

# **Response to Public Comments on the Minnesota Department of Health's Atrazine Human Health Assessment**



Minnesota Department of Health ♦ Division of Environmental Health ♦ Health Risk Assessment Unit

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## I. Introduction

On January 19, 2010, the Minnesota Department of Agriculture (MDA) issued a Notice of Comment Period in the [State Register](#) regarding the completion of a special state registration review of the herbicide atrazine. On MDA's [atrazine website](#), a [summary of the review](#) was presented along with five [agency-specific technical reports](#) prepared by MDA, the Minnesota Department of Health (MDH), and the Minnesota Pollution Control Agency (MPCA). MDA accepted comments on the atrazine registration review documents from January 19, 2010 through March 19, 2010.

The technical report prepared by MDH assessed potential human health risks from dietary (food and drinking water) and occupational exposure to atrazine and its chlorinated metabolites. Many parties, including the atrazine registrant Syngenta and three environmental/public interest groups, commented on specific aspects of MDH's technical assessment. These comments were reviewed by MDH and are summarized below, followed by MDH's response. A list of the names and affiliations of the parties submitting specific comments on the MDH technical assessment appears at the end of this document (See Section VII– List of commenters).

This document is organized by comment topic area, a synopsis of the submitted public comments, and MDH's response.

## II. Response to comments on atrazine toxicity studies

**Comment A.** Additional studies on the toxicological effects of atrazine should be incorporated into MDH's human health assessment.

**MDH Response:** MDH agrees that all of the available and relevant mammalian toxicological data should be considered in the human health risk assessment for atrazine and its chlorinated metabolites. As stated in the MDH assessment document, atrazine remains the subject of active areas of research. This new research is one reason why the US EPA is currently reevaluating atrazine. The ongoing research is also a primary reason why MDH has put its own reassessment of atrazine and metabolites on hold. In addition to the papers cited by commenters (e.g. Laws et al. 2009, Abraikwu et al. 2009, Pogrmic et al. 2009, and Lim et al. 2009) several new scientific papers and reports have been published in 2010. Many of these papers along with presentations from EPA are available in the EPA atrazine Science Advisory Panel (SAP) docket (EPA-HQ-OPP-2010-0481). While some of these papers do show adverse health effects including alterations to the endocrine systems in laboratory animals, the doses administered are above those already identified as the lowest observed adverse effect level (LOAEL) for the critical endpoint of disruption of the release of luteinizing hormone. For the studies that do show effects at lower doses, certain limitations make incorporating that information into a quantitative assessment difficult without follow-up studies. These limitations include the use of laboratory techniques that have not been reproduced by other investigators for atrazine

(e.g. Lim et al. 2009) and study designs that administer mixtures of chemicals (e.g. Enoch et al. 2007 and Stanko et al. 2010) that make it challenging to develop the type of reference dose needed for calculating upper limits for drinking water contaminated with either atrazine or any of its degradates. MDH will continue to follow these active areas of research as well as the EPA's reevaluation and will update the assessment of atrazine and its metabolites at the appropriate time in the future.

**Comment B.** A separate analysis for diaminochlorotriazine (DACT) is not warranted based on the available data.

**MDH Response:** Based on a review of the available studies, MDH has concluded that a human health risk assessment and health-based guidance values are warranted for DACT for two reasons. While some questions still require further investigation, the dataset of available mammalian toxicity studies is more than sufficient to conduct a quantitative risk assessment for this compound. The toxicological database for DACT includes one developmental study, three subchronic studies, and specialty studies that address effects of DACT, as a component of an atrazine metabolite mixture, on mammary gland development and prostate inflammation. In addition, recent studies indicate that atrazine and DACT do not always elicit the same adverse effects suggesting that they do not always work with a common mode of action. This evidence along with studies that show different toxicokinetic profiles for atrazine, DACT, and the other chlorinated metabolites (e.g. deethylatrazine and deisopropylatrazine) raises uncertainty as to whether atrazine is a reliable surrogate for the potential health effects caused by DACT.

Secondly, DACT is not only the predominant mammalian metabolite of atrazine, it is also an important environmental degradate of atrazine as well as other triazine pesticides found in groundwater monitoring. Therefore, rather than rely on the assessment of a surrogate compound (e.g. atrazine), it is more appropriate to apply chemical-specific guidance when DACT is detected in potential drinking water sources.

Deriving health-based guidance values for a contaminant that meets the criteria of 1) having been found in Minnesota groundwater and 2) having adequate mammalian toxicological studies is consistent with MDH's approach of utilizing the available science to ensure public health protection.

**Comment C.** It is premature to conclude that carcinogenicity is not a potential outcome. Although atrazine is not known to be mutagenic, studies have indicated that atrazine's demonstrated capacity to disrupt hormone system function can create conditions ripe for carcinogenesis (e.g., Fenton 2006).

The results of the mammary gland development assay in which pregnant rats were administered a high dose of atrazine or low doses of an atrazine metabolite mixture show that developmental delays can occur (Enoch et al. 2007). While it is biologically plausible that this type of delay may lead to increased susceptibility for a subsequent insult to the affected tissue (i.e. tumor initiation), studies showing this actually occurring *in vivo* have not yet been conducted for atrazine. Therefore it is not possible at this time

to assess what type of disruption (e.g., length of delay) in mammary gland development would change an organism's susceptibility to a carcinogen. It is important to understand that MDH's current guidance for atrazine, and any future reference dose derived for developmental effects, is protective for both atrazine's effect on mammary gland development and any subsequent change in cancer susceptibility. Questions remain, however, about the toxicity of mixtures of atrazine and its degradates. As stated in a previous response to comments, at this time MDH is unable to develop chemical-specific reference doses from study designs that administer mixtures of chemicals. MDH will continue to follow these active areas of research as well as the EPA's reevaluation and will update the assessment of atrazine and its metabolites at the appropriate time in the future.

### **III. Response to comments on atrazine epidemiology studies**

**Comment A.** Epidemiology studies of atrazine exposure and birth defects and reproductive outcomes should be incorporated into MDH's human health assessment. Epidemiological studies of adverse developmental impacts associated with atrazine in drinking water cumulatively represent a body of scientific evidence of harm.

**MDH Response:** In most cases, pesticide risk assessment has only relied on experimental animal studies as the basis for risk assessment, as the experimental toxicity database is usually extensive compared to the human epidemiology database. Although more epidemiology studies are available for atrazine compared to most other currently-registered pesticides, the experimental animal toxicity database for atrazine is still considerably more robust. Nonetheless, MDH agrees that application of epidemiological data to pesticide risk assessment has received inadequate attention. Epidemiology studies have the potential to help inform multiple components of the risk assessment process; including hazard identification, identification of susceptible human subpopulations, and dose-response assessment.

Submitted comments were specific to several recent epidemiology studies of atrazine drinking water exposure and birth defects/reproductive outcomes. One must be cautious of combining studies of disparate health effects into one "weight-of-evidence" conclusion, as birth defects and birth outcomes (such as small-for-gestational age or low birth weight), should not be assumed to have the same etiology. Even within health outcome "type", such as birth defects, different anomalies should not be indifferently combined, either between or within studies, unless there is an indication that they may be homogeneous with respect to presumed etiology.

Drinking water epidemiology studies in particular present limitations to their use in risk assessment due to complexity and uncertainty in exposure assessment. Studies of drinking water fundamentally involve exposure to mixtures, which make it difficult to evaluate single chemicals in isolation. Unvalidated surrogates for atrazine exposure, such as regional raw water measurements or proximity to corn fields, introduce additional uncertainty. Further, without information on individual water use (e.g., exposures outside

the home) and residential history during pregnancy, the validity of the drinking water data as a measure of exposure in dose-response assessment is limited.

Prior to looking across studies of atrazine and birth outcomes or birth defects and drawing an overall weight-of-evidence conclusion, each of the studies must be critically evaluated in terms of study design, bias, potential confounders or effect modifiers, appropriate statistical analysis, etc. Then, a framework for how to incorporate the studies into the existing health risk assessment paradigm must be determined. In September 2010, EPA sought peer review from the FIFRA Science Advisory Panel (SAP) on its plan for incorporating atrazine (non-cancer) epidemiology studies into regulatory risk assessment, including studies which were not available to MDH at the time the original assessment was conducted (e.g., Waller et al. 2010, Sathyanarayana et al. 2010). Materials from this meeting can be found at [www.regulations.gov](http://www.regulations.gov), Docket #EPA-HQ-OPP-2010-0481. Creating a concurrent, similar peer review process at the state level was deemed redundant and would require a longer time frame to achieve the same level of review. After minutes from the September 2010 FIFRA SAP meeting are made available, MDH will critically evaluate EPA's proposed approach to considering and incorporating epidemiological evidence into the risk assessment, along with the SAP's comments on this approach. MDH may or may not concur with EPA on its proposed approach. As a result of MDH's critical review, MDH will determine if its level of concern regarding atrazine human health risks has changed. Additional recommendations on the status of atrazine registration in Minnesota may be provided to MDA at this time.

**Comment B. Results from epidemiological studies should not be disregarded when reported effects are similar to those reported in mammalian toxicology studies.**

**MDH Response:** Both recent experimental toxicology and epidemiology research have largely focused on the potential for reproductive and developmental effects arising from atrazine's known disruption of the hypothalamus-pituitary-gonadal axis. Disruption of the neuroendocrine system is assumed to be a concern for exposures to humans as well as rodents. With regard to low birth weight or small-for-gestational age effects reported in the epidemiology literature, the animal data show that atrazine and/or its metabolites do cause weight effects in offspring, but only at high (higher than any potential human drinking water exposure), maternally-toxic doses, indicative of generalized toxicity. Other recent epidemiology studies have focused on birth defects such as abdominal wall defects. Based on available experimental data reported in the US EPA 2003 IRED document, atrazine and its metabolites have been shown to cause developmental effects (e.g. decreased fetal body weight and delayed ossification) in rat and rabbit studies, however these effects only occur at dose levels that compromise maternal health. In more recent studies, administration of an atrazine metabolite mixture (AMM) to pregnant rats resulted in delayed mammary gland development in female offspring (Enoch et al. 2007) and delayed puberty and chronic prostate inflammation in male offspring (Stanko et al. 2010). In both cases, these effects occurred at doses that are lower than those reported in previous studies and that did not result in maternal toxicity. While some scientific debate exists regarding the biological significance of developmental delays that may not lead to a functional deficit, chemical exposures that lead to altered development remain a

concern for developing health-protective guidance. As noted previously, the use of mixture data in any quantitative assessment is difficult based on current risk assessment methodology.

MDH recognizes that humans may be more sensitive or respond differently than laboratory animals to the toxicological effects of atrazine, as has been demonstrated with other contaminants (e.g., arsenic). It is important to note that EPA and MDH's current risk assessments are based on the health effect that the current weight of scientific evidence supports as the critical effect. This critical effect identified in experimental toxicology studies is the attenuation of luteinizing hormone surge (a disruption of the hypothalamic-pituitary-gonadal axis). A reference dose based on this effect will be lower than a reference dose based on any other health effect. Generally, disruption of the hypothalamic-pituitary-gonadal axis occurs at a dose about two- to five-fold lower than the dose that would cause other effects. As stated above, studies that do show effects at lower doses (e.g. Lim et al., 2009, and Enoch et al., 2007) have certain limitations that make it challenging to develop the type of reference dose needed for calculating upper limits for drinking water contaminated with either atrazine or any of its degradates. MDH addresses the concern for potential adverse effects at these lower doses by the application of a database uncertainty factor when deriving the reference dose.

#### **IV. Response to comments on atrazine drinking water monitoring**

**Comment A.** The assessment of atrazine contamination in drinking water is improperly based on very limited sampling data in Minnesota community water systems. MDH did not include monitoring data from more frequently monitored public water systems representing 10 other states.

**MDH Response:** MDH chose to evaluate drinking water data from 2000 onwards to account for restrictions on the use of atrazine implemented in the early-mid 1990's, which was expected to have reduced the amount of atrazine entering surface water and groundwater. A total of 4,995 samples were available from public water supplies (community water systems=2,782, non-transient non-community water systems=2016, transient non-community water systems=197) during this 9-year time period. MDH acknowledges that infrequent sampling from public water systems means that peak atrazine concentrations are unlikely to be captured; particularly since public water systems are not required to sample for atrazine during the season of greatest agricultural use. However, no sample taken during this time period resulted in an atrazine concentration above 3 ppb, with 1.8 ppb being the highest detected concentration (in a NTNC public water system).

To supplement limited sampling data from public water systems, MDH also evaluated atrazine results from MDA's groundwater monitoring program, which focuses on the regions of Minnesota considered most vulnerable to pesticide contamination (Central Sand Plains and Southeast Karst regions). These concentration results represent a "worst-case" scenario for shallow drinking water wells finished in glacial outwash sand aquifers and karst bedrock aquifers. No sample has exceeded 3 ppb in wells or springs monitored

by MDA since 2003. The 2003 exceedance (3.04 ppb for combined atrazine+DEA+DIA) was in a well located in the Central Sands region. Data from the MDA monitoring program indicate that atrazine concentrations in this area continue to decline. Additionally, MDA analysis of atrazine in groundwater samples collected from shallow, vulnerable aquifers indicates no seasonality to atrazine concentrations.

While no seasonal “spikes” have been observed in groundwater, surface water systems may exhibit different tendencies. Systems using surface water are significantly more vulnerable to contamination than those using ground water and seasonal spikes of atrazine are more likely to occur in surface water systems. In Minnesota, there are only three community water systems and zero non-community public water systems using surface water in areas of high atrazine use potential (i.e., corn growing counties, see Appendix A). These three systems use either powdered activated carbon filtration (Fairmont), Ranney wells/membrane filtration (Mankato) or conventional treatment (St. Cloud). In 1995, Mankato (designated as “groundwater under the influence of surface water” due to the shallow nature of the Ranney collector-type well) increased its monitoring beyond SDWA-mandated regulatory requirements to determine if seasonal concentration spikes of agrichemicals were occurring in drinking water. Weekly testing of finished water was conducted from 4/25/95 through 7/12/95. All atrazine results were at or below the limit of detection of 0.30 ppb. Forty water samples have been collected from the St. Cloud CWS, from February 1993-February 2010. Eight-five percent of these samples were taken during the 2<sup>nd</sup> or 3<sup>rd</sup> quarter of the year, including 2-week interval sampling from 5/15/95 through 6/25/95. All results were below the limit of detection of 0.1-0.3 ppb except for 6 samples collected in June in the mid-1990’s (0.3-0.5 ppb). Thirty-nine samples are available from the Fairmont system from January 1994 through February 2010. Eighty-two percent of these samples were taken during the 2<sup>nd</sup> or 3<sup>rd</sup> quarter of the year. Concentrations ranged from less than detection limit (64% of samples) to 0.70 ppb. The dearth of surface water systems in Minnesota’s corn-growing region, the treatment methods employed by these systems and the available drinking water data suggest that large, seasonal spikes in atrazine concentration may not be of major concern in Minnesota. However, MDH is still internally discussing the merits of more intensive monitoring for atrazine during the use season in select systems and areas considered most vulnerable to contamination.

Public water system monitoring under the Safe Drinking Water Act (SDWA) is also limited by lack of data on atrazine degradates. In response, MDH, in conjunction with MDA, recently undertook a special pesticide degradate study in 83 community water supply wells, with a focus on those considered vulnerable to pesticide contamination. Analytes included parent atrazine along with DEA, DIA, and DACT. Atrazine and its degradates were detected in 6% of samples with the highest concentration of 0.10 ppb found for DACT. The study report is available on the MDH Drinking Water Protection website at <http://www.health.state.mn.us/divs/eh/water/pesticide.pdf>.

The 100+ more frequently monitored systems in 10 other states were among those identified by EPA as the most vulnerable to atrazine contamination in the U.S. No Minnesota systems were included in this list. Based on results from the available drinking

water and groundwater data described above, MDH believes that it is more appropriate to use Minnesota-specific monitoring data to describe atrazine contamination potential rather than rely on results from other states, which may represent disparate atrazine use practices, source water protection scenarios, water system characteristics, or other factors not relevant to circumstances in Minnesota.

**Comment B.** Infrequent monitoring data will always skew towards not finding atrazine detections and therefore, systems granted waivers may be just as susceptible to high atrazine spikes as are other systems.

**MDH Response:** Although it is possible that systems both with and without sampling waivers may demonstrate seasonal spikes in agrochemicals, there are prerequisites which make it less likely that such systems would be granted a waiver for reduced monitoring. Between 1993 and 1995, EPA required all public water systems 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, and whether the system was ultimately granted an atrazine sampling waiver. When a water provider can show that certain contaminants have not been in, and are not likely to enter water supplies, the water provider becomes eligible for waivers from testing. Systems can only petition the state for a 3-year waiver after 3 consecutive annual sampling results below the detection limit. Based on multiple sources of evidence described above, MDH has no reason to believe that Minnesota public water systems are comparable to the more intensively monitored systems in other states in terms of high concentration spikes.

**Comment C.** Minnesota's review is based on a drinking water standard that continues to rely on running annual averages. The result is that spikes in atrazine concentrations are effectively ignored.

**MDH Response:** In the MDH human health assessment, sampling results are compared to 3 ppb, as this concentration is the current MCL and state-based Health Risk Limit (HRL) value for atrazine. Although regulatory compliance with the MCL is based on a running annual average, the MDH human health assessment reported drinking water results in a variety of formats, including maximum concentrations. Since 2000, no *single* sample from public water systems or private drinking water wells in Minnesota has been found to be above 3 ppb. HRL values are not used for regulatory purposes, but rather are provided by MDH to risk assessors and risk managers for use in making decisions and evaluating health risks related to groundwater contaminants. HRLs are not based on running annual averages. Further, when MDH re-assesses its groundwater guidance for atrazine (anticipated within the next year), the result will be separate HRL values based on specific durations of exposure, including values for acute (one-day) and short-term (up to 30 day) exposure durations. These acute and short-term risk values will provide a basis for comparison to any temporary spikes in atrazine concentration.

**Comment D.** Minnesota should take immediate steps to increase the frequency of its atrazine monitoring regime.

**MDH Response:** Minnesota continues to supplement standard SDWA monitoring requirements for atrazine with a variety of state-specific studies. Past projects, as described in the human health assessment, include the 2004 MDA Drinking Water Survey, a 2009 MDA Potable Well Study in Southeast Minnesota using an immunoassay method to screen for atrazine and its degradates, and a joint MDH-MDA study of pesticide degradates in vulnerable community water system wells. In addition to projects targeting drinking water, Minnesota is one of few states with a comprehensive pesticide monitoring program in surface and groundwater. Atrazine has been included in this program since 1985 with atrazine degradate analysis (DEA and DIA) added in 2000 and DACT added in 2008.

## **V. Response to comments on MDH risk assessment framework**

**Comment A.** Applicators are exposed to unsafe levels of atrazine. If Minnesota was to reduce the amount of atrazine that can be applied (or phase out its use altogether), one immediate positive effect for Minnesota farmers would be reducing contamination of their bodies.

**MDH Response:** EPA's current occupational risk assessment for atrazine indicates that all mixer/loader/applicator scenarios, even those conservatively assuming the maximum label rate of 2 lbs/acre and an exposure duration of up to 6 months, are above the margin of exposure (MOE) of 100, meaning that estimated exposures are at least 100-fold lower than the no-observed-adverse-effect-level from critical toxicology studies. Several Minnesota-specific pesticide use surveys conducted over the past decade indicate that typical use rates of atrazine by Minnesota growers are declining and are well below the 2 lbs/acre maximum label rate. In 2007, atrazine was used on 22% of surveyed Minnesota corn acres, with an average annual application rate per farmer of 0.57 lbs/acre/year statewide (down from 0.67 lbs/acre/year in 2003), and 0.59 lbs/acre/year in southeast Minnesota counties, where atrazine is often used at higher rates compared to other regions of the state. Thus, the margins of exposure in typical Minnesota scenarios would likely be even higher than those suggested by EPA's current occupational risk assessment.

EPA's existing occupational risk assessment for atrazine may be revised during EPA's current re-review of atrazine due to more recently available toxicology or epidemiology studies and/or more protective occupational risk assessment approaches. Currently "acceptable" occupational risks may be found "unacceptable" at some point during the review. MDH plans to critically evaluate EPA's selection of toxicology/epidemiology studies for use in occupational risk assessment as well as any additional revisions proposed to the assessment and will then determine if the MDH's level of concern regarding occupational risks has changed. Additional recommendations on the status of atrazine registration in Minnesota may be provided to MDA at this time.

**Comment B.** A drinking water limit of 1 ppb or lower for atrazine and degradates is necessary to protect public health, based on lower concentrations linked to health effects in epidemiology studies.

**MDH Response:** Epidemiology studies can be used to inform or develop the dose-response component of risk assessment. A critical aspect for inclusion in dose-response analysis is the validity and specificity of the study's exposure assessment. Individual exposure in many atrazine epidemiology studies is estimated indirectly using surrogates such as geometric mean atrazine levels in regional surface water. This makes it difficult to directly estimate chemical intake and integrate the information into quantitative risk assessment. Although study limitations are present, Ochoa-Acuña et al. (2009) may lend itself best to use in quantitative risk assessment, as this study used more detailed monitoring data from several community water systems and adjusted for several individual-level potential confounders in the final models. In this study, atrazine concentrations less than 1 ppb in drinking water were associated with a significant increase in the prevalence of small-for gestational-age birth.

EPA presented its evaluation of each epidemiology study and its overall plan for incorporating epidemiology studies into the atrazine risk assessment to the FIFRA SAP in September 2010. Creating a concurrent, similar process at the state level was determined to be redundant and would require a longer time frame to achieve the same level of study review and peer-review. Once meeting minutes from the September SAP meeting are made available, MDH plans to critically evaluate EPA's approach to considering and/or incorporating epidemiology into the atrazine risk assessment, along with the SAP's recommendations on this approach. As a result of MDH's critical review, MDH will determine if its level of concern regarding atrazine human health risks has changed. Additional recommendations on the status of atrazine registration in Minnesota may be provided to MDA at this time. Looking beyond the current EPA re-evaluation of atrazine, MDH remains committed to tracking emerging science to ensure that Minnesota's health-based guidelines for atrazine are scientifically sound. If at any time new atrazine data indicate new risk concerns, MDH will provide MDA with the risk assessment support necessary for MDA to take appropriate action.

**Comment C.** Precautionary measures should be taken to protect public health in the face of uncertainty, as reported health effects for atrazine have been observed among vulnerable population sub-groups (infants, fetuses, pregnant women) and as seen with other chemicals, it may take many years to fully understand the impacts of atrazine exposure.

**MDH Response:** The current MDH assessments of atrazine and DACT are being conducted using risk assessment methodology revised and promulgated into rule in 2009. This methodology incorporates the stipulations of the 2001 Health Standards Statute that

requires guidance developed for water to be protective of susceptible subpopulations. MDH methodology meets this requirement through the use of multiple durations of exposure in the assessments that account for periods of development and by incorporating life-stage specific water intake rates.

**Comment D.** High-level, brief spikes in atrazine concentrations in drinking water present risks of concern that are not addressed in the human health assessment.

**MDH Response:** As stated in the MDH human health assessment document, MDH has put its own reassessment of atrazine and metabolites on hold pending the EPA re-evaluation of atrazine. In the reassessment that MDH is conducting, mammalian toxicity information for four exposure durations are being evaluated for atrazine and DACT. These time periods include up to 24 hours (acute), greater than 24 hours and up to 30 days (short-term), greater than 30 days and up to 10 percent of a lifetime (subchronic), and greater than 10 percent of a lifetime (chronic). Assessments that include these four exposure durations will provide guidance to address concerns over potential high-level spikes in atrazine (and DACT) concentrations.

## VI. References

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## **VII. List of commenters on Atrazine Human Health Assessment**

1. Dave Flakne  
State Government Relations  
Syngenta Crop Protection
2. Andrew Wetzler, Jennifer Sass, Mae Wu  
Natural Resources Defense Council
3. Samuel Yamin  
Public Health Scientist  
Minnesota Center for Environmental Advocacy
4. Ryan Stockwell  
Director of Energy and Agriculture  
The Minnesota Project

Appendix A. Corn production by Minnesota county

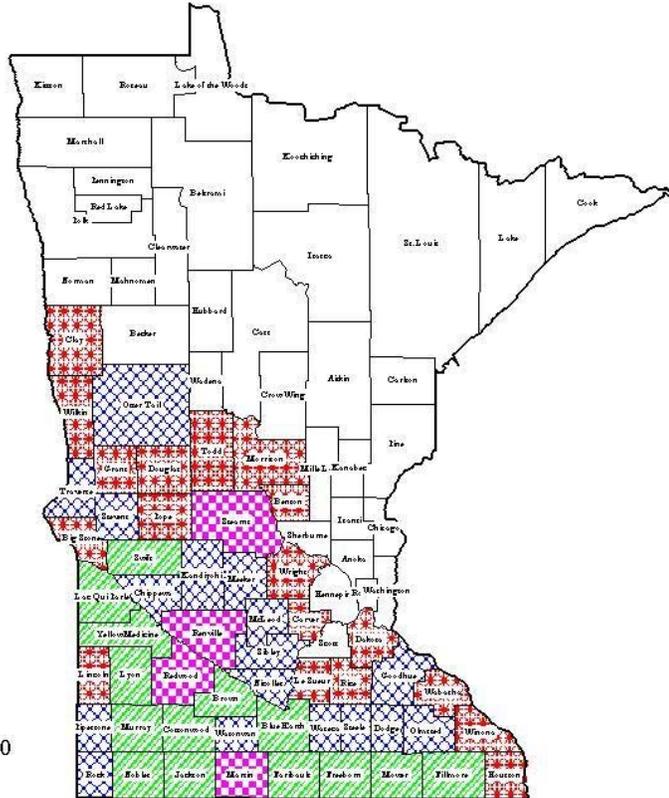
# Minnesota Corn Production

**CORN ACRES PLANTED**



State total corn acres planted = 7,500,000

Prepared by J.L. Farmakis, Inc. 5/05



Source: MN Agricultural Statistics '04