

## 1. Introduction

The primary purpose of this Interaction Profile for atrazine, deethylatrazine, diazinon, nitrate, and simazine is to evaluate data on the toxicology of the “whole” mixture and the joint toxic action of the chemicals in the mixture in order to recommend approaches for assessing the potential hazard of this mixture to public health. To this end, the profile evaluates the whole mixture data (if available), focusing on the identification of health effects of concern, adequacy of the data as the basis for a mixture Minimal Risk Level (MRL), and adequacy and relevance of physiologically-based pharmacokinetic/ pharmacodynamic (PBPK/PD) models for the mixture. The profile also evaluates the evidence for joint toxic action—additivity and interactions—among the mixture components. A weight-of-evidence (WOE) approach is commonly used in these profiles to evaluate the influence of interactions in the overall toxicity of the mixture. The weight-of-evidence evaluations are qualitative in nature, although the Agency for Toxic Substances and Disease Registry (ATSDR) recognizes that observations of toxicological interactions depend greatly on exposure doses and that some interactions appear to have thresholds. Thus, the interactions are evaluated in a qualitative manner to provide a sense of what influence the interactions may have when they do occur. The profile provides environmental health scientists with ATSDR Division of Toxicology and Environmental Medicine’s (DTEM) recommended approaches for the incorporation of the whole mixture data or the concerns for additivity and interactions into an assessment of the potential hazard of this mixture to public health. These approaches can then be used with specific exposure data from hazardous waste sites or other exposure scenarios.

The atrazine, deethylatrazine, diazinon, nitrate, and simazine mixture was chosen as the subject for this interaction profile based on analyses of frequently occurring mixtures in groundwater. As part of the National Water-Quality Assessment Program of the U.S. Geological Survey, untreated groundwater samples were collected from 1,255 domestic (rural) wells and 242 public water-supply wells, and analyzed for 60 volatile organic compounds (VOCs), 83 pesticides, and nitrate (Squillace et al. 2002). The most frequently occurring four-chemical mixture in these groundwater samples consisted of two triazine herbicides and a metabolite (atrazine, simazine, and deethylatrazine), plus nitrate. Concentrations of the 144 monitored chemicals were screened against drinking water standards and health advisories. Nitrate was the chemical that most frequently exceeded its standard or criterion (maximum contaminant level [MCL] for nitrate = 10 mg/L as nitrogen). Atrazine and simazine did not exceed their MCLs (0.003 and 0.004 mg/L, respectively). Diazinon was the most frequently detected organophosphorus insecticide, and exceeded its drinking water health advisory (0.0006 mg/L) in one well. Diazinon was selected for the mixture in order to evaluate possible interactions of organophosphates with other

pesticides. The primary route of exposure for this mixture is likely to be oral and the durations of concern are intermediate and chronic.

Before evaluating the relevance of joint toxic action data for these chemicals, some understanding of endpoints of concern for oral exposure to this mixture is needed. The endpoints of concern include the critical effects that are the bases for MRLs or other health guidance values, and any other endpoints that may become significant because they are shared targets of toxicity or due to interactions (ATSDR 2001a).

In order to satisfy the requirements of the Food Quality Protection Act (FQPA) to assess the cumulative effects of chemicals that have a common mechanism of toxicity, certain triazine herbicides, including atrazine, its metabolite deethylatrazine (also known as desethylatrazine, desethyl s-triazine), and simazine, are being reevaluated by the Environmental Protection Agency's (EPA) (2002c) Office of Pesticide Programs. The EPA (2002c) has concluded that these triazines should be considered as a *Common Mechanism Group* based on suppression of the luteinizing hormone ovulatory surge and the resulting effects on reproductive function and reproductive development. EPA (2002b) has derived a new chronic reference dose (RfD) for atrazine and its chlorinated metabolites, including deethylatrazine, based on reproductive effects; this RfD is not on the Integrated Risk Information System (IRIS) (2003), but its derivation includes a consideration of mechanistic and toxicological data that have become available since the RfD on IRIS was derived. EPA has not yet derived a new RfD for simazine. Further explanation is provided in Appendices A and B. ATSDR (2003) evaluated atrazine in a toxicological profile. ATSDR (2003) derived an intermediate oral MRL of 0.003 mg/kg/day based on reproductive effects (delayed onset of estrus) in pigs. Thus, reproductive effects are the effects of concern for atrazine, deethylatrazine, and simazine.

Diazinon's critical effect, which is the basis of ATSDR (1996) MRLs and EPA (2000; IRIS 2003) RfDs, is neurological, due to inhibition of acetylcholinesterase. Nitrate, through reduction to nitrite, causes methemoglobinemia, which is the critical effect for EPA's (IRIS 2003) RfD.

None of these chemicals has been classified as a carcinogen (see Appendices), but a chemical interaction between atrazine and nitrite and between simazine and nitrite results in the formation of N-nitrosoatrazine and N-nitrososimazine. These nitrosamines have not been adequately tested for carcinogenicity, but structure-activity considerations raise a concern that they may have carcinogenic potential.

Thus, the endpoints of concern for this mixture are reproductive, neurological, hematological, and carcinogenic. The structures and the Chemical Abstracts Service (CAS) Registry Numbers of these chemicals are provided in Appendix E.