

2. Hydroxyatrazine

For hydroxyatrazine, MDH has reviewed information compiled by EPA, described in the 2006 RED document for atrazine. In a developmental study in rats, delayed ossification effects were observed but only at the highest dose tested and were not considered by EPA to be an appropriate acute or short-term toxicity endpoint of concern. For the subchronic and chronic durations, the endpoint of concern is kidney lesions and not reproductive effects via an endocrine disruption mechanism. This determination is based in part on the observations of adverse renal effects in both the subchronic and chronic rat studies. Unlike atrazine, hydroxyatrazine was not carcinogenic in female SD rats. Since neuroendocrine effects are postulated to be part of atrazine's mode of action in causing mammary gland tumors in female SD rats, EPA does not expect the other neuroendocrine effects associated with atrazine (e.g., attenuation of the LH surge) to occur following exposure to hydroxyatrazine.

3. Conclusions

While providing new RfDs or health-based guidance values for groundwater is beyond the scope of this report, some qualitative indications as to the nature of the proposed values are presented here.

For atrazine, the available database is relatively complete and MDH plans to continue assessing the information available for the acute, short-term, subchronic, and chronic durations of exposure. Based on the current level of review of the information available and the magnitude of uncertainty factors that may be applied, it is unlikely that a new MDH value for atrazine will be lower than the current HRL of 3 ppb.

MDH will also complete an assessment for all four noncancer exposure durations for DACT. The toxicological information available for DACT indicates that the critical effects are observed at doses lower than the same effects seen for atrazine. While the nature of these dose differences bears further examination, based on current information, the health-based assessment for DACT indicates a potentially higher level of toxicity than for atrazine for some health endpoints. MDH is continuing to research the potential magnitude of this difference in potency. While available data suggest that DEA and DIA are intermediate metabolites that are quickly converted to DACT, recent studies report that prior to metabolism to DACT, DIA (and potentially DEA) may affect some health endpoints (e.g. hypothalamic pituitary adrenal axis). Due to the limited information available for DEA and DIA, MDH will assess DEA and DIA as compounds having similar effects at similar doses as DACT; however, MDH will consider whether this approach is valid for all MOAs.

For hydroxyatrazine, a quantitative assessment is not being conducted by MDH at this time. In establishing priorities for chemical reviews and assessments, MDH has engaged intra- and interagency partners for input. These partners, including representatives from MDA, MDH, and MPCA, have designated hydroxyatrazine as a low priority chemical. This designation and evidence of a differing mode of action for hydroxyatrazine have led MDH to defer a complete review of this chemical to a later time.

The information and conclusions stated in this summary reflect MDH's current understanding of the available information regarding the noncancer and cancer toxicity of atrazine and its chlorinated metabolites. These chemicals remain a subject of active research as well as a pending EPA re-evaluation.

B. Epidemiology

For epidemiological evaluation, MDH relied on peer reviewed studies and a 2003 review conducted by EPA (EPA 2003b). Epidemiology studies have linked atrazine exposure to adverse health outcomes. The following summaries are presented for health effects for which multiple studies are available and/or there has been suggestive evidence of an association with atrazine; specifically, non-Hodgkin's lymphoma, prostate cancer, reproductive effects, birth outcomes and birth defects.

1. Prostate Cancer and Non-Hodgkin's Lymphoma

The hypothesis that higher risk of prostate cancer is linked to pesticide exposure has been tested in a number of studies (see reviews by Van Maele-Fabry and Willems 2004, Bassill et al. 2007). Epidemiological evaluations of atrazine exposure and prostate cancer have largely focused on a study of workers at the St. Gabriel manufacturing plant in Louisiana. A statistically significant increase in the incidence of prostate cancer was reported among the plant workers (MacLennan et al. 2002). This study, initially funded by atrazine registrant Ciba-Geigy, later by Novartis, and now by Syngenta, has been updated a number of times over the years as more data on the mortality and incidence of disease have become available. The overall conclusion from the most recent EPA review of this study is that most of the increase in prostate cancer incidence at the St. Gabriel plant in Louisiana is likely due to intensive PSA³ screening. EPA asked the Scientific Advisory Panel (SAP) to comment on this conclusion in 2003⁴. The SAP concluded that PSA screening may be only a "partial explanation" for the increase in prostate cancer. The SAP further described the exposure assessment in the St. Gabriel study as "limited" and concluded, "At best, the information permits only a very crude assessment of relative exposure among company employees. Bias towards the null and distortion of dose-response relationships can be expected from the non-differential misclassification bias resulting from the use of this information to classify exposures." The most recently published study of this cohort concluded that the increase in cases was entirely attributable to the confounding effect of increased PSA screening (Hessel et al. 2004).

The Agricultural Health Study (AHS) also evaluated the risk of prostate cancer from exposure to atrazine (Alavanja et al. 2003, Rusiecki et al. 2004). The AHS is a prospective cohort study of 55,332 pesticide applicators in Iowa and North Carolina. Unlike many studies, the pesticide exposure estimates considered the "intensity" of participants' past exposures. Two exposure metrics were used (quartiles of lifetime days of exposure and quartiles of "intensity-weighted" lifetime days of exposure) based on applicator-specific use practices reported in questionnaires.

³ Prostate-specific antigen (PSA) is a protein produced by cells of the prostate gland. Prostate cancer or certain benign conditions of the prostate can increase the level of PSA in the blood.

⁴ See: http://www.epa.gov/scipoly/sap/meetings/2003/071703_mtg.htm

Based on a limited validation exercise using biomonitoring data from a small sub-set of participants (Coble et al. 2005), intensity scores appear to provide a reasonably valid, albeit crude measure of exposure intensity.

In the most recent AHS evaluation of atrazine exposure and prostate cancer (Rusiecki et al. 2004), Poisson regression analyses were carried out to estimate rate ratios for individual cancer sites for which there were at least 20 case patients with atrazine exposure. Rate ratios were adjusted for relevant covariates (such as age, family history of cancer in first-degree relatives, cigarette smoking history) as well as exposure levels of other pesticides strongly correlated with atrazine. Never-exposed applicators and the lowest-quartile exposed applicators served as reference groups. No increased risk of prostate cancer was observed among 554 atrazine exposed cases. These findings are consistent with a previous AHS publication (Alavanja et al. 2003) that also found no association between prostate cancer incidence and atrazine exposure.

Overall evidence from a large number of studies on Non-Hodgkin's Lymphoma (NHL), and more recently certain NHL subtypes, collectively suggest increased risk from agricultural pesticide use. Several individual pesticides and pesticide groups (e.g., chlorophenol and phenoxyacetic acid herbicides, organochlorines, organophosphates, carbamates, and fungicides) have mainly shown weak, positive associations with NHL. Atrazine has also been positively associated with NHL in some case-control studies of agricultural workers (DeRoos et al. 2003, Schroeder et al. 2001, Cantor et al. 1992, Hoar et al. 1986, Hoar Zahm et al. 1993). A mortality study based on triazine manufacturing workers in Louisiana also found a statistically significant increased standardized mortality ratio for non-Hodgkin lymphoma (MacLennan et al. 2003). In the Agricultural Health Study's most recent evaluation of atrazine exposure and cancer incidence (Rusiecki et al. 2004), no association between NHL and atrazine exposure was found, although rate ratios for NHL increased with exposure. However, confidence intervals were wide and tests for trend were not statistically significant. The small number of cancers occurring during the 6.5-year average follow-up period in this analysis is a major limitation that will become less of a concern during subsequent phases of the study. In its 2003 review, EPA concluded that based on studies to date, there was not sufficient evidence to specifically implicate atrazine as a likely cause of NHL (EPA 2003b).

EPA further examined prostate cancer and NHL within the context of animal mode of action. EPA concluded that, "1) the prostate glands in male laboratory animals do not appear to be a target of atrazine toxicity; 2) multiple animal bioassays do not reveal an increased incidence of tumors at any endocrine site other than mammary gland in female SD rats; 3) no increase in any dose group for a lymphoma of any type was seen in atrazine treated SD or F344 rats and 4) no mechanistic role for atrazine contributing to NHL has been identified in laboratory studies" (EPA 2003b).

2. Agricultural Health Study - Additional cancer sites

In the AHS, exposure to atrazine was not associated with overall cancer incidence and there were no clear associations between atrazine exposure and any individual cancer site analyzed (Rusiecki et al. 2004). There was a slight suggestion of trend for the following sites: lung, bladder, non-Hodgkin lymphoma, and multiple myeloma. A strength of this study is that

exposure information was gathered prior to cancer diagnosis, minimizing recall bias (although the potential for incomplete/erroneous recall remains). However, there were only 6.5 years of follow-up, resulting in a small number of selected cancers. Another limitation is the focus on adult exposures, whereas early-life atrazine exposures may play an important role in cancer development. In its 2003 evaluation, the SAP pointed to limitations in the AHS; mainly the short follow-up time and relatively young cohort. Potential inaccuracies in the exposure assessment were also cited, including possible exposure to atrazine-contaminated drinking water in regions where the herbicide was applied.

3. Reproductive effects and birth outcomes

Reproductive effects are of interest because of the hormonal effects of atrazine reported in experimental studies. The AHS has evaluated reproductive effects among female pesticide applicators and the spouses of pesticide applicators, many of whom also applied pesticides. Risk of gestational diabetes mellitus (GDM) was significantly associated with the reporting of “ever use” of atrazine, as well as several other pesticides (Saldana et al. 2007). No biological mechanism was offered to explain atrazine’s potential role in GDM; inclusion of atrazine was based on having at least five exposed cases rather than on an *a priori* hypothesis. As such, findings should be viewed as exploratory. Atrazine was also included in an AHS cross-sectional analysis on the effects of pesticide use on menstrual cycle characteristics (Farr et al. 2004). Atrazine was grouped with lindane and mancozeb or maneb as a “probable hormonally active pesticide.” Controlling for age, body mass index, and current smoking status, ever use of pesticides in this grouping was significantly associated with long cycles, missed periods, and intermenstrual bleeding compared with never use of these pesticides. Associations remained significant after excluding mancozeb or maneb. However, no statistically significant associations were found between these menstrual cycle characteristics and use of atrazine or cyanazine compared with never use of pesticides. These studies are the first of their kind to examine the effect of atrazine, along with other hormonally active pesticides, on GDM and menstrual function. As such, findings should be interpreted as preliminary and more studies are needed to further elucidate any associations.

Fertile men in an agricultural area of Missouri have been shown to have sperm counts about 40% lower than men in three urban US areas, and to also have higher urinary concentrations of atrazine, alachlor and diazinon (Swan et al. 2003, Swan 2006). Differences among the groups remained significant after controlling for potential confounders such as abstinence time, smoking, and age, which suggest that these chemicals may have contributed to the reduced semen quality seen in the men. One strength of this study is that exposure was based on pesticide concentrations in urine collected at the time of semen collection, which eliminates many issues related to self-reported exposure. However, study limitations still exist; for example, the results are based on a small number of men and exposure to other chemicals was not well controlled for in the study making causal inference about any single chemical difficult.

Several studies have evaluated whether atrazine plays a role in adverse birth outcomes or birth defects. A study by Munger et al. (1997) examined exposure to atrazine and adverse birth outcomes (low birth weight (LBW), prematurity, and intrauterine growth retardation (IUGR)). Thirteen communities getting drinking water from a community water system (CWS) with

elevated levels of atrazine (Rathbun system) were compared to nearby communities of similar size getting their water from other water supplies. Contaminant levels were taken from a 1986-1987 state-wide survey and ascertainment of birth outcomes was taken from 1984-1990 birth certificates. The number of available water samples per system was not reported. Analyses were adjusted for community-wide characteristics mainly derived from the 1980 U.S. Census. Levels of atrazine, metolachlor and cyanazine in finished water were each significant predictors of age-adjusted community rates of IUGR, with the association strongest for atrazine. A major study strength is that the level of atrazine in the Rathbun system was found to be relatively stable both seasonally and annually, increasing confidence that within-system variability was minor. In addition, atrazine levels in the Rathbun system were high relative to the neighboring systems, with a median concentration of 2.1 µg/L atrazine in the Rathbun system compared to median concentrations ranging from 0-0.44 µg/L in the comparison systems. However, there are general limitations in the ecologic study design used, including the limited reliability and validity of vital records, aggregate rather than individual measures of exposure, and lack of control for individual-level confounding factors. Specifically, exposure was based on place of residence at time of birth, with no consideration of personal water consumption factors or change in residence during pregnancy. Other potential water contaminants were not evaluated. The herbicide levels in the analysis were correlated; making it impossible to discern the independent contribution of each herbicide to IUGR risk.

Villanueva et al. (2005) evaluated the association between atrazine levels in municipal drinking water in an agricultural region of France and increased risk of preterm delivery, LBW, and small-for-gestational age (SGA) status. One strength of this study was the evaluation of associations between atrazine exposures and birth outcomes during specific trimesters of pregnancy. Atrazine levels throughout pregnancy were not associated with an increased risk of LBW or SGA birth at the levels to which the study population was exposed, with the exception of SGA status for exposure to the “peak atrazine period” (May-Sept.) during the third trimester. In addition to general limitations in ecologic assignment of exposure, a major study weakness was that overall atrazine levels in the municipal systems were low and the exposure range was extremely narrow. Due to lack of data, all atrazine measurements over an 8-year period were used, irrespective of when each pregnancy occurred. There was no consideration of potential confounders or other contaminants.

Ochoa-Acuña et al. (2009) evaluated whether atrazine concentrations in some Indiana CWS are associated with increased prevalence of SGA and preterm birth. In contrast to the two previously described studies, models controlled for individual-level demographic characteristics, prenatal care, reproductive history, and behavioral risk factors reported in the Indiana Birth Records Database. Another strength of this study is the inclusion of additional CWS monitoring datasets for atrazine to provide greater temporal resolution. When comparing groups (low, medium, and high based on atrazine concentrations), atrazine in drinking water during the 3rd trimester and the entire pregnancy was associated with a significant increase in the prevalence of SGA status. This finding is difficult to interpret because co-occurring chemicals were not evaluated beyond the determination that acetochlor, alachlor and metolachlor were all correlated with atrazine. Another potential problem is that other differences among the CWS were not controlled for. However, restricting the analysis to just one CWS with the most data resulted in a similar trend with the highest exposure group having an increase in the prevalence of SGA compared to the

lowest exposure group. As with the previous two studies, exposure was based on concentrations in water systems with no consideration for individual water consumption and use practices. Assignment to water systems was based on address at birth and did not account for change in residence during pregnancy.

Although several studies have investigated the relationship between birth defects and proximity to agricultural land or certain crop types (e.g., Ochoa-Acuña and Carbajo 2009, Schreinemachers 2003), only two studies have specifically focused on birth defects and exposure to atrazine. Both studies rely on ecologic data. Mattix et al. (2007) compared reports of abdominal wall defects from Centers for Disease Control and Prevention (CDC) data and Indiana state registry data to average monthly surface water atrazine and nitrate concentrations collected from United States Geological Survey (USGS) data. This monthly comparison demonstrated a statistically significant positive correlation between abdominal wall defects (based on last menstrual period or estimated date of conception) and mean atrazine levels, with peak incidence of each seen in June. Winchester et al. (2009) investigated whether annual peaks in atrazine, nitrates, and other pesticides seen in surface water from April-July correlated with greater risk of birth defects in pregnancies conceived in those same months. Elevated surface water concentrations of atrazine, nitrates, and other pesticides from April-July coincided with higher risk of birth defects conceived in these months. In simple regression models, atrazine exposure increased the odds of 9 of 11 selected birth defects associated with last menstrual periods in April-July. Limitations of both studies are the limited reliability and validity of vital records and reliance on USGS water data as a proxy for human exposure, which is not necessarily reflective of finished drinking water exposure, actual household exposures at the tap, nor of personal habits of water consumption or use.

4. Summary

Overall, interpretation of atrazine epidemiology studies is often hindered by methodologic limitations which reduce the number and kinds of inferences that can be made. Frequent limitations include the use of aggregate rather than individual measures of exposure, lack of high-quality exposure data, small sample size, limited statistical power for certain outcomes, and/or limited ability to control for confounding factors. Exposure assessment for pesticide epidemiology studies in general is problematic and efforts to improve exposure characterization are clearly needed. Ecologic studies evaluating exposure to atrazine in drinking water and birth outcomes are suggestive but must be interpreted cautiously because the studies lack individual-level exposure information. While ecological studies are a good first step to investigate possible exposure-disease relationships between atrazine and adverse birth outcomes/birth defects, positive findings must be verified by more detailed epidemiologic studies. Even among individual-level exposure studies, there is a lack high-quality quantitative personal exposure estimates and surrogate measures are likely poor proxies for actual levels of exposure. Yet having an accurate ordering of subjects by increasing exposure category is necessary to carry out meaningful exposure-response analysis. This weakness alone may limit the ability of studies to find stronger or more specific associations between pesticides such as atrazine and certain health outcomes. Even studies that collect detailed use records from participants have a high potential for incomplete recall or erroneous recall, as past use is often reported over many decades for diseases with long latency such as adult cancers. Inaccuracies in exposure assessment are

typically expected to be non-differential with respect to disease status and would most likely result in underestimating risk from pesticide exposures.

Although the weight-of-evidence from reviewed studies can be currently summarized as insufficient to establish causal relationships between atrazine exposure and certain adverse effects, atrazine remains a subject of on-going, active research and review. In particular, EPA plans to solicit expert advice on how to more effectively incorporate the epidemiology studies into the atrazine risk assessment in February 2010 and to seek peer review of its evaluation of atrazine epidemiology studies in September 2010. EPA's review will include the most recent results from the National Cancer Institute's Agricultural Health Study, anticipated for publication in 2010. For the purposes of this review, animal toxicity studies remain, at this time, the most reliable and reproducible data on which to base human health assessments for atrazine.

III. Human Exposure

A. Dietary Exposure

1. Food

Based on a review conducted by MDH as well as EPA, food-related exposure appears to be negligible. Atrazine is predominately used as a pre-emergent herbicide in soil directed sprays (rather than foliarly applied) or is applied early in the growing season. USDA (Food Safety and Inspection Service) data and registrant-supplied metabolism and field trial data all show no detectable residues of atrazine and its metabolites. Residue data from USDA's Pesticide Data Program (PDP) have shown low levels of atrazine or its metabolites in/on wheat grain. For example, atrazine was detected in 13/687 or 2% of PDP wheat samples in 2006 (the latest year with wheat data) at levels close to the level of detection of 3 ppb for atrazine in wheat. The tolerance level⁵ for wheat is 250 ppb. Atrazine has also been found sporadically by PDP at very low levels in some foods for which no tolerance exists (e.g., lettuce, blueberries), possibly due to pesticide spray drift, atmospheric deposition⁶, or residue transfer through crop rotation.

EPA has conducted a food-based dietary risk assessment for atrazine, summarized below. Separate assessments were conducted for atrazine and the chlorinated metabolites; and the hydroxylated atrazine metabolites. The hydroxy metabolites are the dominant plant metabolites of atrazine. The population adjusted dose (or PAD) is a term that EPA uses to characterize the dietary risk of a chemical. The PAD reflects the Reference Dose (RfD), either acute or chronic, that has been adjusted to account for the FQPA safety factor. A risk estimate that is less than 100% of the acute PAD (aPAD) or chronic PAD (cPAD) does not exceed EPA's level of concern.

⁵ A tolerance is the maximum quantity of a pesticide residue allowable by law on a raw agricultural commodity.

⁶ Atrazine is widely detected in rainfall. In 2008, atrazine was detected in 6/9 samples at MDA's precipitation monitoring site in southern Minnesota, with a maximum concentration of 0.16 ppb (MDA 2008).

Atrazine and its chlorinated metabolites (EPA 2003a):

- Estimated acute exposure for the relevant population subgroup (females 13 to 50 years old) corresponded to <1% of the aPAD at the 99.9th percentile of exposure. Average exposure for all exposed population subgroups corresponded to <1% of the cPAD value. These estimates of risk based on one-day and long-term exposures to atrazine and its chlorinated metabolites from residues on food alone are well below EPA's level of concern.

Hydroxyatrazine (EPA 2003a):

- Chronic dietary risk from hydroxyatrazine in/on food is well below EPA's level of concern with <1% of the cPAD consumed. EPA did not select an acute endpoint for hydroxyatrazine as no toxicologically significant endpoint representing a single exposure was found in the toxicology database.

2. Drinking Water

For the general population, the oral route via drinking water is the dominant exposure pathway for atrazine and its metabolites based on atrazine's use patterns, persistence and mobility in the environment, and its occurrence in Minnesota surface and groundwater. This section presents an overview of the water monitoring data considered most relevant to characterize atrazine concentrations in Minnesota's drinking water; not the entirety of available data on atrazine's occurrence in water resources. Additional monitoring data (e.g., urban groundwater, precipitation monitoring, stream monitoring) are described in MDA's and MPCA's supporting documents for the registration review of atrazine or on MDA's atrazine information website:

<http://www.mda.state.mn.us/chemicals/pesticides/atrazine.aspx>.

a. Atrazine monitoring in public water supplies

The requirement to monitor for atrazine in public water supplies (PWS) under the Safe Drinking Water Act (SDWA) became effective in 1993 when the maximum contaminant level (MCL) was established at 3 micrograms per liter ($\mu\text{g/L}$) or parts per billion (ppb)⁷. The maximum contaminant level goal is also set at 3 ppb. PWS required to monitor for atrazine under the SDWA includes community and non-transient non-community PWS. A PWS is in violation of the atrazine standard if the running annual average of quarterly samples at any sampling point exceeds the MCL.

Between 1993 and 1995, EPA required PWS to collect water samples every 3 months for one year to find out if detectable levels of atrazine were present. After initial testing, sampling frequencies were modified depending on the size of the system, whether initial samples were above or below the limit of detection (LOD), and whether the system was granted an atrazine sampling waiver. Systems can petition the state for a waiver after 3 consecutive annual sampling results below the detection limit. The following table describes the sampling schedule for atrazine in public drinking water supplies:

⁷ Under SWDA, only parent atrazine is required to be analyzed.

Table 1. PWS sampling schedule for atrazine

Sampling schedule for systems < LOD			
Population >3,300; waiver	Population >3,300; no waiver	Population ≤ 3,300; waiver	Population ≤ 3,300; no waiver
One sample at each entry point to the distribution system; once every 3 years	Two consecutive quarterly samples at each entry point to the distribution system; once every 3 years	One sample at each entry point to the distribution system; once every 3 years	One sample at each entry point to the distribution system; once every 3 years
Sampling schedule for systems > LOD			
Reliably and consistently ≤ MCL		Not reliably and consistently ≤ MCL	
One sample at each entry point to the distribution system every year.		Four quarterly samples at each entry point to the distribution system every year.	

In addition to the sampling waivers described above, systems may apply for “use” and “susceptibility” waivers for synthetic organic chemicals (SOCs). Use waivers can be granted when no SOC is present near a source while a susceptibility waiver can be issued when SOC are present but cannot contaminate a source of water. These types of waivers can reduce the monitoring frequency for a specific SOC, such as atrazine, to as little as once every 9 years.

This evaluation focuses on community water supplies (CWS) in Minnesota, as these systems represent the drinking water consumed in people’s homes. CWS have at least 15 service connections used by year-round residents or regularly serve 25 year-round residents. Examples of community systems are municipalities, mobile home parks, home owners associations and nursing homes. There are currently 961 active CWS serving an estimated 4,187,627 Minnesotans⁸. This is 80% of the population based on a total state population of 5,220,393 (U.S. Census 2008 estimate). The remainder of the population presumably receives residential drinking water from private wells.

CWS data from 1/1/2000 to 12/31/2008 were evaluated for atrazine. In Minnesota, the atrazine LOQ (level of quantitation) was 0.3 µg/L until 2005 when it was lowered to 0.1 µg/L. For the purpose of calculating annual mean concentrations, non-detections were assigned a concentration value equal to ½ LOQ (i.e., either 0.15 or 0.05 µg/L). Only currently active CWS were included in this analysis. Concentration results from 107 inactive CWS that were in operation for some duration during the 9-year period were all below the LOQ. For CWS that rely upon a combination of groundwater and surface water, the primary source of water was used to classify the system. CWS using groundwater under the influence of surface water were classified as surface water systems.

b. Atrazine monitoring results for Minnesota’s community water systems

Due to sampling waiver criteria, only 544 of 961 or 57% of CWS were required to monitor for atrazine between 1/1/2000 and 12/31/2008 (Table 2). All non-consecutive CWS on surface water sources monitored for atrazine and 60% of non-consecutive CWS on groundwater monitored for

⁸ As of June 19, 2009

atrazine during the 9-year period⁹. Atrazine was detected in 9 CWS using groundwater (2%) and 3 CWS using surface water (12%) between 2000 and 2008.

A total of 2,782 atrazine samples were available from the 544 CWS that monitored for atrazine (Table 2). Atrazine was detected in 1% of groundwater-source samples and 6% of surface water-source samples. This corresponds to < 1% of the population on groundwater-source CWS and 36% of the population on surface water-source CWS (Table 2). The high percentage of the population on surface water source CWS with any detection from 2000-2008 is attributable to a single, low-level detection in the Minneapolis CWS (MN1270024) in 2003 (Table 4).

The highest concentration detected in any sample from 2000-2008 was 1.2 ppb in the Goodhue CWS in 2000 (Table 4). That same year, the Goodhue CWS also had the highest annual mean concentration from 2000-2008 of 0.93 ppb (Table 4). With the exception of a single detection in the Minneapolis CWS, all detections occurred in Pesticide Monitoring Region (PMR) 4 (Central Sands), PMR 8 (South Central) and PMR 9 (Southeast) during this 9-year period (Table 4). These regions are considered geologically sensitive to atrazine contamination and/or high atrazine use areas.

As shown in Table 3, there appears to be a downwards trend in maximum atrazine concentrations over time in CWS on surface water and groundwater. Since the inception of the SDWA compliance monitoring program for atrazine in the early 1990's, no single or running-average atrazine concentration has been above the MCL of 3 ppb.

⁹ Out of 961 currently active systems, 75 are consecutive systems, which are not typically required to conduct monitoring since they purchase water from another CWS. Seven consecutive systems monitored for atrazine from 2000-2008.

Table 2. Atrazine occurrence in MN CWS based on SDWA compliance monitoring, 2000-2008

	Groundwater	Surface water	All
<u>Data</u>			
Number of samples	2,677	105	2,782
Number (%) of detections	27 (1)	6 (6)	33 (1)
Number of detections \geq 1 ppb	3	0	3
Number of detections $>$ 3 ppb	0	0	0
<u>Concentration (ppb)</u>			
Minimum detected concentration	0.1	0.3	0.1
Maximum detected concentration	1.2	0.5	1.2
<u>CWS</u>			
Number of CWS	922	39	961
Number of consecutive CWS	59	16	75
Number (%) of CWS with data	519 (56)	25 (64)	544 (57)
Number (%) of <i>non-consecutive</i> CWS with data	514 (60)	23 (100)	537 (61)
Number (%) of CWS with no detections	510 (98)	22 (88)	532 (98)
Number (%) of CWS with detections	9 (2)	3 (12)	12 (2)
Number of CWS with detections \geq 1 ppb	2	0	2
Number of CWS with detections $>$ 3 ppb	0	0	0
<u>Populations</u>			
Population on CWS*	2,854,861	1,332,766	4,187,627
Population (%) served by CWS with data	2,326,509 (82)	1,187,746 (89)	3,514,255 (84)
Population (%) with detections	11,834 (0.51)	428,378 (36)	440,212 (13)
Population with detections \geq 1 ppb	2,408	0	2,408

*Population estimate as of June 19, 2009

Table 3. Atrazine occurrence in Minnesota CWS by year based on SDWA compliance monitoring data, 2000-2008

Source	Year	CWS		Number of		Max Detected Concentration (ppb)
		Monitored	With Detections	Samples	Detections	
GW	2000	178	3	283	7	1.2
GW	2001	127	2	235	2	0.8
GW	2002	167	6	348	10	0.8
GW	2003	165	0	300	0	-
GW	2004	148	1	295	1	0.4
GW	2005	129	3	255	3	0.5
GW	2006	125	1	256	1	0.4
GW	2007	159	1	320	1	0.2
GW	2008	177	2	385	2	0.2
SW	2000	8	1	10	1	0.5
SW	2001	2	1	2	1	0.4
SW	2002	17	2	24	3	0.4
SW	2003	8	1	13	1	0.3
SW	2004	4	0	8	0	-
SW	2005	5	0	6	0	-
SW	2006	9	0	14	0	-
SW	2007	12	0	18	0	-
SW	2008	7	0	10	0	-

Table 4. Atrazine annual mean concentrations for Minnesota CWS with detections from SDWA compliance monitoring, 2000-2008.

PWS ID	Name	County	Primary water source	Year	Samples	Samples with detects	Annual mean (ppb)*	Max (ppb)
MN1850018	Altura	Winona	GW	2005	2	1	0.08	0.10
MN1560001	Battle Lake	Otter Tail	GW	2002	1	1	0.30	0.30
MN1560004	Battle Lake MHP	Otter Tail	GW	2004	1	1	0.40	0.40
MN1730006	Cold Spring	Stearns	GW	2002	4	1	0.19	0.30
MN1250005	Goodhue	Goodhue	GW	2000	4	4	0.93	1.20
MN1250005	Goodhue	Goodhue	GW	2001	1	1	0.80	0.80
MN1250005	Goodhue	Goodhue	GW	2002	1	1	0.80	0.80
MN1250005	Goodhue	Goodhue	GW	2005	1	1	0.50	0.50
MN1250005	Goodhue	Goodhue	GW	2006	1	1	0.40	0.40
MN1250005	Goodhue	Goodhue	GW	2007	1	1	0.20	0.20
MN1250005	Goodhue	Goodhue	GW	2008	1	1	0.20	0.20
MN1790016	Hiawatha Estates, Subds. I, II & III	Wabasha	GW	2008	4	1	0.06	0.10
MN1850006	Lewiston	Winona	GW	2000	2	2	0.65	1.00
MN1850006	Lewiston	Winona	GW	2001	2	1	0.43	0.70
MN1850006	Lewiston	Winona	GW	2002	5	4	0.35	0.50
MN1790012	Plainview	Wabasha	GW	2000	3	1	0.20	0.30
MN1790012	Plainview	Wabasha	GW	2002	2	2	0.40	0.40
MN1050002	Rice	Benton	GW	2002	1	1	0.40	0.40
MN1050002	Rice	Benton	GW	2005	1	1	0.20	0.20
MN1460003	Fairmont	Martin	SW	2000	1	1	0.50	0.50
MN1460003	Fairmont	Martin	SW	2001	1	1	0.40	0.40
MN1460003	Fairmont	Martin	SW	2002	2	2	0.40	0.40
MN1070009	Mankato	Blue Earth	SW	2002	2	1	0.23	0.30
MN1270024	Minneapolis	Hennepin	SW	2003	2	1	0.23	0.30

* Annual means, based on one or more samples, were averaged together across the entire system for each calendar year. Atrazine LOQ ranged from 0.10 – 0.30 ppb. Non-detections were assigned a concentration value equal to ½ LOQ.

c. Limitations in SDWA monitoring data for atrazine

- Under SWDA, only parent atrazine is required to be analyzed. There are no SDWA compliance data on the chloro-triazine degradates DEA, DIA, and DACT.
- Since DEA, DIA, and DACT result in the same toxicological effects as atrazine, such degradates could exert cumulative effects along with atrazine and together pose greater risk than atrazine alone. Degradate concentrations relative to the parent are expected to be higher in groundwater. In a large rural private well survey of 1,505 wells in 19 high atrazine use states, DEA and DACT concentrations were often comparable to those of atrazine, with the relative order of concentrations: atrazine~DEA~DACT>DIA (Ciba/State groundwater monitoring study, described in EPA 2001b). State-specific data from MDA survey programs have also shown that atrazine breakdown products typically form the majority of the total atrazine present (MDA 2005a). In a limited study on atrazine and its chloro-degradates in 17 surface water source CWS in seven states, atrazine predominated with the relative order of concentrations generally being atrazine>>>DEA>DIA>DACT (EPA 2001b).

- The ability to fully assess concentration patterns or time trends is limited due to infrequent sampling as a result of waivers granted by the state.
- Since waivers are justified by monitoring data showing low atrazine contamination potential, the data are somewhat positively (conservatively) biased with respect to the CWS which are sampled.
- There is also negative bias with respect to the timing and frequency of sampling. Particularly for systems using surface water, atrazine concentrations may demonstrate seasonal fluctuations. Infrequent sampling means that peak concentrations are unlikely to be captured. Systems are not required to sample for atrazine during the season of greatest agricultural use. Of the six surface water source samples with detectable concentrations of atrazine from 2000-2008, five were collected between April and August.

d. Application of regression equation for estimating total atrazine+chloro-degradate concentrations from atrazine concentrations in surface water source CWS.

As described in the Section 2c (“Limitations”) above, only parent atrazine is analyzed for SDWA-compliance purposes. Risk associated with consumption of water containing atrazine is presumed to be additive in effect with the parent compound and its chlorinated degradates. To address this limitation, EPA and Syngenta developed regression equations relating the sum of the chloro-triazine degradates (DEA, DIA, and DACT) concentrations in surface water source CWS to corresponding atrazine concentrations (EPA 2001b). EPA determined that it was not possible to develop regression equations relating degradate to atrazine concentrations in systems using groundwater, which make up the majority of MN systems, due to lack of correlation seen in a large well survey (EPA 2001b, based on the Ciba/State Groundwater Monitoring Survey). The criteria for the sampled surface water-source CWS included being in an area vulnerable to contamination within a high atrazine use state and having a history of previous atrazine detections. EPA linearly regressed the sum of the DEA, DIA, and DACT concentrations against atrazine concentrations in finished water. The regression equation, presented below, is based on the whole year set of data:

$$y = 0.418x + 0.240 \text{ (} r^2=0.541; n=291; df=289 \text{)}$$

where y=sum of DEA, DIA, and DACT degradate concentrations and x=atrazine concentration.

Only 3 Minnesota CWS on surface water have had at least one annual average atrazine concentration > LOD from 2000-2008. Estimated atrazine+degradate concentrations from these three systems are presented in Table 5. Regression-estimated annual mean concentrations of total chloro-triazines in surface water source CWS are below the MCL of 3 ppb. Additional data are needed to determine the accuracy of the regression estimates. As previously stated, the contribution of chloro-triazine degradates to total chloro-triazines may be higher in groundwater-source CWS.

Table 5. Estimation of total atrazine+chloro-degradate concentrations in surface water source CWS with annual mean concentration > LOD

PWS ID	Year	Annual mean concentration (atrazine only)	Total annual mean concentration (atrazine+DEA+DIA+DACT)
MN1070009	2002	0.23	0.57
MN1270024	2003	0.23	0.57
MN1460003	2000	0.50	0.95
	2001	0.40	0.81
	2002	0.40	0.81

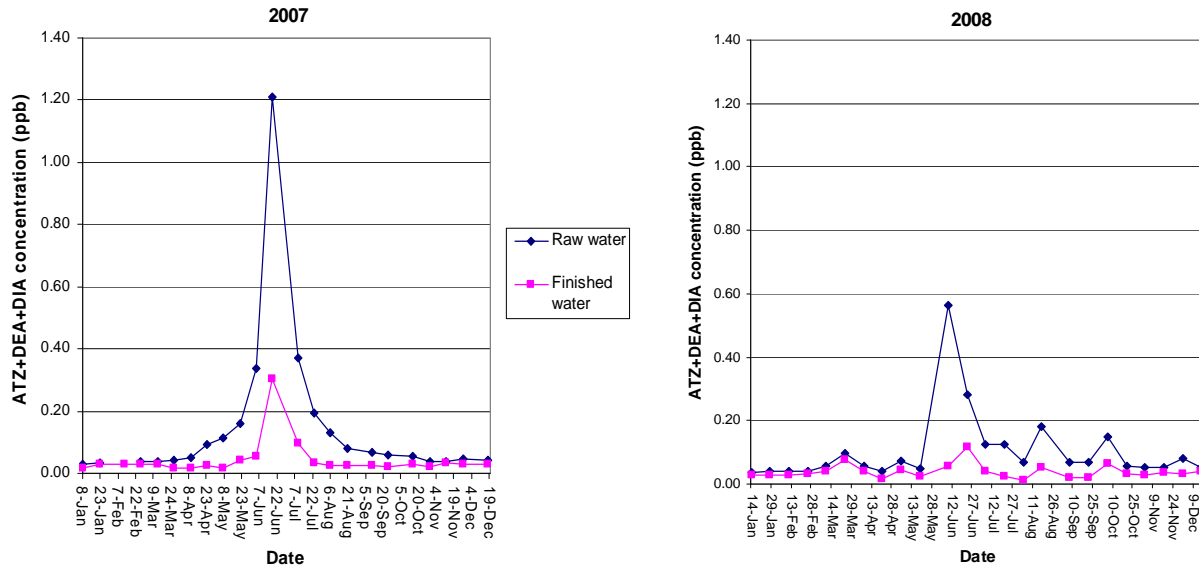
e. USDA Pesticide Data Program - Drinking Water Project

The Pesticide Data Program (PDP) at USDA has been collecting and analyzing samples from select water treatment facilities on a voluntary basis since 2001. Paired samples of both raw water at the intake and finished water exiting the plant are collected. The finished water samples are taken based on the throughput time of the plant to be as close as possible to the same parcel of water taken for the raw sample. The data are of interest for several reasons. First, PDP analyzes for DEA and DIA in addition to atrazine. Second, detection limits are lower (atrazine=2.3 ppt, DEA=24.8 ppt, DIA=9.8 ppt) than required for SDWA compliance monitoring. Third, samples are collected bimonthly which provides valuable information on within-system seasonal variability. Finally, paired samples are useful to determine the extent to which the employed treatment process removes individual pesticides.

To date, only one CWS in Minnesota has participated in PDP's Drinking Water Project, in both 2007 and 2008. This CWS draws from a combination of surface water and groundwater¹⁰. Concentration results are presented in Figure 1. In both years, atrazine levels began to rise in the spring with peak concentrations in June, mainly due to a sharp increase in parent atrazine. The spike in concentration was twice as large in June 2007 compared to June 2008, while a series of small spikes occurred after June in 2008. The water treatment method appears largely effective at removing atrazine from finished water. No single analyte or combined concentration of atrazine+DEA+DIA in raw or finished water samples exceeded the MCL in either year. These data only represent one CWS and results cannot be extrapolated to other systems or years. A summary of atrazine results for all PDP CWS sites is available in PDP's annual reports, available: <http://www.ams.usda.gov/AMSV1.0/pdp>.

¹⁰ The name of the CWS is not provided in accordance with PDP confidentiality requirements.

Figure 1. Atrazine+degradate concentrations in raw and finished drinking water from one mixed-source CWS in Minnesota (USDA PDP, 2007 and 2008)



f. Non-community public water systems

Although this evaluation focuses on community public water systems, as these systems represent the drinking water consumed year-round in people’s homes, atrazine SDWA compliance monitoring data are also available for other types of public water systems in Minnesota and are briefly described here. As with CWS, no non-community public water system in Minnesota has ever violated the atrazine MCL.

Non-transient non-community (NTNC) public water systems serve at least 25 of the same persons per day for more than six months of the year. NTNC systems are typically schools, offices, hospitals, churches and factories. Between 1/1/2000 and 12/31/2008, 2,016 atrazine samples were available from 571 NTNC systems in Minnesota. Atrazine was detected in 34 of these samples (1.7%) representing 11 systems. The maximum detected concentration was 1.8 ppb. Only one NTNC system had concentration results > 1 ppb.

Transient non-community (TNC) public water systems serve at least 25 persons per day for at least 60 days each year. TNC systems typically are campgrounds, restaurants, hotels, rest areas, golf courses or large stores. Between 1/1/2000 and 12/31/2008, 197 atrazine samples were available for 71 TNC systems in Minnesota. Atrazine was detected in 2 samples representing one system. Both samples (taken in the same location 1 year apart) were 0.6 ppb.

g. Private wells

Approximately 20% of Minnesotans receive drinking water at home from private wells. No federal or state regulations mandate testing of atrazine in private wells. Very limited data from Minnesota drinking water wells are available for atrazine, from the Dakota County Ambient Groundwater Quality Study, the Ciba/State Groundwater Monitoring Survey, the 2004 MDA Drinking Water Study, and a recent Potable Well Study also conducted by MDA. These studies are described below.

Since 1999, Dakota County, MN has conducted the Ambient Groundwater Quality Study (AGQS), an on-going survey of the county's major drinking water aquifers (Prairie du Chien, Jordan, and Quaternary wells). The goal is to sample the same set of privately-owned drinking water wells located throughout the county each year to study changes in the water over time and space. Wells were selected to represent the different aquifers and hydrogeological zones in the county. Participation in the AGQS is voluntary for well owners. The following analytes were included: Atrazine, DEA, DIA, DACT¹¹, hydroxyatrazine (HA), deethylhydroxyatrazine (DEHA), and deisopropylhydroxyatrazine (DIHA).

This study is useful for evaluating aggregated concentrations of parent atrazine plus the three chloro-degradates that were classified together by EPA in a Common Mechanism Group¹². Aggregated hydroxy-degradate results are also presented. Results from 1999-2003 monitoring can be found on-line in a summary report (Dakota County 2006). A table presenting results from the last 4 years of sampling (2004-2007) follows. Samples from 2004-2007 were analyzed by a USGS laboratory and the reporting limit for all analytes was 0.05 ppb. Non-detects were treated as zero, in accord with Dakota County's reporting practices.

A total of 224 samples from 68 wells were analyzed for atrazine and atrazine degradates from 2004-2007 (Table 6). Over half of the wells had detectible levels of atrazine and/or chlorinated degradates. Concentrations were low relative to the HRL of 3 ppb and no samples had single or aggregated concentrations of 1 ppb or greater. DACT had the highest concentration (0.75 ppb) of any single atrazine analyte. Out of 224 samples, the number of detections for individual chloro-degradates, DEA, DIA and DACT, were 92, 46, and 96 respectively.

¹¹ The Dakota County AGQS refers to diaminochlorotriazine (DACT) as didealkylatrazine (DDA).

¹² Based on the available weight of evidence, EPA only grouped atrazine, simazine, propazine, DEA, DIA and DACT by a common mechanism of toxicity for disruption of the hypothalamic-pituitary-gonadal axis. Hydroxyatrazine was also initially considered in the common mechanism grouping, as it produces some reproductive and developmental effects consistent with atrazine, but it was ultimately excluded (EPA 2002).

Table 6. Results from the Dakota County AGQS, 2004-2007

	Atrazine parent	Chloro-degradates (DEA+DIA+DACT)	Atrazine+ chloro-degradates (ATZ+DEA+DIA+DACT)	Hydroxy- degradates (HA+DEHA+ DIHA)
Data				
Number of samples*	224	224	224	224
Number (%) of detections	77 (34)	103 (46)	105 (47)	27 (12)
Number (%) of detections \geq 0.5 ppb	1 (<1)	19 (9)	31 (14)	0
Number of detections > 1 ppb	0	0	0	0
Concentration (ppb)				
Minimum detected concentration	0.03	0.02	0.20	0.03
Median detected concentration	0.07	0.22	0.28	0.05
Maximum detected concentration	0.60	0.88	0.96	0.10
Wells				
Number of wells	68	68	68	68
Number (%) of wells with detections	30 (44)	35 (52)	37 (54)	21 (31)
Number of wells with detections \geq 0.5 ppb	1	8	13	0
Number of wells with detections > 1 ppb	0	0	0	0

*Number of samples for DACT=223

A Rural Well Survey in Minnesota was conducted by a previous atrazine registrant, Ciba, in conjunction with MDA, from September 1992 to March 1995 (Ciba/State survey). Use of this study is not appropriate to describe present-day atrazine concentrations since restrictions on the use of atrazine were implemented in the early to mid 1990's, primarily to protect water supplies. However, the study provides valuable information on the relative contribution of atrazine's major degradation products in private wells located in vulnerable areas of Minnesota. Seventy-four private wells were sampled in either the central sandy plain (n=49) or SE karst regions (n=25). Wells were selected by MDA based on groundwater vulnerability and/or previous detections in the area. Participation in the study was voluntary for well owners. One sample per well was analyzed. Atrazine, three chloro-degradation products, hydroxyatrazine and three additional hydroxy-degradation products were analyzed. The LOD for all analytes was 0.1 ppb. Frequency distributions by concentration interval for atrazine, its chloro-degradates, and total chloro-atrazine in the Rural Well Survey are presented in Table 7. Atrazine, or at least one of its chloro-degradates, was detected in approximately half of the wells. The highest concentrations of DEA, DIA, DACT were 1.4 ppb, 1.7 ppb, and 1.7 ppb respectively. The maximum measured value of atrazine and its degradates occurred in a well located in Winona county MN. Results

were 3.4 ppb (atrazine only) and 5.6 ppb (total chlorotriazine). Three additional wells had total chlorotriazine concentrations \geq the HRL of 3 ppb (3.0, 3.2, 5.2 ppb). Hydroxyatrazine was detected in only two wells, both with concentrations of 0.21 ppb. All other hydroxy-degradation products were $<$ LOD.

Table 7. Frequency distribution of atrazine, chloro-degradates, and total chlorotriazines in Ciba-State Rural Well Survey.

Concentration interval (ppb)	Atrazine		Chloro-degradation products						Total chlorotriazines	
	Number of wells	Percent	DEA		DIA		DACT		# wells	%
			# wells	%	# wells	%	# wells	%		
< LOD	46	62.2	43	58.1	59	79.7	49	66.2	38	51.4
0.10-0.29	16	21.6	16	21.6	10	13.5	8	10.8	7	9.5
0.30-0.99	6	8.1	12	16.2	4	5.4	13	17.6	12	16.2
1.00-2.99	5	6.8	3	4.1	1	1.4	4	5.4	13	17.6
3.0-9.9	1	1.4	0	0.0	0	0.0	0	0.0	4	5.4
\geq 10.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Total	74	100	74	100	74	100	74	100	74	100

In 2004, MDA implemented a state-wide survey of 71 public and private drinking water wells located throughout agricultural regions of the state. A grid structured to locate 100 points across the state's primary agricultural regions was randomly placed across the state. Wells nearest to the grid line intersections were located and sampled during early 2004. Ten wells were positive for atrazine and/or one of its degradation products. Results are shown in Table 8.

Table 8. Results of the 2004 MDA Drinking Water Survey

Analyte	Number of wells with detections (%)	Median of all samples (ppb)	90 th percentile of all samples (ppb)	Maximum of all samples (ppb)
Atrazine parent	4 (6)	nd*	nd	1.52
DEA	10 (14)	nd	0.09	0.65
DIA	2 (3)	nd	nd	0.35
Atrazine+DEA+DIA	10 (14)	nd	0.09	2.52

*Values reported as "nd" correspond to levels below the LOQ. DES and atrazine LOQ=0.05 ppb. DIA LOQ=0.20 ppb.

In 2009, MDA conducted a Potable Well Study in Southeast Minnesota's karst bedrock region using an immunoassay method to screen for the presence of atrazine and its degradates. Ninety-two wells in the Volunteer Nitrate Monitoring Network were analyzed. Wells with nitrate-nitrogen concentrations above background level ($>$ 3 mg/L) were over-sampled. The results in Table 9 show that wells with nitrate-nitrogen concentrations above background had a much higher likelihood of containing atrazine. Well water that did not have detectable amounts of nitrate-nitrogen or levels considered to be background (0.1 to 3 mg/L) had no atrazine detections. Fifty-six percent of the wells with nitrate-nitrogen concentrations of 3 to 10 mg/L had detectable amounts of atrazine. Seventy percent of the wells with concentrations above the current standard of 10 mg/L for nitrate-nitrogen in well water had detectable atrazine. Atrazine compounds were detected in wells that were installed after the MDH well code was adopted in 1974 and in wells with geologic protection through an overlaying confining layer. Although the immunoassay best serves as a screen rather than a quantitative tool, concentrations of atrazine compounds reactive

to the method in this study were generally low relative to the HRL and none were found to have concentrations above the HRL.

Table 9. Summary statistics for co-occurrence of nitrate-nitrogen and atrazine presence.

Nitrate Result (mg/L)	Total Wells Sampled (n=92)	Wells with Atrazine Detection	Atrazine Minimum (µg/L)	Atrazine Median (All Samples) (µg/L)	Atrazine Maximum (µg/L)
ND	4	0	nd	nd	nd
0.1 - 3	16	0	nd	nd	nd
>3 - 10	45	25	nd	0.06	0.68
> 10	27	19	nd	0.08	1.26

The immunoassay method does not differentiate between atrazine and closely related compounds, including atrazine breakdown products, but quantifies them at a percentage less than the actual concentration for all compounds except atrazine. Values reported as “nd” correspond to atrazine levels below the LOD (<0.05 ppb). Not all atrazine breakdown products, such as DACT, are reactive to the method. Lower limits of detection for the reactive compounds are as follows: Atrazine=0.053 ppb, DEA=0.017 ppb, DIA=2.31 ppb, HA=0.120 ppb.

h. MDA monitoring wells

MDA serves as the lead state agency for monitoring the occurrence and concentration of pesticides in both groundwater and surface water. MDA began analyzing water samples for parent atrazine in 1985 and two chloro-degradates (DEA, DIA) in 1995. Atrazine has been detected more frequently over more years than any other single compound monitored by MDA (MDA 2008). Groundwater monitoring conducted by the MDA has focused on two Pesticide Monitoring Regions (PMRs) considered most vulnerable to contamination: central sand plains (PMR 4) and southeast karst region (PMR 9). As illustrated in Table 10, atrazine detections are most common in these two regions. In the most recent year with data (2008), PMR 9 had the highest frequency of atrazine detection (100%).

Table 10. Atrazine detection frequency in groundwater samples collected from MDA PMRs, 2008

Pesticide	PMR 1	PMR 4	PMR 5	PMR 6	PMR 7	PMR 8	PMR 9	PMR 10
Atrazine	25%	50%	44%	20%	29%	8%	100%	18%
DEA	37%	65%	55%	30%	29%	17%	96%	41%
DIA	12%	27%	22%	0%	14%	8%	46%	6%
Atrazine+degradates	37%	70%	67%	30%	29%	17%	100%	41%

DES and atrazine method reporting limit (MRL)=0.05 ppb. DIA MRL=0.20 ppb.

Groundwater samples from MDA’s central sand plains and southeast karst regions are collected from reconnaissance wells or springs, not private drinking water wells. However, concentration results summaries are presented here to represent a “worst-case” scenario for shallow private drinking water wells finished in glacial outwash sand aquifers and karst bedrock aquifers.

Table 11 summarizes results from water samples in PMR 4 and 9 from 2003-2008. Results prior to 2003 can be found in earlier MDA water monitoring reports available at <http://www.mda.state.mn.us/chemicals/pesticides/maace.htm>. Within the Central Sands Monitoring network, atrazine (based on atrazine+DEA+DIA) has exceeded the current HRL drinking water standard of 3 ppb three times in two wells since 2000; the most recent being in

August 2003. Exceedences were the result of high levels of DEA and DIA. No samples have exceeded 3 ppb in wells or springs monitored by MDA in the SE karst region.

There is evidence that levels of atrazine and its degradates are declining in Minnesota's groundwater in PMR 4 (MDA 2005a, MDA 2008). Concentration data for PMR 9 show no trend over time, tending to fluctuate up and down around a relatively low level (MDA 2008).

Table 11. MDA results for atrazine and its degradates in groundwater in PMR 4 and PMR 9 (2003-2008).

	PMR 4				PMR 9			
	Atrazine	DEA	DIA	Atrazine+ DEA+DIA	Atrazine	DEA	DIA	Atrazine+ DEA+DIA
Number of samples (% detects)								
2003	51 (38)	104 (78)	36 (27)	106 (80)	41 (68)	58 (97)	8 (13)	59 (98)
2004	55 (51)	89 (82)	36(33)	91(84)	67 (93)	72 (100)	16 (22)	72 (100)
2005	58 (51)	96 (85)	32(28)	97 (86)	61 (97)	63 (100)	16 (25)	63 (100)
2006	63 (56)	90 (80)	28(25)	92 (81)	35 (90)	39 (100)	18 (46)	39 (100)
2007	67 (60)	91 (82)	21(19)	91 (82)	53 (96)	55 (100)	29 (53)	55 (100)
2008	42 (50)	55 (65)	23 (27)	59 (70)	46 (100)	44 (960)	21 (46)	46 (100)
Median, all samples (ppb)								
2003	nd	0.12	nd	0.16	0.06	0.14	nd	0.19
2004	P	0.07	nd	0.12	nd	0.06	nd	nd
2005	P	0.06	nd	0.09	nd	0.05	nd	0.06
2006	P	P	nd	0.05	P	0.10	nd	0.21
2007	P	0.05	nd	0.06	0.05	0.10	P	0.15
2008	P	P	nd	P	P	0.08	nd	0.11
90 th percentile, all samples (ppb)								
2003	0.08	0.28	0.30	0.53	0.14	0.17	P	0.34
2004	0.08	0.22	0.20	0.42	0.10	0.15	P	0.24
2005	0.05	0.15	P	0.28	0.08	0.11	P	0.28
2006	0.05	0.12	P	0.24	0.10	0.14	P	0.33
2007	0.06	0.12	P	0.21	0.11	0.13	P	0.24
2008	P	0.08	P	0.10	0.09	0.11	P	0.19
Maximum (ppb)								
2003	0.25	0.65	2.15	3.04	0.20	0.20	P	0.40
2004	0.26	0.63	1.43	2.32	0.14	0.18	P	0.26
2005	0.32	0.42	0.72	1.17	0.10	0.13	P	0.21
2006	0.18	0.37	0.42	0.91	0.26	0.15	P	0.40
2007	0.17	0.42	0.53	1.11	0.13	0.15	P	0.26
2008	0.18	0.22	0.28	0.65	0.19	0.12	P	0.28

*DES and atrazine MRL=0.05 ppb. DIA MRL=0.20 ppb. 'P' indicates that the pesticide was detected at or below the MRL. "nd" represents a non-detect, the compound was not identified either qualitatively or quantitatively through the applicable chemical analytical method.

MDA began separately analyzing for an additional degradate of atrazine, DACT, in 2007. This analysis is accomplished using an Enzyme Linked Immuno-sorbant Assay (ELISA) method. Table 12 presents summary results for the 151 DACT groundwater samples analyzed in 2008. Forty-two percent of all samples analyzed had detectable levels of DACT. As seen with other atrazine analytes, the highest concentration of DACT was found at a PMR 4 site (1.85 ppb) while PMR 9 had the highest frequency of detection (95%). The maximum concentration of DACT

was 1.85 ppb and when added with the other atrazine constituents at that site, resulted in a total estimated concentration of 2.50 ppb.

Table 12. Summary of DACT results in 151 groundwater samples as determined by ELISA method for 2008.

PMR	Number of samples (% detects)	Median (ppb)	75 th percentile (ppb)	90 th percentile (ppb)	Maximum (ppb)	Maximum atrazine + degradates (ppb)
1	8 (13%)	nd	nd	0.14	0.20	1.09
4	63 (27%)	nd	0.11	0.29	1.85	2.50
5	9 (11%)	nd	nd	0.07	0.12	0.32
6	9 (0%)	nd	nd	nd	nd	nd
7	7 (29%)	nd	0.10	0.16	0.16	0.53
8	12 (8%)	nd	nd	0.09	0.30	0.30
9	43 (95%)	0.21	0.30	0.41	0.50	0.68
All regions	151 (42%)	nd	0.18	0.31	1.85	2.50

‘nd’ represents a non-detect, the compound was not identified either qualitatively or quantitatively through the applicable chemical analytical method.

i. Drinking water summary

Detections in public water supplies are rare and no running annual average (or single sample) has exceeded the atrazine MCL of 3 ppb. Although atrazine is found more often in CWS that use surface water sources (12%) compared to those that use groundwater sources (2%), the highest maximum concentration of 1.2 ppb was found in a groundwater source CWS in SE Minnesota. Without analysis of atrazine degradates, CWS data are of limited use to fully understand atrazine’s presence in the state’s public drinking water. Although one expects to find degradates along with atrazine, combined concentrations are still expected to be absent or low in public water based on atrazine-only results. Infrequent sampling is another major limitation in public water supply monitoring as peak concentrations are unlikely to be captured. Data from CWS and MDA monitoring programs suggest that atrazine concentrations may be declining over time in some areas of the state.

Data are inadequate to fully assess exposure and risk for population subgroups getting their drinking water from private wells. Interpreting the limited amount of available data is further hampered by uncertainties involving the adequacy of the sampling (i.e., appropriate locations, timing, and frequency). Based on the entirety of available drinking water and groundwater monitoring data, atrazine (and atrazine+chloro-degradate) concentrations in private wells are expected to be absent or below established health benchmarks. However, the potential remains for higher concentrations to occur above health benchmarks in high atrazine use areas and geologically sensitive areas.

B. Aggregate Exposure

Aggregate risk assessments conducted by EPA include consideration of exposures to a pesticide from food, drinking water, and residential/non-occupational sources. While atrazine is a widely-used herbicide, it is not available to the general public for home use. Atrazine is classified as a restricted-use pesticide, making it available for retail sale only to certified applicators or persons under their direct supervision. As atrazine exposure from food is considered negligible and there

are no residential uses of atrazine in Minnesota, aggregate exposure only reflects drinking water exposure, described above.

Under the Food Quality Protection Act (FQPA) as it pertains to the Federal Food, Drug and Cosmetic Act (FFDCA), EPA is not legally required to include occupational exposures in its aggregate exposure/risk assessments. EPA has recently released a policy paper that proposes changes to how occupational risk assessments are conducted, including the aggregation of all potential sources of pesticide exposure to workers (EPA 2009). However, an aggregate risk assessment for workers cannot be implemented at this time, for any pesticide, as the associated science policies and methodologies have not yet been developed to perform such an assessment.

C. Occupational Exposure

Exposure to atrazine can result from occupational use with dermal exposure serving as the dominant exposure route. Two atrazine use sites are applicable in Minnesota – corn and Conservation Reserve Program (CRP) grasslands¹³. EPA’s occupational risk assessments developed for the 2003 atrazine interim RED included these two use scenarios and the acreage/rate assumptions for CRP land were covered under the corn scenario. MDH has reviewed EPA’s occupational assessment for MDA’s registration review. Exposure is evaluated by EPA using a baseline clothing exposure scenario and, if required, increasing levels of risk mitigation (personal protective equipment (PPE) and engineering controls) to achieve a margin of exposure (MOE) which does not exceed EPA’s level of concern¹⁴. Occupational risks were of concern (i.e., MOEs < 100) for some mixer/loader scenarios even when maximum PPE was assumed. In its review for the 2003 interim RED, intermediate-term exposures associated with mixing/loading the largest quantities of atrazine were most likely to be of concern. As a result, EPA took mitigation actions to address occupational handler risks. These measures are reflected on current atrazine labels. The following table describes the occupational exposure scenarios with MOEs <100 and the actions that were taken by EPA to mitigate these risks.

¹³ According to MDA, atrazine is not commonly applied to CRP land in Minnesota. If it is applied, it is generally used only during the establishment of grassland on highly erodible soils (rather than on a repeated basis).

¹⁴ The MOE determines how close the occupational exposure comes to a No Observed Adverse Effect Level (NOAEL). MOEs > 100 do not exceed EPA’s level of concern for atrazine. The MOE of 100 for atrazine incorporates uncertainty factors of 10x for interspecies extrapolation and 10x for intraspecies variation. Under FQPA as it pertains to FFDCA, EPA is not legally required to apply atrazine’s additional 3X FQPA Safety Factor to occupational assessments, applicable to pregnant or adolescent workers.

Table 13. Mixer/Loader scenarios with “pre-mitigation” MOEs < 100 (dermal + inhalation) – corn or CRP acreage (EPA 2003a)¹

Scenario with unacceptable MOE	MOE	Exposure duration (short-term or intermediate-term ²)	Level of protection ⁴	Acreage, Rate ³	Mitigation measures resulting in MOE > 100
Incorporating liquid formulations into liquid or dry bulk fertilizer	64	S-T	Engineering controls	960 tons, 2 lbs ai/gal	Restricted to 500 tons. On-farm impregnation prohibited.
	67-72	I-T	Engineering controls	500 tons, 2 lbs ai/gal)	No more than 30 days per calendar year per facility. On-farm impregnation prohibited.
Dry flowable for aerial application	61	S-T	PPE	1200 acres, 2 lbs ai/acre	Aerial application prohibited unless in water-soluble packets
	52	I-T	PPE	350 acres, 2 lbs ai/acre	Aerial application prohibited unless in water-soluble packets
Dry flowable for groundboom application	57	I-T	Baseline	200 acres, 2 lbs ai/acre	Required coveralls, chemical-resistant (CR) gloves, CR footwear, CR apron, respirator
	91	I-T	PPE	200 acres, 2 lbs ai/acre	Not Applicable
Liquid formulations for aerial application	≤ 7	S-T and I-T	Baseline	350 and 1200 acres, 1 and 2 lbs ai/acre	Required CR gloves and CR apron ⁵ .
Liquid formulations for groundboom application	≤ 12	S-T and I-T	Baseline	200 and 450 acres, 1 and 2 lbs ai/acre	Required CR gloves and CR apron ⁵ .
Wettable powders for aerial application	≤ 66	S-T and I-T	Baseline and PPE	350 and 1200 acres, 1 and 2 lbs ai/acre	Required water-soluble packets for all wettable powder formulations

¹ Mixing/loading scenarios do not include exposure contribution from applying atrazine.

² “Short-term” occupational exposures were defined as 1-30 days duration, intermediate-term as one to six months. Most private applicators will be exposed less than 30 days per year. Intermediate-term exposures mainly apply to commercial applicators.

³ For corn, maximum label rate=2 lbs ai/acre/application. Typical rate determined by EPA=1 lb ai/acre.

⁴ “Baseline” includes long-sleeved shirt and long pants. Personal Protective Equipment (“PPE”) includes long-sleeved shirt and long pants, coveralls, chemical resistant gloves, and a respirator. “Engineering controls” include closed application and mixing systems.

⁵ Uncertainty exists for this scenario. EPA did not provide data to assess whether the addition of gloves and apron alone results in MOEs > 100, as the PPE scenario also assumed use of coveralls and respirator.

As shown in Table 13, all scenarios with MOEs < 100 were effectively mitigated with the exception of intermediate-term risk from mixing/loading dry flowable for groundboom application, with an MOE of 91. Although the MOE is presented as a “bright line” threshold, it represents an oversimplification necessary to derive a point estimate of risk. To determine whether this scenario represents a potential risk of concern, MDA should consider the underlying data and assumptions used in EPA’s exposure assessment. Some considerations are as follows: This scenario is mainly relevant to commercial applicators who may be mixing/loading atrazine greater than 30 days per year. The scenario assumes the maximum allowable use rate although NASS survey data suggest that atrazine is typically applied at a rate of approximately 0.5 lbs ai/acre in Minnesota (USDA 2006). However, this scenario, like all of the mixing/loading scenarios listed in Table 13, does not include any exposure contribution from applying atrazine.

Because agricultural workers may be involved in mixing, loading, and applying atrazine, it is important to consider total risk from these operations. This represents a gap in the occupational risk assessment as a whole. Descriptions of all the data and assumptions used in EPA's occupational risk assessment for atrazine are outlined in EPA 2001a.

Post-application occupational exposure is expected to be minimal. In Minnesota, atrazine is applied to corn early in the season, either before weeds emerge or when the crops are less than 12 inches high. This, and the degree of mechanization in cultivating these crops, results in low potential for post-application exposure (EPA 2003a). In EPA's assessment of post-application occupational exposure, atrazine-specific studies were used. All post-application risk estimates were well below EPA's level of concern (i.e., MOEs >100) (EPA 2003a).

EPA has recently proposed a change in methodology to include the FQPA safety factor in its occupational risk assessments, where applicable, to protect infants and children (EPA 2009). Under FQPA as it pertains to FFDCA, EPA is not legally required to apply atrazine's additional 3X FQPA Safety Factor to occupational assessments for hazard-based uncertainty related to the health consequences of exposure on the developing young. The appropriateness of incorporating this factor into occupational risk calculations for atrazine (i.e., for pregnant or adolescent workers) will likely be determined during EPA's 2010 re-assessment.

D. Other Exposure Topics

Biomonitoring:

Urinary biomonitoring data are available for atrazine. CDC measures the atrazine metabolite atrazine mercapturate (AM), a glutathione-derived metabolite, in a population-based sample representing the U.S. population (National Report on Human Exposure to Environmental Chemicals, <http://www.cdc.gov/exposurereport/>). AM is typically detected in <5% of participants. The Minnesota Children's Pesticide Exposure Study (MNCPEs) also analyzed the urine of 89 children 3–13 years of age living in either the Twin Cities (urban households) or Rice and Goodhue Counties (nonurban households) for AM (Adgate et al. 2001). MNCPEs was designed to address multipath exposures from air, water, food, soil, and residential surfaces in the homes of the children. Although analysis of the home environment showed that atrazine was present in 62 of 102 surface wipe samples and in 61 of 102 carpet samples, only 5 of 89 children had levels of AM in their urine above the LOD of 1.0 ppb, with creatinine-adjusted concentrations ranging from 0.6 to 22 µg/g creatinine (Adgate et al. 2001, Liroy et al. 2000). Four out of five of the children were from urban areas. Urinary concentrations of AM in 95 adults and 117 children living in farm/non-farm households of Iowa have also been reported (Curwin et al. 2007). For atrazine, only 23% of the voids had detectible concentrations above the LOD of 1.16 ppb; however, when values below the LOD reported by the laboratory were considered, nearly 80% of the voids had an analytical level. Thirty-five percent and 7% of the voids did not detect atrazine for non-farm and farm family members, respectively. Mixed-effect modeled adjusted geometric mean (GM) levels of AM were significantly higher in fathers (1.1 ppb), mothers (0.65 ppb) and children (0.6 ppb) from farm households compared with those from non-farm households (0.067, 0.031, 0.054 ppb for fathers, mothers, and children respectively).

A recent study investigated whether measuring AM is sufficient to estimate human exposure to atrazine, as the low detection frequencies in CDC's biomonitoring program and individual studies are surprising given atrazine's widespread use, frequent detection in water, and detections from household samples (Barr et al. 2007). It was found that relying on AM underestimates exposure to atrazine-related metabolites and that multiple metabolites, particularly DACT and DEA, must be measured to accurately assess atrazine exposure. As studies-to-date have likely been underestimating exposure by only measuring AM, biomonitoring data are not useful to characterize exposure to atrazine at this time.

Triazine cumulative exposure: MDH has not evaluated cumulative triazine exposure and risk, as this is considered beyond the scope of MDA's atrazine registration review. According to EPA, a common mechanism of toxicity group (CMG) consists of chemicals for which scientifically reliable data demonstrate that the same toxic effect occurs in or at the same organ or tissue by essentially the same sequence of major biochemical events. EPA concluded in 2002 that the triazine-containing pesticides atrazine, simazine, and propazine and their three chlorinated degradates (DEA, DIA, DACT) should be included in a CMG (EPA 2002). Although cyanazine also shares a common mechanism of toxicity with these chemicals, it was not considered in the CMG because all cyanazine products were cancelled in December 1999 with use of existing stocks permitted through December 2002. Although all cyanazine uses have been cancelled, groundwater monitoring data from Minnesota show that cyanazine degradates are still present in drinking water sources and have been recently found at levels above health benchmarks (Dakota County 2006, MDA 2005b).

EPA has conducted a cumulative risk assessment of atrazine and simazine and their chlorinated degradates (EPA 2006). Although propazine is included in the triazine CMG, it was not part of the cumulative risk assessment because its use is restricted to container-grown ornamentals in greenhouses. MDA's registration review only considers atrazine; however, simazine use is minimal in Minnesota according to pesticide sales data¹⁵:

Lbs a.i. sold in MN in 2008 (MDA 2008 pesticide sales data¹⁶):

Atrazine:	3,056,186
Simazine:	10,811

Inerts/adjuvants: MDH has not evaluated other ingredients in products containing atrazine as an active ingredient, as these ingredients are not unique to atrazine and are considered beyond the scope of MDA's atrazine registration review.

Mixtures: MDH has not evaluated products which contain both atrazine as well as other active ingredients. This is considered beyond the scope of MDA's atrazine registration review.

¹⁵ According to MDA, simazine is rarely used in MN because it has a high potential for carryover, resulting in a greater risk for crop injury.

¹⁶ Sales estimates contain some uncertainty, as products sold in MN may not be used in the same year they are sold or in some cases, may be used outside the state.

Pesticide drift and volatilization: MDH has not evaluated risks to bystanders from drift or volatilization of atrazine. EPA has just recently begun to outline the issues associated with assessing non-fumigant pesticide exposure from field volatilization or drift which include a lack of inhalation toxicity studies, air monitoring data and validated fate models to predict the off-site movement of pesticides. Due to the many science issues related to pesticide volatilization, EPA sought input from its FIFRA SAP in December 2009 and is awaiting the SAP's report, due in March 2010, to move forward.

IV. Risk characterization

At the request of MDA, MDH evaluated health effects and exposure data for atrazine, with an emphasis on Minnesota-specific exposures. Toxicology studies and environmental samples are most useful at this time to characterize hazard and exposure respectively; as epidemiologic data are currently insufficient to establish causality and biomonitoring data lack information on key metabolites. Atrazine is rarely found in food samples and when found, it is at very low levels. As the contribution from atrazine residues in or on food is insignificant, the oral route via drinking water is expected to be the dominant dietary exposure pathway. Although detections of parent atrazine in public water supplies are rare, there is concern for private well users living in areas with high corn acreage and/or geologically vulnerable areas. Unlike CWS, private wells are not always properly constructed, located, maintained, and tested. Although the amount of data from private drinking water wells makes a complete assessment of exposure difficult, atrazine and atrazine+chloro-degradate concentrations in private wells are likely to be absent or below established health benchmarks based on the entirety of available groundwater monitoring data. However, the potential exists for higher concentrations to occur above health benchmarks. Wells most at risk of contamination from atrazine or other pesticides are shallow or old, located in areas of pesticide use, and/or located in geologically sensitive areas such as sand plains or karst bedrock areas. Wells with elevated levels of nitrate are also more likely to have detectable levels of atrazine or other pesticides.

Comparing drinking water monitoring results to MCLs or HRLs serves as a way to evaluate data but is not equivalent to a comprehensive health risk assessment. If this initial evaluation indicates no risks of concern, a more refined risk assessment is not deemed necessary. As previously stated, MDH has adopted the EPA MCL of 3 ppb as the HRL for atrazine as per the stipulations of the 2007 Water Level Standards legislation, and currently recommends this value for use in groundwater assessments. Atrazine and atrazine+chloro-degradate concentrations are below this health benchmark in current, available Minnesota drinking water data. Based on the ongoing MDH toxicological evaluation of the available data for atrazine, any new recommended guidance values for atrazine are not likely to be lower than the current HRL. However, new, lower health-based guidance values may be derived for DACT that would also be applicable for DEA and DIA. If the final values are ultimately lowered, MDH will be available to advise MDA on any public health implications.

Exposure is expected for Minnesota agricultural workers mixing, loading, and/or applying atrazine. EPA's current occupational assessment for atrazine does not evaluate risks to workers both mixing/loading and applying atrazine, which precludes MDH from making a final

determination regarding worker risks. It is also anticipated that EPA's existing occupational risk assessment for atrazine will be revised in 2010 to include more protective risk assessment approaches. Currently acceptable risks may be found unacceptable at that time.

V. Recommended action based on registration review

MDH recommends that MDA continue its programs to encourage Best Management Practices adoption by the agricultural community, including application rate recommendations in areas of vulnerable soils and groundwater, and adherence to label-required application setbacks from wells, streams and lakes.

MDH also recommends continued water monitoring by MDA for atrazine and its chlorinated metabolites in both geologically sensitive areas and high-use areas. Future monitoring programs should include analysis of diaminochlorotriazine (DACT) concentrations and combined total chloro-triazine concentrations (i.e., atrazine+DEA+DIA+DACT). Continued monitoring will allow tracking of long-term concentration trends. It will also ensure that current atrazine label restrictions and best management practices remain effective at minimizing off-site movement of atrazine and that drinking water concentrations remain below levels of concern if changes in use practices or greater than normal flooding/storm events occur.

As private well owners are ultimately responsible for the quality of their drinking water, MDH recommends that MDA and MDH collaborate to increase education and outreach efforts to well owners. These efforts should include the development and refinement of web pages with enhanced information on risk factors for pesticide contamination and guidance on when a well should be tested. In the case of atrazine, a low-cost immunoassay screening test is readily available to private well owners through regional laboratories¹⁷ and this information should be made more readily available.

To clarify uncertainties in the occupational risk assessment, additional information is needed to address exposure to workers both mixing/loading and applying atrazine. With the exception of hand-held equipment, EPA does not typically combine exposure estimates for mixing/loading and applying pesticides. As such, this is not an atrazine-specific issue although it was identified as a potential gap during the course of this review. MDH recommends that MDA investigate state-specific handling practices for atrazine and request more information from EPA OPP on its rationale for not combining exposures.

EPA has recently released a policy paper proposing revised risk assessment methods for workers. Based on this policy, it is anticipated that the occupational risk assessment for atrazine will be modified, as part of EPA's 2010 review, to include greater protections for the developing young. Any new unacceptable risks identified in the revised assessment should be addressed by MDA as they pertain to current labeling and worker protection. MDH is committed to continue working with MDA to help resolve outstanding issues related to the human health effects of atrazine.

MDA has played an active role in procuring atrazine toxicity data from EPA considered necessary by MDH to conduct its assessments. MDH encourages MDA to continue facilitating

¹⁷ See <http://www.mda.state.mn.us/news/publications/licensing/waterwells/labsandanalytes.pdf>

discussion between MDH and EPA OPP on key toxicology data and assessments for atrazine; particularly the appropriateness of a separate assessment for DACT.

VI. Citations

Adgate JL, Barr DB, Clayton CA, Eberly LE, Freeman NC, Liroy PJ, Needham LL, Pellizzari ED, Quackenboss JJ, Roy A, Sexton K. Measurement of children's exposure to pesticides: analysis of urinary metabolite levels in a probability-based sample. *Environ Health Perspect*. 2001 Jun;109(6):583-90.

Alavanja MCR, Samanic C, Dosimeci M, Lubin J, Tarone R, Lynch CF, Knott C, Thomas K, Hoppin JA, Barker J, Coble J, Sandler DP, Blair A. (2003). Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study cohort. *American Journal of Epidemiology*, 157(9), 800-814.

Bassil KL, Vakil C, Sanborn M, Cole DC, Kaur JS, Kerr KJ. Cancer health effects of pesticides: systematic review. *Can Fam Physician*. 2007 Oct;53(10):1704-11.

Cantor KP, Blair A, Everett G, Gibson R, Burmeister LF, Brown LM, et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res* 1992;52:2447-55.

Chiu BC, Blair A. Pesticides, chromosomal aberrations, and non-Hodgkin's lymphoma. *J Agromedicine*. 2009;14(2):250-5.

Coble J, Arbuckle T, Lee W, Alavanja M, Dosemeci M. (2005). The Validation of a Pesticide Exposure Algorithm Using Biological Monitoring Results. *Journal of Occupational and Environmental Hygiene*, 2: 194-201.

Curwin BD et al. Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in iowa. *Ann Occup Hyg*. (2007)

Dakota County. 2006. Dakota County Ambient Groundwater Quality Study, 1999-2003 report. Available:
<http://www.co.dakota.mn.us/EnvironmentRoads/Health/Water/DrinkingWaterStudies.htm>

De Roos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, Burmeister LF, Blair A. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med*. 2003 Sep;60(9):E11.

Farr SL, Cooper GS, Cai J, Savitz DA, Sandler DP. (2004). Pesticide Use and Menstrual Cycle Characteristics Among Premenopausal Women in the Agricultural Health Study. *American Journal of Epidemiology*, 160(12):1194-204.

Hessel PA, Kalmes R, Smith TJ, Lau E, Mink PJ, Mandel J. A nested case-control study of prostate cancer and atrazine exposure. *J Occup Environ Med*. 2004 Apr;46(4):379-85.

Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, et al. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA* 1986;256:1141-7.

Hoar Zahm S, Weisenburger DD, Cantor KP, Holmes FF, Blair A. Role of the herbicide atrazine in the development of non-Hodgkin's lymphoma. *Scand J Work Environ Health* 1993;19:108–14.

Lioy PJ, Edwards RD, Freeman N, Gurunathan S, Pellizzari E, Adgate JL, Quackenboss J, Sexton K. House dust levels of selected insecticides and a herbicide measured by the EL and LWW samplers and comparisons to hand rinses and urine metabolites. *J Expo Anal Environ Epidemiol*. 2000 Jul-Aug;10(4):327-40.

MacLennan PA, Delzell E, Sathiakumar N, Myers SL, Cheng H, Grizzle W, Chen VW, Wu XC. Cancer incidence among triazine herbicide manufacturing workers. *J Occup Environ Med*. 2002 Nov;44(11):1048-58.

MacLennan PA, Delzell E, Sathiakumar N, Myers SL. Mortality among triazine herbicide manufacturing workers. *J Toxicol Environ Health A* 2003;66:501–17.

Mattix KD, Winchester PD, Scherer LR. Incidence of abdominal wall defects is related to surface water atrazine and nitrate levels. *J Pediatr Surg*. 2007 Jun;42(6):947-9.

MDA. 2005a. Atrazine in Minnesota Groundwater: A Summary Report. Available: <http://www.mda.state.mn.us/news/publications/chemfert/reports/atrazineingw.pdf>

MDA. 2005b. 2005 Water Quality Monitoring Report. Available: <http://www.mda.state.mn.us/chemicals/pesticides/maacearchive.htm>

MDA. 2008. 2008 Water Quality Monitoring Report. Available: <http://www.mda.state.mn.us/news/publications/chemfert/2008wqmreport.pdf>

Munger R, Isacson P, Hu S, Burns T, Hanson J, Lynch CF, Cherryholmes K, Van Dorpe P, Hausler WJ Jr. Intrauterine growth retardation in Iowa communities with herbicide-contaminated drinking water supplies. *Environ Health Perspect*. 1997 Mar;105(3):308-14.

Ochoa-Acuña H, Carbajo C. Risk of limb birth defects and mother's home proximity to cornfields. *Sci Total Environ*. 2009 Jul 15;407(15):4447-51.

Ochoa-Acuña H, Frankenberger J, Hahn L, Carbajo C. Drinking water herbicide exposure in Indiana and prevalence of small-for-gestational-age and preterm delivery. *Env Health Perspect*. 2009 Oct;117(10):1619-1624.

Rusiecki JA, De Roos A, Lee WJ, Dosemeci M, Lubin JH, Hoppin JA, Blair A, Alavanja MCR. Cancer incidence among pesticide applicators exposed to Atrazine in the Agricultural Health Study. *J Natl Cancer Inst*. 2004 Sep 15;96(18):1375-82.

Schreinemachers DM. Birth malformations and other adverse perinatal outcomes in four U.S. Wheat-producing states. *Environ Health Perspect*. 2003 Jul;111(9):1259-64.

Schroeder JC, Olshan AF, Baric R, Dent GA, Weinberg CR, Yount B, Cerhan JR, Lynch CF, Schuman LM, Tolbert PE, Rothman N, Cantor KP, Blair A. Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. *Epidemiology*. 2001 Nov;12(6):701-9.

Swan SH. Semen quality in fertile US men in relation to geographical area and pesticide exposure. *Int J Androl*. 2006 Feb;29(1):62-8; discussion 105-8.

Swan SH, Kruse RL, Liu F, Barr DB, Drobnis EZ, Redmon JB, Wang C, Brazil C, Overstreet JW. Semen quality in relation to biomarkers of pesticide exposure. *Environ Health Perspect*. 2003 Sep;111(12):1478-84.

USDA NASS. 2006. Agricultural Chemical Usage 2005 Field Crops Summary. National Agricultural Statistics Service.

USEPA. 2001a. Atrazine: Occupational and residential exposure assessment and recommendations for the Reregistration Eligibility Decision document. January 18, 2001 memorandum.

USEPA. 2001b. Drinking water exposure assessment for atrazine and various chloro-triazine and hydroxyl-triazine degradates. January 23, 2001 memorandum.

USEPA. 2002. The Grouping of a Series of Triazine Pesticides Based on a Common Mechanism of Toxicity. Document ID: EPA-HQ-OPP-2005-0481-0011. Available in Docket #: EPA-HQ-OPP-2005-0481.

USEPA. 2003a. Revised Atrazine Interim Reregistration Eligibility Decision Document. Available: http://www.epa.gov/oppsrd1/REDs/atrazine_combined_docs.pdf

USEPA. 2003b. Review of Atrazine Cancer Epidemiology. October 28, 2003 Memorandum.

USEPA. 2006. Triazine Cumulative Risk Assessment. HED Human Health Risk Assessment in Support of the Reregistration Eligibility Decisions for Atrazine, Simazine and Propazine.

USEPA. 2009. Revised Risk Assessment Methods for Workers, Children of Workers in Agricultural Fields, and Pesticides with No Food Uses. Document ID: EPA-HQ-OPP-2009-0889-0002. Available in Docket #: EPA-HQ-OPP-2009-0889.

U.S. Census Bureau, Population Division. 2008. Annual Estimates of the Resident Population for the United States, Regions, States, and Puerto Rico: April 1, 2000 to July 1, 2008 (NST-EST2008-01) December 22, 2008.

Van Maele-Fabry G and Willems JL. Prostate cancer among pesticide applicators: A meta-analysis. *Int Arch Occup Environ Health*. 2004 77:559-570.

Villanueva CM, Durand G, Coutté MB, Chevrier C, Cordier S. Atrazine in municipal drinking water and risk of low birth weight, preterm delivery, and small-for-gestational-age status. *Occup Environ Med.* 2005 Jun;62(6):400-5.

Winchester PD, Huskins J, Ying J. Agrichemicals in surface water and birth defects in the United States. *Acta Paediatr.* 2009 Apr;98(4):664-9.