

# Inclusion of Pesticide Transformation Products Is Key to Estimating Pesticide Exposures and Effects in Small U.S. Streams

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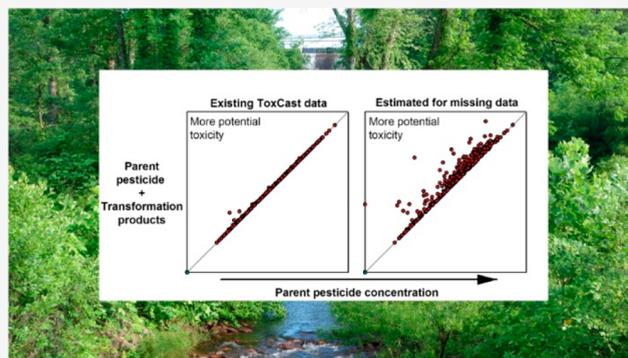


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**ABSTRACT:** Improved analytical methods can quantify hundreds of pesticide transformation products (TPs), but understanding of TP occurrence and potential toxicity in aquatic ecosystems remains limited. We quantified 108 parent pesticides and 116 TPs in more than 3 700 samples from 442 small streams in mostly urban basins across five major regions of the United States. TPs were detected nearly as frequently as parents (90 and 95% of streams, respectively); 102 TPs were detected at least once and 28 were detected in >20% samples in at least one region—TPs of 9 herbicides, 2 fungicides (chlorothalonil and thiophanate-methyl), and 1 insecticide (fipronil) were the most frequently detected. TPs occurred commonly during baseflow conditions, indicating chronic environmental TP exposures to aquatic organisms and the likely importance of groundwater as a TP source. Hazard quotients based on acute aquatic-life benchmarks for invertebrates and nonvascular plants and vertebrate-centric molecular endpoints (sublethal effects) quantify the range of the potential contribution of TPs to environmental risk and highlight several TP exposure–response data gaps. A precautionary approach using equimolar substitution of parent benchmarks or endpoints for missing TP benchmarks indicates that potential aquatic effects of pesticide TPs could be underestimated by an order of magnitude or more.



## INTRODUCTION

Pesticide degradation is often considered a beneficial attribute that can reduce threats posed by pesticide use to wildlife and people.<sup>1</sup> The “disappearance” of a pesticide active ingredient (hereafter referred to as “parent”) in the environment, however, often is the result of biological and chemical degradation (transformation) that creates one or more transformation products (TPs).<sup>2</sup> Biota may have greater exposure to TPs than to many parents, as TPs tend to be more mobile and more persistent in hydrologic systems than the parent compound.<sup>3–7</sup> TPs have been detected in hydrologic systems more frequently and at higher concentrations than corresponding parent compounds<sup>8–11</sup> but historically have received far less attention in terms of assessment of effects,<sup>12</sup> regulation,<sup>13</sup> and monitoring and risk analysis.<sup>12–15</sup>

Transformation of pesticide compounds was documented at least as early as the 1950s.<sup>16,17</sup> Investigation of TP environmental occurrence and fate intensified in the 1990s with an initial focus on characteristics, occurrence, and fate of herbicide TPs, particularly those of chloroacetanilide herbicides (alachlor, metolachlor, and acetochlor) and triazine herbicides (atrazine, cyanazine), in U.S. agricultural soils and underlying groundwater.<sup>2,18–21</sup> Investigations of pesticide TPs have since

expanded to include insecticides<sup>22–25</sup> and fungicides,<sup>13,26,27</sup> as well as additional herbicides (including those of glyphosate, the most heavily used pesticide worldwide);<sup>28,29</sup> diverse environmental compartments, including surface water,<sup>5,11,23,30,31</sup> precipitation,<sup>32</sup> and air;<sup>33</sup> and urban landscapes.<sup>14,23,25,27,34</sup>

The toxicity of TPs has been recognized since the 1970s,<sup>35</sup> with one survey of 89 TPs and 34 parents reporting that 70% of TPs were as or less toxic and 30% were more toxic than the parent.<sup>36</sup> In a few cases the parent undergoes metabolic activation so that the TP is the pesticidal form, here the parent is called a propesticide. Monitoring and risk assessments focus on TPs that are “major metabolites” (>10% of the parent in laboratory tests) and/or are known to have high intrinsic toxicity. Because of regulatory concern for toxicity (i.e., hazard), less attention has been paid to TPs that are environmentally mobile and persistent but not considered

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toxicologically relevant.<sup>13</sup> Historically, the toxicological relevance of some TPs has been recognized only 20 to 30 years after commercial introduction of the parent.<sup>13</sup>

Measurement of TPs—known or hypothesized to exist—has been hampered by inadequate analytical capabilities and insufficient reference materials.<sup>13,27</sup> The greater solubility and polarity and lesser volatility of TPs than parents make TPs less amenable to historical methods based on gas chromatography. Initial field studies (e.g., refs 2 and 34) measured 10 or fewer TPs, but that number has continued to increase with improved analytical methods. Liquid chromatography/tandem mass spectrometry analytical instruments now provide increased sensitivity and selectivity that allows for the determination of parents and their more polar TPs at environmentally relevant concentrations.<sup>37–39</sup> The U.S. Geological Survey (USGS), a pioneer in the measurement of pesticide TPs,<sup>5</sup> evolved from measuring 8 TPs in surface water and groundwater in the 1990s<sup>10</sup> to measuring 40 TPs in the 2000s.<sup>22,40</sup> More recently, target methods, including those of the USGS, have expanded to measure more than 100 TPs.<sup>12,26,41,42</sup> Newer target and suspect-screening methods measure hundreds to more than a thousand TPs,<sup>27,43</sup> although their application in field studies has been limited to a relatively small number of samples. Despite these analytical advances, research regarding TP exposure and toxicological effects of TPs in stream communities continues to be the exception rather than the rule.<sup>6,15,27</sup>

Here we present results of an extensive investigation of pesticide parents ( $n = 108$ ) and TPs ( $n = 116$ ) in 442 small streams across five major regions of the United States with basins that span a range of land uses. We test the hypotheses that TPs in small U.S. streams, especially in urban areas, are more widespread and diverse than previously known, that groundwater is an important source of TPs to streams, and that the potential toxicity of TPs is underestimated. We use a recently developed (2013) analytical method to quantify concentrations of 224 pesticide compounds in samples collected weekly during one spring-summer growing season in each region. We interpret parent–TP relations in the context of streamflow conditions and evaluate the contribution of TPs, individually and as a component of pesticide–compound mixtures, to the risk to instream biota. To our knowledge, this is the most spatially extensive study to date of pesticide TPs in surface water, the first to quantify the potential contribution of a large suite (>100) of TPs to potential instream biological effects at this scale, and the first to evaluate sublethal effects of TPs using molecular endpoints.

## METHODS

**Site Selection and Study Design.** The USGS Regional Stream Quality Assessment sampled from 76 to 100 small (wadeable) streams in each of five regions of the United States (Figure 1; Supporting Information Figure S1A–E; <https://webapps.usgs.gov/rsqa/#/>), about three-quarters of which are headwater streams (i.e., stream order 1–3) (Table S1). The five regions (Midwest, Southeast, Pacific Northwest, Northeast, and Coastal California) were selected to represent diverse natural climatic and geographic settings across the United States, but all contained extensive agricultural and/or urban development. Sampling-site basins within each region span gradients of agricultural and urban land use: Developed land in Midwest basins was largely agricultural and developed land in basins in the other four regions was largely urban (Table S1).<sup>44</sup>



**Figure 1.** Small streams were investigated in five regions of the United States: Midwest (2013), Southeast (2014), Pacific Northwest (2015), Northeast (2016), and Coastal California (2017). Detailed maps of the study areas and information on stream sites sampled and their basins are available in the [Supporting Information](#).

One region was assessed each year (2013–2017) during the spring and early summer growing season; samples for analysis of water quality were collected weekly for 4–12 weeks, with the exception of 11 reference sites in the Northeast that were sampled once. Basin boundaries and site characteristics are available for download.<sup>45,46</sup>

**Sample Collection and Analytical Methods.** Weekly discrete water samples were collected following USGS protocols.<sup>47–52</sup> In brief, samples were collected using depth- and width-integrating methods in which subsamples were collected at 10 increments across the stream and composited into a single sample. Thus, one sample represents a single date and time. From this composited sample, 20-mL subsamples were filtered (0.7- $\mu\text{m}$  pore-size glass fiber disk filter) into 40-mL amber glass vials, stored on ice, and shipped on ice within 1–2 days of collection to the USGS National Water Quality Laboratory (Denver, CO). A broad-spectrum direct-aqueous-injection LC/MS-MS method<sup>53</sup> was used to quantitate concentrations of 108 parent pesticides and 116 TPs in water: 57 herbicide parent compounds and 66 herbicide TPs, 40 insecticide parents and 47 insecticide TPs, and 11 fungicide parents and 3 fungicide TPs. A list of analytes and analyte-specific information are provided in Table S2. This list largely comprises current-use pesticides; of the 108 parent pesticides analyzed, 6 had been canceled at the start of this study in 2013, 2 more were canceled by 2016 (Table S2),<sup>54</sup> and no additional cancellations occurred during 2016–2020.

**Quality Control.** Laboratory quality control included reagent spike and blank samples and addition of surrogate compounds to every sample. Quality control for environmental samples consisted of field blanks, replicates, and spikes. Spike recoveries for 2013–2015 are published and interpreted.<sup>55</sup> Results of quality-control samples are discussed and summarized in the [Supporting Information text](#) and Tables S3–S6.

**Data Handling and Analysis.** Analytes, their method detection levels, and laboratory reporting levels are reported in Table S2. Some censored data (i.e., reported nondetections) have raised reporting levels because of analytical or environmental circumstances such as interference in the sample, changed instrumental sensitivity during a run, or failure to meet one of the three required criteria for determining a detection.<sup>55</sup> In cases where censored data had raised reporting

levels that were above the next highest calibration standard, these results were dropped from the data set (i.e., considered to be missing data) because the analysis did not meet the desired laboratory analytical resolution (see the [Supporting Information](#) for details). This occurred in <4% of sample results.

Several compounds required additional consideration. Dichlorvos is both a parent insecticide and a TP of the insecticide naled; for this study, dichlorvos was categorized as a parent. Similarly, methamidophos is both a parent insecticide and a TP of the insecticide acephate, but because the use of methamidophos as a pesticide was canceled in 2009 we categorized it as a TP. Carbendazim (parent thiophanate-methyl) has industrial use in caulks and other building supplies, but its only conventional use is in tree injection; residues of carbendazim therefore are likely from transformation of the parent, and carbendazim was categorized as a TP. The TP 1H-1,2,4-triazole (parent propiconazole, a fungicide) had an extreme number of raised reporting levels; censoring at the calibration-standard reporting level affected 82% of the 3705 chemical determinations for this TP. The remaining results therefore were not considered representative, and 1H-1,2,4-triazole was excluded from this study, although it is included in [Table S2](#). Three TPs, 2-chloro-*N*-(2-ethyl-6-methylphenyl)acetamide, 2-(1-hydroxyethyl)-6-methylaniline (HEMA), and sec-acetochlor-OA, can be derived from either of the herbicides acetochlor or metolachlor; for simplicity they were assigned acetochlor as a parent for interpretative comparisons.

Computations and analyses, with the exception of the screening assessment, were primarily done using functionality of base R and R packages *dplyr*,<sup>56</sup> *ggplot2*,<sup>57</sup> and *rcompanion*.<sup>58</sup> Summations of TP concentrations ( $\Sigma[\text{TP}]$ ) were done on a molecular-weight basis.

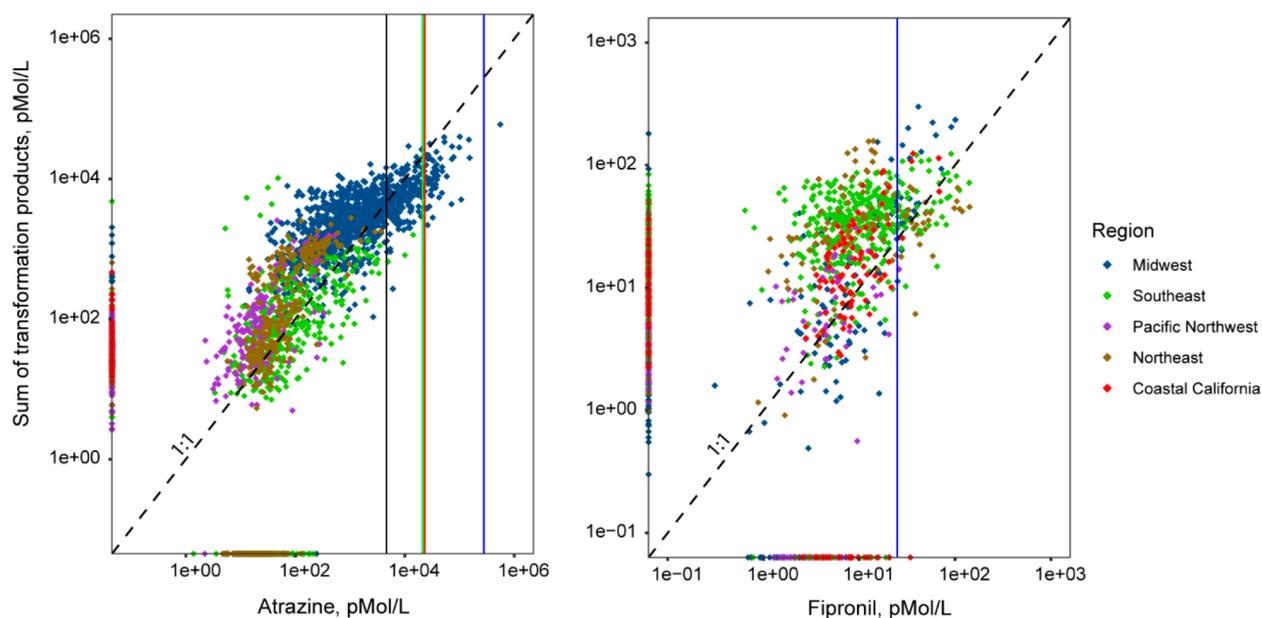
**Determination of Baseflow Fraction.** Baseflow as a fraction of streamflow (baseflow fraction) was calculated for each sample day at all sites where stream-gaging data were available. Daily streamflow derived from USGS gaging stations, available at 168 of the 442 study sites, was separated into surface flow and baseflow using a baseflow-separation model with nonlinear storage–discharge relations.<sup>59,60</sup> Surface flow represents the rapidly varying component of streamflow generated by overland and shallow subsurface runoff, though the water that contributes to surface flow may have had a long residence time in the soil column prior to being “pushed” out by younger water. Baseflow represents the sustained component of streamflow typically generated by groundwater discharge to a stream, engineered subsurface drainage systems (agricultural drains), point-source discharges, and streamflow that has traveled through channels over long distances from stream headwaters. Travel times in most of the small streams in this study generally are less than the recession time scales, so we expect that little surface flow is present in samples during baseflow conditions.<sup>61</sup> Snowmelt did not contribute to streamflow at any of the sites during sampling.

The storage-discharge relation for the baseflow-separation model was calibrated at each site to maximize the baseflow component of streamflow within the physical constraint that baseflow cannot exceed streamflow, using daily streamflow records retrieved from the USGS National Water Information System<sup>62</sup> for the 10-year period prior to and including the sample year at each site.<sup>60</sup> Baseflow as a fraction of streamflow (baseflow fraction) was calculated for each sample day. The

daily values of baseflow fraction depend on the characteristic streamflow recession rate for a stream, antecedent streamflow conditions, and the magnitude of the event. Baseflow fraction is generally low and may be close to 0 during rain events when baseflow is a negligible portion of streamflow. Baseflow fraction approaches 1 over sustained dry periods. Most sampling for this investigation was conducted during dry weather—across the 168 gaged sites, the median of the median baseflow fractions was 0.7, the median of the minimum baseflow fractions was 0.2, and the median of the maximum baseflow fractions was 1.0.<sup>60</sup>

**Screening Assessments.** Screening-level assessments of potential parent and TP effects on instream biota were done for potential toxicity and for bioactivity at the molecular level and for individual compounds and cumulatively (i.e., mixtures). Individual parent and TP effects were screened by comparing detected concentrations to compound-specific acute-toxicity invertebrate and plant benchmarks using the most sensitive benchmarks available from the U.S. Environmental Protection Agency Office of Pesticide Programs at the time of assessment ([Table S2](#)). Chronic benchmarks, which are applicable to 21-day average concentrations, are included on some figures for context. Detected concentrations were divided by the acute invertebrate or nonvascular plant benchmark to obtain a toxicity quotient (TQ) for that pesticide compound in that sample toward invertebrates or nonvascular plants. Site-specific cumulative risk for pesticide mixtures under a maximum-exposure scenario was estimated as the sum of the maximum TQ measured for each compound at a site<sup>63</sup> using the *toxEval* version 1.1.1 package of the open source statistical software R.<sup>63–65</sup>

Sublethal effects were explored using exposure-activity ratios (EAR)<sup>66,67</sup> based on the ToxCast database, which provides vertebrate-centric exposure-response metrics for more than 9000 organic chemicals to as many as 1100 molecular bioassay endpoints that include such groups as DNA binding and oxidoreductase.<sup>66</sup> The approach is analogous to the comparison to screening-level benchmarks. For each compound detected in a sample that had corresponding ToxCast data, the EAR was computed as the ratio of the compound concentration to the activity concentration at cutoff (ACC, from the Toxicity ForeCaster, ToxCast; high-throughput screening data),<sup>68–70</sup> which is the concentration at which measured bioactivity first exceeds a baseline.<sup>63,66</sup> An EAR of 0.001 has been reported to be approximately equivalent to the widely used TQ screening-level threshold of concern of 0.1, in that a majority of chemicals with TQ > 0.1 also had EAR > 0.001.<sup>63</sup> Site-specific maximum exposures for pesticide mixtures were defined as the sum of the maximum EAR for each pesticide compound at a site ( $\Sigma\text{EAR}_{\text{max}}$ ) (presumptive additive effects<sup>63</sup>).  $\Sigma\text{EAR}_{\text{max}}$  were estimated using the *toxEval* version 1.1.1 package<sup>65</sup> in R<sup>69</sup> as described.<sup>66,71–73</sup> ACC data in *toxEval* v1.1.1 were from the August 2019 *invitroDBv3.2* release of the ToxCast database.<sup>74</sup> ToxCast data for non-specific-endpoint, baseline, and unreliable response-curve assays were excluded.<sup>66,75</sup> To provide a presumptive upper bound for the extent to which missing toxicity data may underestimate TP effects on aquatic biota, the site-specific sum of maximum TQs and EARs also were calculated using the equimolar concentration of the corresponding parent pesticide as a surrogate for those detected TPs that lacked aquatic-life benchmarks or ToxCast data.



**Figure 2.** Comparison of molar concentration of parent compound and the sum of the concentrations of the measured transformation products (TPs) for atrazine and fipronil from the five Regional Stream Quality Assessment regions: Midwest, Southeast, Pacific Northwest, Northeast, and Coastal California. Points plotting on an axis represent a nondetection of corresponding TP (*x*-axis) or parent (*y*-axis); samples for which neither parent nor TP was detected are not shown. Dashed line, 1:1 relation. Also shown are relevant aquatic life benchmarks: black, acute nonvascular plant; green, acute vascular plant; red, chronic fish; blue, chronic invertebrate. Graphs for additional frequently detected TPs are provided in the Supporting Information.

## RESULTS AND DISCUSSION

### Pesticide and Transformation Product Occurrence.

Parent pesticides were widespread in small streams in the five regions of the U.S., with 103 parents detected at least once, and at least one parent detected at least once at 418 of the 442 stream sites (95%) (complete parent and TP data provided in companion data release<sup>76</sup>). However, TPs were nearly as pervasive—102 were detected at least once, and at least one TP was detected at least once at 396 stream sites (90%).<sup>76</sup> The number of unique TPs detected was highest in the Midwest (100), followed by the Pacific Northwest and the Northeast (77 each), the Southeast (74), and Coastal California (68), and were diverse: 55 herbicide TPs, 44 insecticide TPs, and 3 fungicide TPs (detection frequencies by region in Table S2, Figure S2). About one-half of detected TPs (48) occurred rarely, i.e., were detected in <1% of samples from any region. More than one-third occurred fairly commonly—38 occurred in  $\geq 5\%$  of samples from at least one region and 28 were detected in  $\geq 20\%$  of samples from at least one region. The latter primarily were TPs of the acetanilide and amide and triazine herbicide classes but also included TPs of the phenylpyrazole insecticide, isoxaflutole herbicide, sulfonylurea and urea herbicide, and fungicide (polychlorinated aromatic degradate) classes. These 28 compounds were termed “frequently detected TPs” (Tables S7 and S8). Parents chlorothalonil and thiophanate-methyl, both fungicides, of two frequently detected TPs (4-hydroxychlorothalonil and carbendazim, respectively) were not analyzed. The other 26 frequently detected TPs are TPs of 10 parents; those 10 frequently detected TP groups (TPs and parents) and the TPs 4-hydroxychlorothalonil and carbendazim are the focus of additional investigation.

Occurrence of TPs at 90% of the 442 sites studied across five regions of the U.S., just slightly less than the parents (95% of

sites), demonstrates that TPs likely are widespread in small U.S. streams, including many headwater streams. The presence of pesticides and TPs in headwater streams is of particular interest because such streams comprise the majority of river network length<sup>77,78</sup> and have a higher proportion of biodiversity than larger water bodies.<sup>79,80</sup> Although the numbers of herbicide and insecticide TPs measured (66 and 46, respectively) and detected at least once (55 and 44, respectively) are relatively similar, herbicide TPs were detected substantially more frequently than insecticide TPs, comprising 9 of the 12 parent-frequently detected TP groups. The preponderance of herbicide-TP detections may result from the generally much higher rates of application of herbicides relative to insecticides and fungicides. For example, a maximum recommended rate for application of the herbicide atrazine on turf is 0.54 kg/ha,<sup>81</sup> more than 40 times a recommended nonagricultural application rate for the insecticide fipronil of 0.014 kg/ha,<sup>82</sup> and recommended atrazine application rates for agricultural uses are even higher.<sup>83</sup> Acreage and frequency of application may also play a role. The less intensive application of insecticides does not translate, however, to lower potential toxicity, as insecticides tend to be acutely toxic to invertebrates at concentrations orders of magnitude lower than herbicides and in some cases similar to or lower than the analytical reporting level (e.g., dichlorvos) (Table S2).

Detection frequencies of TPs had distinct regional patterns. Herbicide TPs were detected most frequently in the Midwest, where the 21 TPs detected in >15% of samples all had herbicide parents (Table S2, Figure S2). The midwestern U.S. is characterized by intensive row cropping, and 96 of the 100 Midwest basins had >5% agricultural land use;<sup>44</sup> in agricultural applications, herbicide use dwarfs insecticide use.<sup>34,84</sup> Land use in the basins in the other four regions, however, generally spanned an urban gradient,<sup>44</sup> and urban contributions of

fungicides and insecticides to surface waters often exceed those of agriculture.<sup>34,41,85</sup> The two frequently detected fungicide TPs (4-hydroxychlorothalonil and carbendazim) were detected more frequently in the Southeast, Pacific Northwest, Northeast, and Coastal California regions than in the Midwest. Concentrations and detection frequencies of the insecticide fipronil and its frequently detected TPs were substantially higher in the Southeast than in other regions, likely related to the warm climate, which is conducive to numerous insect pests found in and around the home—including fleas, chiggers, ticks, mosquitos, cockroaches, termites, and fireants—for which fipronil is recommended.<sup>86</sup>

For several frequently detected TP groups (parent and frequently detected TPs), the sum of TP molar concentrations ( $\Sigma[\text{TP}]$ ; nondetections considered as zeroes) exceeded the parent concentration  $[\text{P}]$  for the subset of samples in which either a parent or TP in that group was detected (Figure 2, Figure S3, Table S9). All regions combined,  $\Sigma[\text{TP}] > [\text{P}]$  in  $\geq 50\%$  of this sample subset for 6 of the 10 frequently detected TP groups: the herbicides atrazine, metolachlor, acetochlor, isoxaflutole, and metribuzin, and the insecticide fipronil (Table S7). Other parent–TP groups that were less frequently detected also had  $\Sigma[\text{TP}] > [\text{P}]$  for more than 50% of the samples with detections: of eight additional parent–TP groups with a parent or TP detected in  $>100$  samples,  $\Sigma[\text{TP}] > [\text{P}]$  for parent–TP groups alachlor and norflurazon (both herbicides), the insecticide diazinon, and the fungicide propiconazole (Table S2).

The prevalence of TPs relative to the parent (Figure S3) is affected by many factors, including persistence of the parent compound (persistence data from ref 87). For the herbicides diuron and hexazinone, the parent compound is persistent in soils, and  $[\text{P}] > \Sigma[\text{TP}]$ . Conversely, the parent herbicides acetochlor, metolachlor, and isoxaflutole (a propesticide) are relatively nonpersistent in soils, and  $\Sigma[\text{TP}] > [\text{P}]$ . And although the insecticide fipronil is persistent in soils, the persistence of its TPs is even greater<sup>88</sup> and might explain why  $\Sigma[\text{TP}] > [\text{P}]$ . Additionally, the analytical method used here quantifies six TPs of fipronil, the most of any parent compound, increasing the likelihood that  $\Sigma[\text{TP}] > [\text{P}]$ . For atrazine,  $\Sigma[\text{TP}]$  tended to exceed  $[\text{P}]$ , despite moderate persistence of the parent in soils. Here, however, changes in agricultural practices may play a role. Downward trends in atrazine concentrations in U.S. streams and upward trends in concentrations of the TP deethylatrazine from 2002–2012 have been attributed in part to changes in agricultural practices intended to limit runoff (including a decrease in application rates), resulting in more atrazine degradation in soils.<sup>89</sup> Such changes could promote higher concentrations of TPs relative to the parent for other agricultural pesticides.

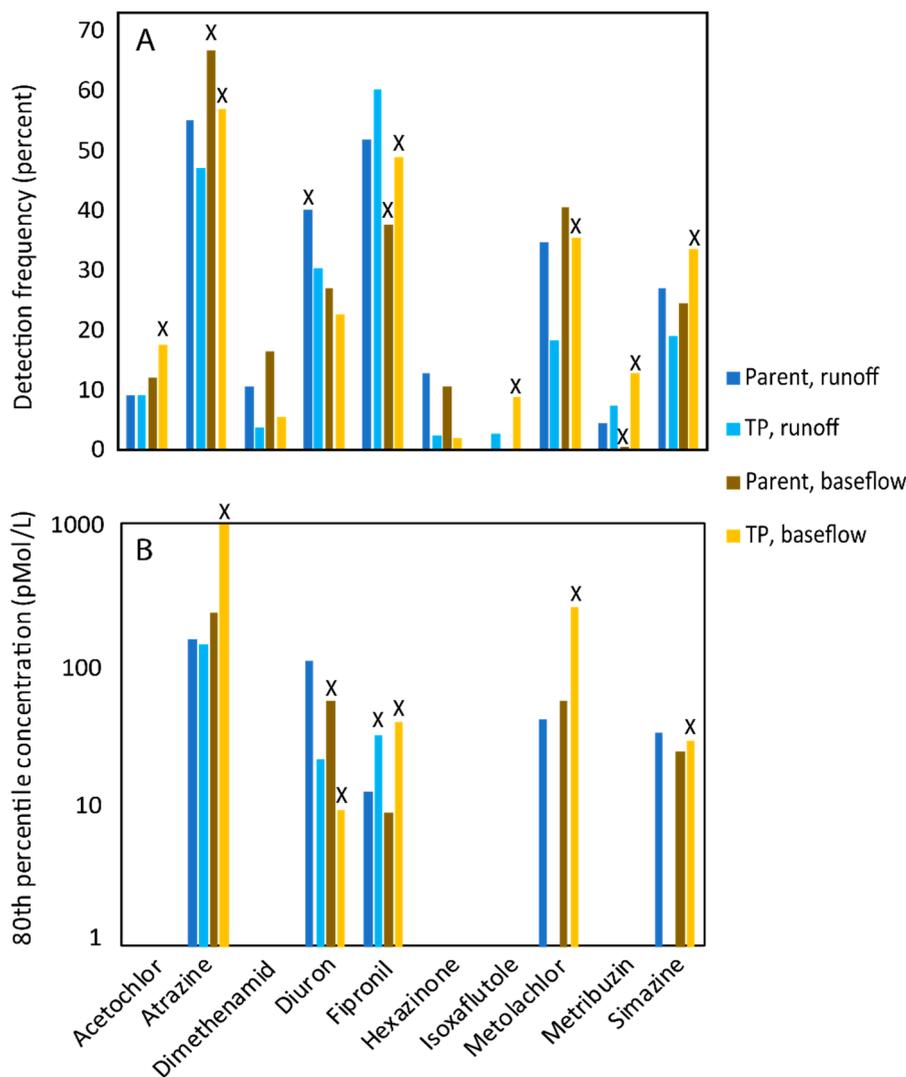
Changing patterns of pesticide use in response to regulation, pest pressures, or other factors may also contribute to relative concentrations of parents and TPs, as decreased use of the parent pesticide may result in greater proportional occurrence of the TP(s) over time, particularly in streams with a greater fraction of baseflow. Agricultural use of metribuzin decreased into the mid-2000s,<sup>84</sup> when its use then began to increase primarily for soybeans, a major crop in the midwestern U.S.<sup>41</sup> Consistent with use patterns, metribuzin  $\Sigma[\text{TP}] > [\text{P}]$  for all regions except the Midwest. As of 2013 (when Midwest samples were collected), dimethenamid use on corn had decreased since peak use in 1996; parents and their TPs were detected primarily and at higher concentrations in the

Midwest, where corn is the dominant crop,<sup>41</sup> than in other regions, and generally  $\Sigma[\text{TP}] > [\text{P}]$ . Use of the herbicide simazine on corn has remained relatively steady but has decreased on orchards and grapes and is considered moderately persistent in soils and stable in water, consistent with  $[\text{P}] > \Sigma[\text{TP}]$  in all regions but Coastal California, where decreasing use on grapes may favor the relative occurrence of the simazine TP (agricultural simazine use in Coastal California counties during January–May 2017 was mostly on wine grapes (<https://calpip.cdpr.ca.gov/main.cfm>)).

The frequently detected TPs represent a wide variety of degradation pathways, including oxidation, reduction, dealkylation of an amino group, and chlorine substitution by a hydroxyl group. Fate processes involved in TP formation are equally numerous and include hydrolysis, anaerobic or aerobic soil metabolism, and aqueous and soil photolysis. Some of the frequently detected TPs can be formed by multiple processes; for example, DCPMU, a TP of the herbicide diuron, can be formed by soil photolysis, aerobic soil metabolism, and anaerobic and aerobic aquatic metabolism. Additionally, the fate processes leading to the transformation of a pesticide can shift with time. For example, the prevalence of hydroxyatrazine as the major TP of atrazine detected in the streams reflects the recent evolution and adaptation of soil microorganisms capable of hydroxylation pathways that lead to complete degradation.<sup>90,91</sup> The relatively frequent occurrence of many of the TPs measured in this study therefore cannot be attributed to one or a few common degradation pathways or fate processes.

The fungicide chlorothalonil has a more complex story. Chlorothalonil was not measured for this study (insufficient ionization for electrospray), but one of its eight TPs, 4-hydroxychlorothalonil, was measured and was detected in  $>20\%$  of samples in the Southeast and in  $>10\%$  of samples in the Northeast and Coastal California. Given its high reporting level relative to other TPs measured for this study (98 ng/L, exceeding the 75th percentile reporting level for TPs [Table S2]), the presence of 4-hydroxychlorothalonil in the small streams studied may be underestimated. The frequent occurrence of 4-hydroxychlorothalonil indicates the probable occurrence of other TPs of chlorothalonil that were not measured for this study. A screening study of 31 samples of Swiss groundwater detected 8 TPs of chlorothalonil in at least 1 sample, including the first environmental detection of TP R471811, which occurred in every sample collected and had the highest concentration of the more than 1 400 compounds measured.<sup>27</sup> Chlorothalonil is a high-production fungicide used on a number of specialty crops<sup>84</sup> and also is commonly used on turf grass, including golf courses.<sup>92</sup> In California, for which nonagricultural pesticide-use data are available, chlorothalonil is the most intensively used pesticide on “recreational areas.”<sup>93</sup> A study of golf-course-green leachate reported that, although the parent compound chlorothalonil was rarely detected, the TP hydroxychlorothalonil occurred in 87% of leachate samples.<sup>94</sup> In our study, 46% of all basins had at least one golf course but 82% of study basins with a detection of 4-hydroxychlorothalonil had at least one golf course (see Table S10 for breakout by region). This significant difference highlights the potential contribution of use of chlorothalonil on golf courses to occurrence of 4-hydroxychlorothalonil in small streams.

**Relation to Flow.** Occurrence and concentrations of frequently detected TP groups were investigated in samples collected during runoff conditions (“runoff”) and baseflow



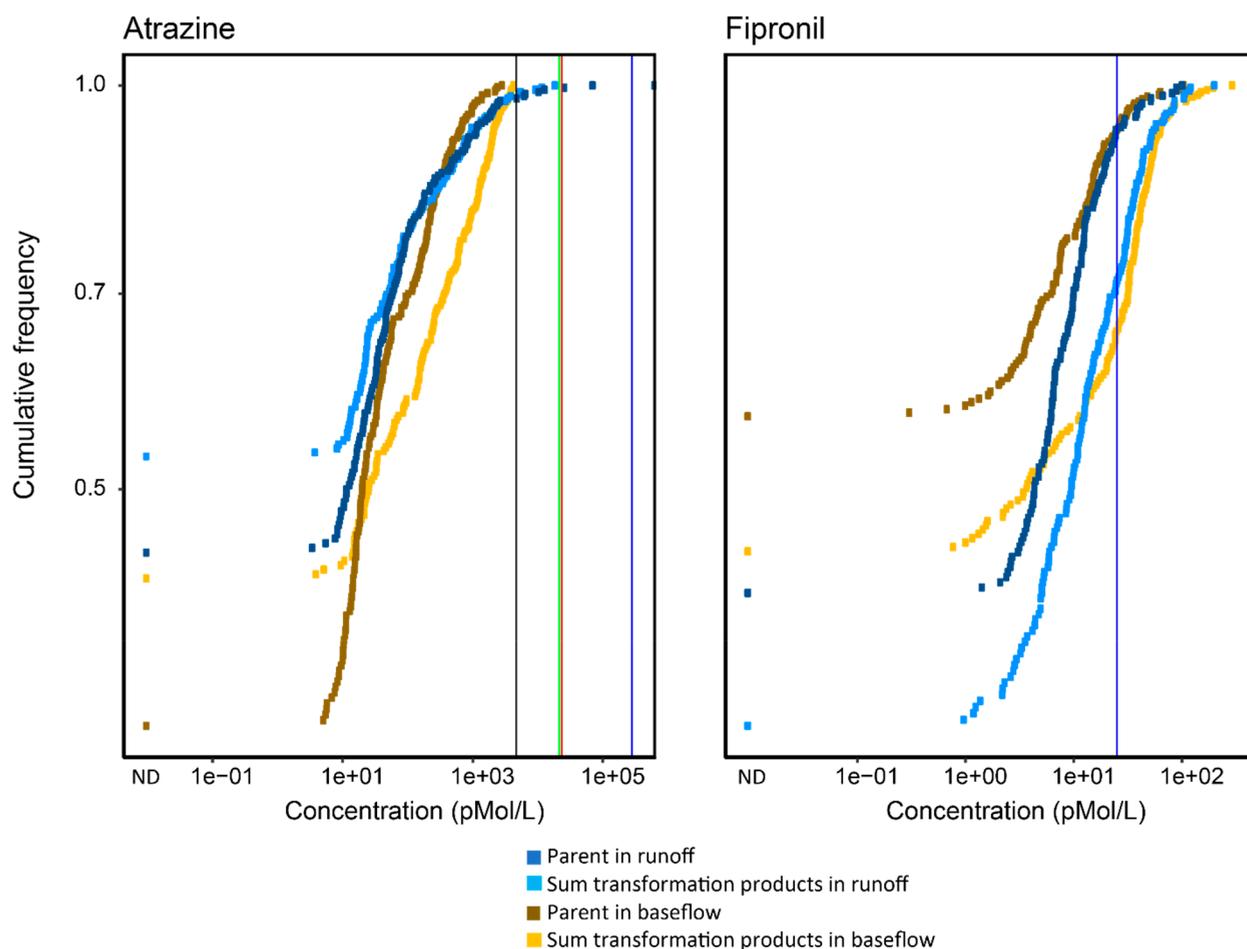
**Figure 3.** Comparison of detection frequencies (A) and 80th percentile concentrations (B) of frequently detected transformation products (TP) and their parent pesticides during runoff and baseflow conditions. X indicates that the detection frequency or concentration during baseflow conditions is significantly ( $p < 0.05$ ) different from that during runoff conditions.

conditions (“baseflow”) in the streams. Flow data were available for computation of baseflow fraction for 168 of the 442 study sites (Midwest,  $n = 25$ ; Southeast,  $n = 53$ ; Pacific Northwest,  $n = 12$ ; Northeast,  $n = 49$ ; Coastal California,  $n = 29$ )<sup>60</sup> (Table S11). Detection frequencies for TPs were computed as the detection of any TP in a frequently detected TP group, i.e.,  $\Sigma[\text{TP}] > 0$ . Parent compounds did not tend to occur more frequently in one or the other flow endmember: The detection frequency of the parent was significantly greater ( $p < 0.05$ ) during runoff for 3 of 10 frequently detected TP groups and greater during baseflow for 1 group; for the remaining 6 groups there was no significant difference between flow endmembers (Figure 3A) (detection frequencies by region shown in Figure S4). TPs, in contrast, tended to occur more frequently during baseflow than runoff: The detection frequency was significantly greater during baseflow for six frequently detected TP groups and during runoff for two.

The “typical” assemblage of concentrations of frequently detected TPs and associated parents differed between runoff and baseflow. This assemblage was evaluated by determining the 80th percentile concentration (i.e., the concentration

exceeded in 20% of samples) of [P] and  $\Sigma[\text{TP}]$  for each frequently detected TP group (Figure 3B) (80th percentile concentrations by region are shown in Figure S5) in runoff and baseflow stream samples. For all regions combined, this 80th percentile assemblage had detectable concentrations of five frequently detected TP groups (parent and at least one TP) during both runoff and baseflow, except metolachlor and simazine TPs, which were detected in less than 20% of runoff samples. For four of five TPs with 80th percentile concentrations that are detections, the 80th percentile concentration was significantly higher during baseflow than during runoff (permutation test,  $p < 0.05$ ); the highest 80th percentile concentrations were for a TP of atrazine and of metolachlor in baseflow.

Contrasting patterns of pesticide and TP occurrence and concentration during runoff and baseflow are illustrated for the most commonly detected herbicide and insecticide groups (atrazine and fipronil and their TPs) (Figure 4; cumulative frequency distributions for the other frequently detected TP groups are provided in Figure S6.). For the atrazine group, elevated concentrations of  $\Sigma[\text{TP}]$  in baseflow occurred more



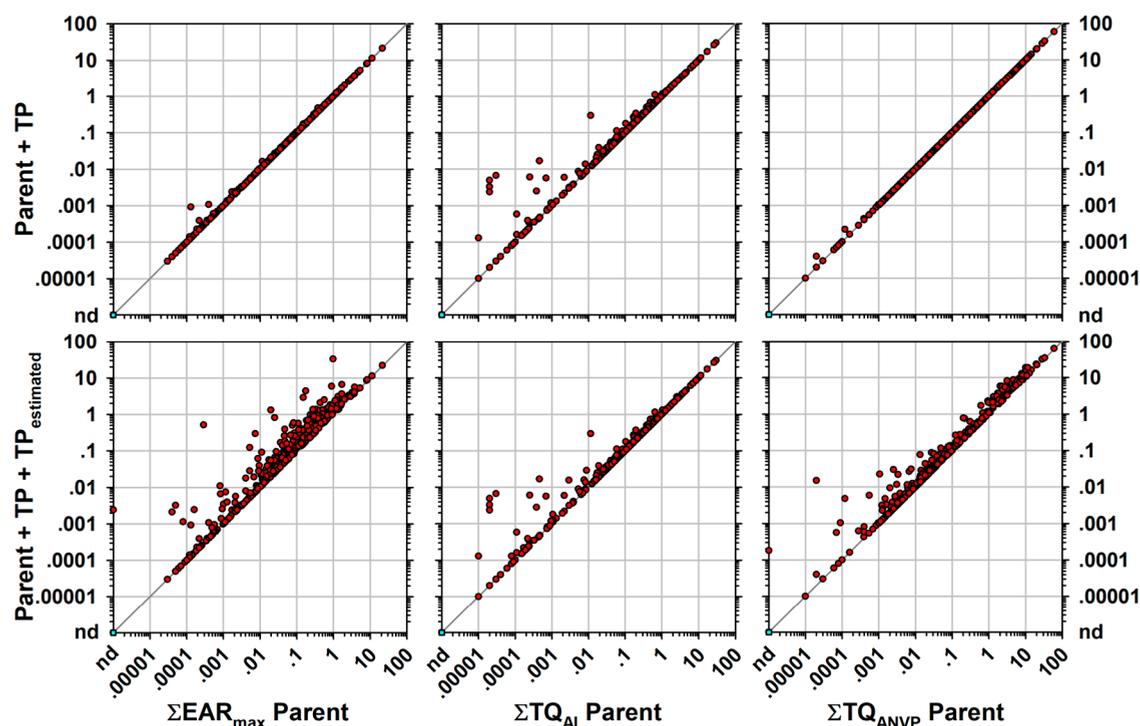
**Figure 4.** Cumulative frequency distributions of molar concentrations of pesticide parent and sum of transformation products during runoff and baseflow conditions for atrazine and fipronil. ND, nondetection. Also shown are relevant aquatic life benchmarks: black, acute nonvascular plant; green, acute vascular plant; red, chronic fish; blue, chronic invertebrate. Note that the *y*-axis is log scale. Cumulative frequency distributions for other frequently detected transformation products and their parents are provided in Figure S6.

frequently than in runoff and more frequently than elevated concentrations of the parent in either flow endmember. For fipronil, elevated concentrations of  $\Sigma$ [TP] in both baseflow and runoff occurred more frequently than those of [P], and distributions of  $[\Sigma$ TP] in runoff and baseflow were similar, especially at higher concentrations. Although concentrations of fipronil were orders of magnitude lower than concentrations of atrazine, a substantial number of samples contained fipronil at a concentration that exceeded the chronic invertebrate benchmark.

Relative proportions of parent and TP, particularly during runoff, will depend on timing of use, with more recent use reflected by a higher proportion of the parent compound in runoff and streams.<sup>95,29</sup> Samples for this study were collected during the spring growing season and therefore may bias the TP/parent ratio low at the beginning of the season, particularly for herbicides. Pre-emergent herbicides (e.g., atrazine) are likely to be applied at the beginning of the growing season and post-emergent herbicides (e.g., glyphosate) are likely to be applied throughout the growing season, affecting the timing of peak concentration.<sup>29</sup> Higher pesticide application during the spring growing season, however, pertains more to agricultural areas and to herbicides than to urban areas and to insecticides and fungicides.<sup>96</sup> Additionally, timing of use is likely to have a greater effect on pesticide assemblages during runoff than

during baseflow.<sup>28</sup> Little attenuation of most compounds is expected to occur during transport downstream: A Lagrangian study of in-stream transport of wastewater-derived chemicals indicated that most of the >200 organic contaminants (including pesticides) had little attenuation relative to boron.<sup>97</sup> Another Lagrangian study, however, noted rapid removal of the insecticide imidacloprid downstream from a wastewater treatment plant and attributed it to sorption to organic matter rather than transformation.<sup>98</sup>

Concentrations of pesticides and TPs in baseflow have several potential sources, including wastewater treatment plant discharges, distant (upstream) sources, atmospheric deposition, and groundwater discharge. Of the 168 gaged sites considered here, 111 do not have a wastewater treatment plants in the basin (Table S1),<sup>46</sup> therefore effluent is unlikely to be a major source of pesticides and TPs in baseflow at most sites. Most of the basins are sufficiently small that flow originating as runoff at the uppermost end of the stream would rapidly arrive at the sampling point, i.e., before baseflow conditions are reached. The median basin area is 57 km<sup>2</sup> and has a stream length of about 15 km; assuming an average flow velocity during base flow of 0.3 m/s, water starting at the top of the stream would arrive at the sampling point in about 14 h. The stream length of the 95th percentile basin-area stream (870 km<sup>2</sup>) is about 65 km, translating to a travel time of <3



**Figure 5.** Comparison of maximum-exposure scenario hazard ratios for detected parent pesticides only and parents plus transformation products (TPs) for existing screening levels (top row) and with substitution of parent compound screening levels for those TPs lacking them (bottom row).  $\Sigma\text{EAR}_{\text{max}}$ , maximum scenario for exposure-activity ratio;  $\Sigma\text{TQ}_{\text{Ai}}$ , maximum exposure scenario for acute invertebrate toxicity;  $\Sigma\text{TQ}_{\text{ANVP}}$ , maximum exposure scenario for acute nonvascular plants; and nd, nondetection.

days. We therefore conclude that runoff from distant sources likely is a minor contributor to pesticides measured during baseflow conditions. Pesticides can be delivered to the catchment by wet and dry deposition, particularly in areas of high pesticide use.<sup>99</sup> The vast majority of this deposition, however, will not occur on the water surface, as stream surface area is negligible relative to basin area. As a result, we hypothesize that pesticides and TPs associated with atmospheric deposition might be associated with runoff conditions but not with baseflow conditions. We therefore conclude that groundwater discharge likely is a dominant source of pesticides and TPs in baseflow. This is consistent with the many studies that have documented occurrence of pesticides and their TPs in U.S. groundwater (e.g., refs 2 and 18). A 2021 study reported that about 30% of more than 1 204 groundwater wells across the U.S. contained a pesticide TP and that TPs were detected more frequently than parent compounds.<sup>100</sup> Further, detection frequencies were substantially higher in shallow groundwater: at least one pesticide or TP was detected in 86% of 344 shallow monitoring wells in the study.<sup>100,101</sup> The results of our study are consistent with those that have demonstrated groundwater discharge to be a source of pesticide compounds in baseflow, albeit at smaller geographic scales.<sup>30,102–107</sup>

The occurrence of parent pesticides and TPs in baseflow has implications for chronic toxicity to aquatic organisms. Because baseflow comprises much of the flow in small streams,<sup>108</sup> aquatic organisms are likely to be exposed to the pesticide-TP signature in baseflow throughout much of the year. Our results indicate that higher concentrations of many TPs are more likely to occur in baseflow than runoff (Figure 3B). Additionally, under the right geochemical conditions, baseflow can be contaminated by legacy pesticides in groundwater discharge,<sup>105,109</sup> although in our study occurrence of TPs of

the eight discontinued parents in baseflow was rare (two TPs of discontinued pesticides, fenamiphos sulfoxide and alachlor OA, were detected during baseflow, once each). Nonetheless, the frequent detection of TPs in baseflow indicates that chronic exposures of aquatic communities is one of many compelling reasons to improve our understanding of TP toxicity.

**Potential Toxicity to Aquatic Life.** Parent pesticides exceeded an aquatic life benchmark substantially more frequently than did TPs (Figure S7). Nine parent compounds had an acute invertebrate  $\text{TQ} > 1$  (potential toxicity) in at least one sample, and seven had an acute nonvascular plant  $\text{TQ} > 1$  in at least one sample, but only one TP (of the insecticide malathion) had an acute invertebrate  $\text{TQ} > 1$  and none had an acute nonvascular plant  $\text{TQ} > 1$  (Figures S7 and S8). Thirty-four parent compounds had at least one acute invertebrate or acute nonvascular plant  $\text{TQ} > 0.1$  (threshold of concern);<sup>63</sup> two TPs—of the insecticides acephate and terbufos—had an acute invertebrate  $\text{TQ} > 0.1$ . The contribution of TPs to potential acute toxicity, however, is underrepresented because only about one-quarter of the 116TPs measured have an aquatic life benchmark, whereas 95% of the 108 parent pesticides have an acute invertebrate or acute nonvascular plant benchmark (Table S2). To explore the envelope of potential toxicity, TQs for those TPs that lack a published benchmark were computed using the benchmark for the parent (equimolar substitution), excluding 7 TPs likely to be substantially less toxic than their parent (Figures S7 and S8) (see the Supporting Information for detailed discussion). Using this upper bound, TPs of the insecticides bifenthrin and malathion also had at least one acute invertebrate  $\text{TQ} > 1$  and an additional five had at least one acute invertebrate  $\text{TQ} > 0.1$ . Similarly, TPs of the herbicide acetochlor had at least one

acute nonvascular plant  $TQ > 1$ , and an additional seven TPs had at least one acute nonvascular plant  $TQ > 0.1$ .

Vertebrate-centric sublethal effects were investigated using the *in vitro* EAR determined from the ToxCast database.<sup>66</sup> An EAR  $> 1$  indicates a concentration (exposure) reported to modulate a molecular target *in vitro*; an EAR  $\leq 1$  indicates a lower likelihood of biological reactivity. An EAR = 0.001 has been suggested to be equivalent to a  $\Sigma TQ = 0.1$  (i.e., threshold of concern).<sup>63</sup> Nine parent compounds had an EAR  $> 1$  and 62 parents had an EAR  $> 0.001$ ; no TP had EAR  $> 1$ , although 10 parents had at least one TP with an EAR  $> 0.001$  (Figure S9). However, similar to TP TQs, EARs underrepresent potential sublethal toxicity because most TPs lack data in ToxCast: Acceptable ToxCast data<sup>75</sup> were available at the time of access for 97 of the 108 pesticides (90%) but only 24 of the 116TPs (21%). To explore an upper bound on potential sublethal toxicity, EARs were computed using the parent ACC (equimolar substitution) for those TPs that lack an ACC in ToxCast. The 7 TPs excluded from the TQ upper-bound analysis were included in the EAR analysis, as their bioactivity at the molecular level is unknown. Under this scenario, TPs of acetochlor and the fungicide chlorothalonil had at least one EAR  $> 1$ , and TPs of another 13 parents had an EAR  $> 0.001$ .

We explored the potential acutely toxic and sublethal effects of pesticide mixtures using a site-specific maximum-exposure scenario, i.e., summing the maximum acute invertebrate and acute nonvascular plant TQs for each compound ( $\Sigma TQ_{AI}$  and  $\Sigma TQ_{ANVP}$ ) and maximum EARs ( $\Sigma EAR_{max}$ ) determined for all samples at each site (Figure 5, upper panels). Because of the under-representation of potential toxicity related to TPs, the upper bound of the toxicity envelope was estimated by computing  $\Sigma TQ$  and  $\Sigma EAR$  using the aquatic life benchmark or ACC of the parent for those TPs lacking them (Figure 5, lower panels). Under this upper-bound extrapolation, the number of sites with a  $\Sigma TQ_{AI} > 1$  was the same (56), but the number with a  $\Sigma TQ_{ANVP} > 1$  increased 8% from 87 to 94 and the number with an  $\Sigma EAR_{max} > 1.0$  increased 94% from 35 to 68 (Figure 5). Summed EAR and benchmark-based risk quotient results are summarized in Romanok et al.<sup>110</sup>

The paucity of data on toxicity of TPs to aquatic organisms results in an underestimate of potential toxicity associated with pesticide compounds as a group, unless assumptions are made to assign toxicity thresholds to TPs. The scarcity of acute nonvascular plant benchmarks and ACCs for TPs results in potential toxicity to nonvascular plants or biological reactivity for parent+TP that are nearly identical to those for the parent only and that differ at relatively few sites for toxicity to aquatic invertebrates (Figure 5). The  $\Sigma TQ_{AI}$ ,  $\Sigma TQ_{ANVP}$ , and  $\Sigma EAR_{max}$  that used parent screening-level substitution for those TPs without screening levels (upper bound extrapolation) indicated substantially more potential acute toxicity to nonvascular plants and more vertebrate-centric molecular bioactivity than when only those TPs with an existing benchmark or ACC were considered (Figure 5, upper and lower panels on far right). There was little change, however, to predicted acute toxicity to aquatic invertebrates (Figure 5, upper and lower panels in center). We attribute this difference to the comparatively high availability of invertebrate benchmarks for fipronil TPs, the only insecticide TPs that were frequently detected (Table S2); the most frequently detected TPs were TPs of herbicides (Figure S2), which tend to be substantially less toxic than insecticides to aquatic invertebrates (Table S2). Existing acute invertebrate benchmarks therefore do a reasonable job of

predicting acute toxicity to invertebrates for the suite of pesticides and TPs we measured. However, some insecticides that occurred frequently in our study, such as the neonicotinoid imidacloprid (38% of samples), have TPs that we did not measure but that may contribute to toxicity.<sup>111</sup> Further, despite our relatively extensive analyte list, there are some commonly used insecticides and their TPs, such as the neonicotinoid clothianidin and the ryanoid chlorantraniliprole, that we did not measure. This data gap highlights the importance—and challenge—of updating analyte lists to keep pace with changes in pesticide use.

**Implications.** Our assessment indicates that TPs may be contributing substantially more to instream toxicity than currently known. Additionally, although we estimated an upper-bound on toxicity associated with pesticides and TPs in the 442 small streams presented here, there are several reasons why potential instream toxicity ( $\Sigma TQ$ ) or molecular response ( $\Sigma EAR$ ) might be greater than our estimate. Some TPs are more toxic than the parent,<sup>4</sup> therefore globally substituting the parent benchmark underestimates their contribution to toxicity. This will be counterbalanced to an unknown extent by TPs that are less toxic than the parent; the net result depends on which TPs are more prevalent. Second, because of the few existing toxicity tests for TPs, even existing TP benchmarks may not be adequately protective of the most sensitive species because of insufficient data. Standard test organisms (e.g., *Daphnia magna* for invertebrates) may be less sensitive toward some pesticides than species of benthic invertebrates present in many streams.<sup>112</sup> In a mesocosm experiment that investigated the toxicity of fipronil and its TPs, for example, the concentration values for three fipronil TPs protective of 95% of the aquatic invertebrates in the mesocosm were 10 to almost 3 000 times lower than the EPA chronic invertebrate benchmarks.<sup>112</sup> Similarly, the bioassay endpoints used in ToxCast for development of EARs are predominantly for vertebrate molecular effects<sup>67</sup> and may not fully capture effects to aquatic invertebrates. Third, reporting levels for TPs in this study tended to be greater than those of the parents (Table S2); as a result, some TPs might be present but not detected and therefore are not included in  $\Sigma TU$  or  $\Sigma EAR$ . This becomes particularly important when toxic thresholds are in the same range as reporting levels, as for some insecticides. Fourth, although this study included a broad range of pesticides and TPs, it represents only a small slice of those potentially present in the environment. Some parents occurred frequently (e.g., imidacloprid), but their TPs were not measured for this study. In other cases, not all TPs of a parent were measured—for example, of the eight TPs of chlorothalonil that have been identified,<sup>27</sup> only one was measured for this study. Finally, although samples were collected more frequently (weekly) for our study than for many monitoring studies, this timing nonetheless can miss a substantial number of ephemeral but potentially toxic “events.”<sup>29,113</sup> Thus, the results of weekly sampling at 442 small U.S. streams reported here may underpredict the maximum potential toxicity to aquatic organisms.

This continental-scale study of pesticide TPs, the most geographically extensive to date, highlights the near ubiquity of TPs in small U.S. streams in both urban and agricultural areas. TPs occurred nearly as frequently as parents, and the sum of concentrations of TPs of a given parent often exceeded those of the parent. Consistent with earlier studies, herbicide TPs were the most widely detected and occurred at the highest

concentrations, but TPs of the insecticide fipronil and the fungicides chlorothalonil and carbendazim also occurred frequently and at concentrations of potential concern for aquatic life. The results reveal the presence of numerous TPs in baseflow at concentrations similar to those in runoff, indicating probable chronic exposures of aquatic organisms to TPs and, potentially, long-term exposure associated with TPs in groundwater discharging to streams. Finally, the lack of toxicity data and bioassay endpoints of biological activity for most TPs precludes a robust understanding of potential toxicity of pesticide compounds to aquatic organisms. Our quantitative estimate of an upper bound on toxicity, in some cases orders of magnitude higher than that based on existing benchmarks and biomarkers, exposes the importance of this data gap.

## ■ ASSOCIATED CONTENT

### SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.est.0c06625>.

Description of analytical methods and reporting levels; results for laboratory and field quality control; description of the toxicity quotient approach; maps of the five study areas; figures illustrating detection frequency, 80th percentile concentrations, and cumulative frequency distributions of frequently detected TP groups under flow endmember conditions; and figures illustrating ranges of acute aquatic invertebrate toxicity quotients, acute nonvascular plant toxicity quotients, and exposure activity ratios as boxplots (PDF)

Tables providing site descriptions and a numerical key to sites shown on the maps; information on analytes and detection frequencies; quality-control summaries for surrogate compounds, field blanks, replicates, and spikes; detection frequencies and routes of formation for frequently detected TPs; sampling data for the frequently detected TPs and their parents; percentage of samples in frequently detected TP groups for which the sum of the TP molar concentrations exceeded that of the parent; data on golf course occurrence; and discharge and baseflow fraction for samples collected at gaged sites (XLSX)

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## Notes

The authors declare no competing financial interest.

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Data and additional information on the Regional Stream Quality Assessments can be found at <https://webapps.usgs.gov/rsqa/#/>. Machine readable data files are available as USGS data releases at [10.5066/P9YYD8DI](https://pubs.usgs.gov/of/2020/10.5066/P9YYD8DI) (pesticide concentrations), [10.5066/P9PSU28Y](https://pubs.usgs.gov/of/2020/10.5066/P9PSU28Y) (comparison to aquatic life benchmarks and ToxCast ACCs), and [10.5066/P9AIPHEP](https://pubs.usgs.gov/of/2020/10.5066/P9AIPHEP) (baseflow separation).

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## ■ REFERENCES

- (1) Fishel, F. *Pesticides and the Environment*, <https://extension2.missouri.edu/g7520> (accessed 08-05-2020).
- (2) Kolpin, D. W.; Thurman, E. M.; Linhart, S. M. Finding minimal herbicide concentrations in ground water? Try looking for their degradates. *Sci. Total Environ.* **2000**, *248* (2), 115–122.
- (3) Kolpin, D. W.; Schnoebelen, D. J.; Thurman, E. M. Degradates provide insight to spatial and temporal trends of herbicides in ground water. *Groundwater* **2004**, *42* (4), 601–608.
- (4) Boxall, A. B. A.; Sinclair, C. J.; Fenner, K.; Kolpin, D.; Maund, S. J. When synthetic chemicals degrade in the environment. *Environ. Sci. Technol.* **2004**, *38* (19), 368A–375A.
- (5) Huntscha, S.; Singer, H.; Canonica, S.; Schwarzenbach, R. P.; Fenner, K. Input dynamics and fate in surface water of the herbicide metolachlor and of its highly mobile transformation product metolachlor ESA. *Environ. Sci. Technol.* **2008**, *42* (15), 5507–5513.
- (6) Hintze, S.; Glauser, G.; Hunkeler, D. Influence of surface water-groundwater interactions on the spatial distribution of pesticide metabolites in groundwater. *Sci. Total Environ.* **2020**, *733*, 139109.
- (7) Escher, B. I.; Stapleton, H. M.; Schymanski, E. L. Tracking complex mixtures of chemicals in our changing environment. *Science* **2020**, *367* (6476), 388.
- (8) Thurman, E. M.; Goolsby, D. A.; Meyer, M. T.; Mills, M. S.; Pomes, M. L.; Kolpin, D. W. A reconnaissance study of herbicides and their metabolites in surface water of the midwestern United States using immunoassay and gas chromatography/mass spectrometry. *Environ. Sci. Technol.* **1992**, *26* (12), 2440–2447.
- (9) Kolpin, D. W.; Thurman, E. M.; Goolsby, D. A. Occurrence of selected pesticides and their metabolites in near-surface aquifers of the

- midwestern United States. *Environ. Sci. Technol.* **1996**, *30* (1), 335–340.
- (10) Gilliom, R. J.; Barbash, J. E.; Crawford, C. G.; Hamilton, P. A.; Martin, J. D.; Nakagaki, N.; Nowell, L. H.; Scott, J. C.; Stackelberg, P. E.; Thelin, G. P.; Wolock, D. M. *Pesticides in the Nation's Streams and Ground Water, 1992–2001*; U.S. Geological Survey Circular 1291; 2006; p 172.
- (11) Masiá, A.; Campo, J.; Vázquez-Roig, P.; Blasco, C.; Picó, Y. Screening of currently used pesticides in water, sediments and biota of the Guadalquivir River Basin (Spain). *J. Hazard. Mater.* **2013**, *263*, 95–104.
- (12) Moschet, C.; Wittmer, L.; Simovic, J.; Junghans, M.; Piazzoli, A.; Singer, H.; Stamm, C.; Leu, C.; Hollender, J. How a complete pesticide screening changes the assessment of surface water quality. *Environ. Sci. Technol.* **2014**, *48* (10), 5423–5432.
- (13) Fenner, K.; Canonica, S.; Wackett, L. P.; Elsner, M. Evaluating pesticide degradation in the environment: Blind spots and emerging opportunities. *Science* **2013**, *341* (6147), 752.
- (14) Hensen, B.; Lange, J.; Jackisch, N.; Zieger, F.; Olsson, O.; Kümmerer, K. Entry of biocides and their transformation products into groundwater via urban stormwater infiltration systems. *Water Res.* **2018**, *144*, 413–423.
- (15) Ji, C.; Song, Q.; Chen, Y.; Zhou, Z.; Wang, P.; Liu, J.; Sun, Z.; Zhao, M. The potential endocrine disruption of pesticide transformation products (TPs): The blind spot of pesticide risk assessment. *Environ. Int.* **2020**, *137*, 105490.
- (16) Radomski, J. L.; Davidow, B. The metabolite of heptachlor, its estimation, storage, and toxicity. *J. Pharmacol. Exp. Ther.* **1953**, *107* (3), 266–272.
- (17) Glasser, R. F. *Evidence of the Presence of a Toxic Metabolite of Aldrin in Carrot Plant Material*; Cornell University, 1956.
- (18) Potter, T. L.; Carpenter, T. L. Occurrence of alachlor environmental degradation products in groundwater. *Environ. Sci. Technol.* **1995**, *29* (6), 1557–1563.
- (19) Kolpin, D. W.; Kalkhoff, S. J.; Goolsby, D. A.; Sneek-Fahrer, D. A.; Thurman, E. M. Occurrence of selected herbicides and herbicide degradation products in Iowa's ground water, 1995. *Groundwater* **1997**, *35* (4), 679–688.
- (20) Boyd, R. A. Herbicides and herbicide degradates in shallow groundwater and the Cedar River near a municipal well field, Cedar Rapids, Iowa. *Sci. Total Environ.* **2000**, *248* (2), 241–253.
- (21) Aga, D. S.; Thurman, E. M. Formation and transport of the sulfonic acid metabolites of alachlor and metolachlor in soil. *Environ. Sci. Technol.* **2001**, *35* (12), 2455–2460.
- (22) Hancock, T. C.; Sandstrom, M. W.; Vogel, J. R.; Webb, R. M. T.; Bayless, E. R.; Barbash, J. E. Pesticide fate and transport throughout unsaturated zones in five agricultural settings, USA. *J. Environ. Qual.* **2008**, *37* (3), 1086–1100.
- (23) Weston, D. P.; Lydy, M. J. Toxicity of the insecticide fipronil and its degradates to benthic macroinvertebrates of urban streams. *Environ. Sci. Technol.* **2014**, *48* (2), 1290–1297.
- (24) Saini, S.; Rani, M.; Kumari, B. Persistence of fipronil and its metabolites in soil under field conditions. *Environ. Monit. Assess.* **2014**, *186* (1), 69–75.
- (25) Stehle, S.; Bline, A.; Bub, S.; Petschick, L. L.; Wolfram, J.; Schulz, R. Aquatic pesticide exposure in the U.S. as a result of non-agricultural uses. *Environ. Int.* **2019**, *133*, 105234.
- (26) Reemtsma, T.; Alder, L.; Banasiak, U. Emerging pesticide metabolites in groundwater and surface water as determined by the application of a multimethod for 150 pesticide metabolites. *Water Res.* **2013**, *47* (15), 5535–5545.
- (27) Kiefer, K.; Müller, A.; Singer, H.; Hollender, J. New relevant pesticide transformation products in groundwater detected using target and suspect screening for agricultural and urban micro-pollutants with LC-HRMS. *Water Res.* **2019**, *165*, 114972.
- (28) Battaglin, W. A.; Kolpin, D. W.; Scribner, E. A.; Kuivila, K. M.; Sandstrom, M. W. Glyphosate, other herbicides, and transformation products in Midwestern streams, 2002. *J. Am. Water Resour. Assoc.* **2005**, *41*, 323–332.
- (29) Mahler, B. J.; Van Metre, P. C.; Burley, T. E.; Loftin, K. A.; Meyer, M. T.; Nowell, L. H. Similarities and differences in occurrence and temporal fluctuations in glyphosate and atrazine in small Midwestern streams (USA) during the 2013 growing season. *Sci. Total Environ.* **2017**, *579*, 149–158.
- (30) Kalkhoff, S. J.; Lee, K. E.; Porter, S. D.; Terrio, P. J.; Thurman, E. M. Herbicides and herbicide degradation products in upper midwest agricultural streams during August base-flow conditions. *J. Environ. Qual.* **2003**, *32* (3), 1025–1035.
- (31) Lundqvist, J.; von Brömssen, C.; Rosenmai, A. K.; Ohlsson, Å.; Le Godec, T.; Jonsson, O.; Kreuger, J.; Oskarsson, A. Assessment of pesticides in surface water samples from Swedish agricultural areas by integrated bioanalysis and chemical analysis. *Environ. Sci. Eur.* **2019**, *31*, 53.
- (32) Majewski, M. S.; Foreman, W. T.; Goolsby, D. A. Pesticides in the atmosphere of the Mississippi River Valley, part I — rain. *Sci. Total Environ.* **2000**, *248* (2), 201–212.
- (33) López, A.; Yusà, V.; Millet, M.; Coscollà, C. Retrospective screening of pesticide metabolites in ambient air using liquid chromatography coupled to high-resolution mass spectrometry. *Talanta* **2016**, *150*, 27–36.
- (34) Hoffman, R. S.; Capel, P. D.; Larson, S. J. Comparison of pesticides in eight U.S. urban streams. *Environ. Toxicol. Chem.* **2000**, *19* (9), 2249–2258.
- (35) Metcalf, R. L.; Kapoor, I. P.; Lu, P.-Y.; Schuth, C. K.; Sherman, P. Model ecosystem studies of the environmental fate of six organochlorine pesticides. *Environ. Health Perspect.* **1973**, *4*, 35–44.
- (36) Sinclair, C. J.; Boxall, A. B. A. Assessing the ecotoxicity of pesticide transformation products. *Environ. Sci. Technol.* **2003**, *37* (20), 4617–4625.
- (37) Alder, L.; Greulich, K.; Kempe, G.; Vieth, B. Residue analysis of 500 high priority pesticides: better by GC-MS or LC-MS/MS? *Mass Spectrom. Rev.* **2006**, *25* (6), 838–65.
- (38) Greulich, K.; Alder, L. Fast multiresidue screening of 300 pesticides in water for human consumption by LC-MS/MS. *Anal. Bioanal. Chem.* **2008**, *391* (1), 183–97.
- (39) He, P.; Aga, D. S. Comparison of GC-MS/MS and LC-MS/MS for the analysis of hormones and pesticides in surface waters: advantages and pitfalls. *Anal. Methods* **2019**, *11* (11), 1436–1448.
- (40) Steele, G. V.; Johnson, H. M.; Sandstrom, M. W.; Capel, P. D.; Barbash, J. E. Occurrence and fate of pesticides in four contrasting agricultural settings in the United States. *J. Environ. Qual.* **2008**, *37* (3), 1116–1132.
- (41) Nowell, L. H.; Moran, P. W.; Schmidt, T. S.; Norman, J. E.; Nakagaki, N.; Shoda, M. E.; Mahler, B. J.; Van Metre, P. C.; Stone, W. W.; Sandstrom, M. W.; Hladik, M. L. Complex mixtures of dissolved pesticides show potential aquatic toxicity in a synoptic study of Midwestern U.S. streams. *Sci. Total Environ.* **2018**, *613–614*, 1469–1488.
- (42) Schreiner, V. C.; Link, M.; Kunz, S.; Szöcs, E.; Scharmüller, A.; Vogler, B.; Beck, B.; Battes, K. P.; Cimpean, M.; Singer, H. P.; Hollender, J.; Schäfer, R. B. Paradise lost? Pesticide pollution in a European region with considerable amount of traditional agriculture. *Water Res.* **2021**, *188*, 116528.
- (43) Fonseca, E.; Renau-Pruñonosa, A.; Ibáñez, M.; Gracia-Lor, E.; Estrela, T.; Jiménez, S.; Pérez-Martín, M. Á.; González, F.; Hernández, F.; Morell, I. Investigation of pesticides and their transformation products in the Júcar River Hydrographical Basin (Spain) by wide-scope high-resolution mass spectrometry screening. *Environ. Res.* **2019**, *177*, 108570.
- (44) USGS Regional Stream Quality Assessment (RSQA). <https://webapps.usgs.gov/rsqa/#/> (accessed 07-29-2020).
- (45) Qi, S. L.; Nakagaki, N. *Geospatial Database of the Study Boundaries, Sampled Sites, Watersheds, and Riparian Zones for the U.S. Geological Survey Regional Stream Quality Assessment*; U.S. Geological Survey Data Release, 2020; DOI: 10.5066/P90YQ9TW.
- (46) Qi, S. L.; Nakagaki, N. *Selected Environmental Characteristics of Sampled Sites, Watersheds, and Riparian Zones for the U.S. Geological*

Survey Regional Stream Quality Assessment, 2013 to 2017; U.S. Geological Survey Data Release, 2020; DOI: 10.5066/P962N215.

(47) Garrett, J. D.; Frey, J. W.; Van Metre, P. C.; Journey, C. A.; Nakagaki, N.; Button, D. T.; Nowell, L. H. *Design and Methods of the Midwest Stream Quality Assessment (MSQA), 2013*; U.S. Geological Survey Open-File Report 2017-1073; 2017; 59 pages and 4 appendixes.

(48) Journey, C. A.; Van Metre, P. C.; Bell, A. H.; Garrett, J. D.; Button, D. T.; Nakagaki, N.; Qi, S. L.; Bradley, P. M. *Design and Methods of the Southeast Stream Quality Assessment (SESQA), 2014*; U.S. Geological Survey Open-File Report 2015-1095; U.S. Geological Survey: Reston, VA, 2015; p 46.

(49) Sheibley, R. W.; Morace, J. L.; Journey, C. A.; Van Metre, P. C.; Bell, A. H.; Nakagaki, N.; Button, D. T.; Qi, S. L. *Design and Methods of the Pacific Northwest Stream Quality Assessment (PNSQA), 2015*; U.S. Geological Survey Open-File Report 2017-1103; U.S. Geological Survey: Reston, VA 2017; p 46.

(50) Coles, J. F.; Riva-Murray, K.; Van Metre, P. C.; Button, D. T.; Bell, A. H.; Qi, S. L.; Journey, C. A.; Sheibley, R. W. *Design and Methods of the U.S. Geological Survey Northeast Stream Quality Assessment (NESQA), 2016*; U.S. Geological Survey Open-File Report 2018-1183; Reston, VA, 2019.

(51) May, J. T.; Nowell, L. H.; Coles, J. F.; Button, D. T.; Bell, A. H.; Qi, S. L.; Van Metre, P. C. *Design and Methods of the California Stream Quality Assessment (CSQA), 2017*; U.S. Geological Survey Open-File Report 2020-1023; U.S. Geological Survey: Reston, VA, 2020.

(52) U.S. Geological Survey. *Collection of Water Samples (ver. 2.0): National Field Manual for the Collection of Water-Quality Data*; U.S. Geological Survey: Reston, VA, 2006; Vol. Book 9.

(53) Sandstrom, M. W.; Kanagy, L. K.; Anderson, C. A.; Kanagy, C. J. Determination of pesticides and pesticide degradates in filtered water by direct aqueous-injection liquid chromatography-tandem mass spectrometry. In *U.S. Geological Survey Techniques and Methods*; 2015; Book 5, Chapter B11,

(54) Donley, N. The USA lags behind other agricultural nations in banning harmful pesticides. *Environ. Health* **2019**, *18*, 44.

(55) Shoda, M. E.; Nowell, L. H.; Stone, W. W.; Sandstrom, M. W.; Bexfield, L. M. *Data analysis considerations for pesticides determined by National Water Quality Laboratory Schedule 2437*; U. S. Geological Survey Scientific Investigations Report 2018-5007; Reston, VA, 2018; <http://pubs.er.usgs.gov/publication/sir20185007>.

(56) Wickham, H.; François, R.; Henry, L.; Müller, K. *Dplyr: A Grammar of Data Manipulation: R Package version 0.8.4*; 2018.

(57) Wickham, H. *Ggplot2: Elegant Graphics for Data Analysis*; Springer-Verlag: New York, 2016.

(58) Mangiafico, S. *rcompanion: Functions to Support Extension Education Program Evaluation: R package version 2.3.25*; <https://CRAN.R-project.org/package=rcompanion>.

(59) Konrad, C. P. Longitudinal hydraulic analysis of river-aquifer exchanges. In *AGU Fall Meeting Abstracts*; 2006; Vol. 2006, pp H41E-0455.

(60) Konrad, C. P. *Non-Linear Baseflow Separation Model Parameters and Results for Selected Streamflow Gages*; U.S. Geological Survey Data Release, 2020; DOI: 10.5066/P9AIPHEP.

(61) Konrad, C. P.; Schmadel, N. M.; Harvey, J. W.; Schwarz, G. E.; Gomez-Velez, J.; Boyer, E. W.; Scott, D. Accounting for temporal variability of streamflow in estimate of travel time. *Front. Water* **2020**, *2*, 29.

(62) U.S. Geological Survey. *USGS Water Data for the Nation: U.S. Geological Survey National Water Information System Database*, DOI: 10.5066/F7P55KJN (accessed 10-15-2020).

(63) Corsi, S. R.; De Cicco, L. A.; Villeneuve, D. L.; Blackwell, B. R.; Fay, K. A.; Ankley, G. T.; Baldwin, A. K. Prioritizing chemicals of ecological concern in Great Lakes tributaries using high-throughput screening data and adverse outcome pathways. *Sci. Total Environ.* **2019**, *686*, 995–1009.

(64) R Development Core Team. *R: A Language and Environment for Statistical Computing*, ver. 3.5.2; R Foundation for Statistical Computing: Vienna, Austria, 2019.

(65) DeCicco, L.; Corsi, S. R.; Villeneuve, D.; Blackwell, B. R.; Ankley, G. T. *toxEval: Evaluation of measured concentration data using the ToxCast high-throughput screening database or a user-defined set of concentration benchmarks*. In *R Package*, ver. 1.0.0; <https://owi.usgs.gov/R/gran.html> (accessed 07-10-2020).

(66) Blackwell, B. R.; Ankley, G. T.; Corsi, S. R.; DeCicco, L. A.; Houck, K. A.; Judson, R. S.; Li, S.; Martin, M. T.; Murphy, E.; Schroeder, A. L.; Smith, E. R.; Swintek, J.; Villeneuve, D. L. An “EAR” on environmental surveillance and monitoring: A case study on the use of exposure-activity ratios (EARs) to prioritize sites, chemicals, and bioactivities of concern in Great Lakes waters. *Environ. Sci. Technol.* **2017**, *51* (15), 8713–8724.

(67) Bradley, P. M.; Journey, C. A.; Button, D. T.; Carlisle, D. M.; Huffman, B. J.; Qi, S. L.; Romanok, K. M.; Van Metre, P. C. Multi-region assessment of pharmaceutical exposures and predicted effects in USA Wadeable urban-gradient streams. *PLoS One* **2020**, *15* (1), No. e0228214.

(68) U.S. Environmental Protection Agency. *ToxCast & Tox21 Summary Files from invitrodb v2*. <https://www.epa.gov/chemical-research/toxicity-forecaster-toxcastmdata> (accessed 07-10-2020).

(69) U.S. Environmental Protection Agency. *ACToR*. <https://actor.epa.gov/actor/home.xhtml> (accessed 07-10-2020).

(70) U.S. Environmental Protection Agency. *iCSS ToxCast Dashboard*. <https://actor.epa.gov/dashboard/>.

(71) Li, H.; Cheng, F.; Wei, Y.; Lydy, M. J.; You, J. Global occurrence of pyrethroid insecticides in sediment and the associated toxicological effects on benthic invertebrates: An overview. *J. Hazard. Mater.* **2017**, *324*, 258–271.

(72) Schroeder, A. L.; Ankley, G. T.; Houck, K. A.; Villeneuve, D. L. Environmental surveillance and monitoring—The next frontiers for high-throughput toxicology. *Environ. Toxicol. Chem.* **2016**, *35* (3), 513–525.

(73) Becker, R. A.; Friedman, K. P.; Simon, T. W.; Marty, M. S.; Patlewicz, G.; Rowlands, J. C. An exposure:activity profiling method for interpreting high-throughput screening data for estrogenic activity—Proof of concept. *Regul. Toxicol. Pharmacol.* **2015**, *71* (3), 398–408.

(74) U.S. Environmental Protection Agency. *Exploring ToxCast Data: Downloadable Data*. <https://www.epa.gov/chemical-research/exploring-toxcast-data-downloadable-data> (accessed 07-10-2020).

(75) Bradley, P. M.; Journey, C. A.; Berninger, J. P.; Button, D. T.; Clark, J. M.; Corsi, S. R.; DeCicco, L. A.; Hopkins, K. G.; Huffman, B. J.; Nakagaki, N.; Norman, J. E.; Nowell, L. H.; Qi, S. L.; VanMetre, P. C.; Waite, I. R. Mixed-chemical exposure and predicted effects potential in Wadeable southeastern USA streams. *Sci. Total Environ.* **2019**, *655*, 70–83.

(76) Morace, J. L.; Nowell, L. H.; Mahler, B. J.; Sandstrom, M. W.; Button, D. T.; Van Metre, P. C.; Medalie, L.; Bexfield, L. M. *Dissolved pesticides in weekly water samples from the NAWQA Regional Stream Quality Assessments (2013–2017)*, U.S. Geological Survey Data Release, 2020; DOI: 10.5066/P9D2BDBY.

(77) U.S. Environmental Protection Agency. *Headwater Streams Studies*. <https://www.epa.gov/water-research/headwater-streams-studies> (accessed 06-16-2018).

(78) Spycher, S.; Mangold, S.; Doppler, T.; Junghans, M.; Wittmer, I.; Stamm, C.; Singer, H. Pesticide risks in small streams—How to get as close as possible to the stress imposed on aquatic organisms. *Environ. Sci. Technol.* **2018**, *52* (8), 4526–4535.

(79) Lorenz, S.; Rasmussen, J. J.; Süß, A.; Kalettka, T.; Golla, B.; Horney, P.; Stähler, M.; Hommel, B.; Schäfer, R. B. Specifics and challenges of assessing exposure and effects of pesticides in small water bodies. *Hydrobiologia* **2017**, *793* (1), 213–224.

(80) Biggs, J.; von Fumetti, S.; Kelly-Quinn, M. The importance of small waterbodies for biodiversity and ecosystem services: implications for policy makers. *Hydrobiologia* **2017**, *793* (1), 3–39.

(81) U.S. Environmental Protection Agency. *Atrazine: Proposed Interim Registration Review Decision Case Number 0062*; 2019; [https://www.epa.gov/sites/production/files/2019-12/documents/atrazine\\_pid\\_signed\\_12\\_18\\_19.pdf](https://www.epa.gov/sites/production/files/2019-12/documents/atrazine_pid_signed_12_18_19.pdf).

- (82) Quali-Pro Fipronil 0.0143G Broadcast; [https://s3-us-west-1.amazonaws.com/agrian-cg-fs1-production/pdfs/Fipronil\\_0.0143G\\_Label1.pdf](https://s3-us-west-1.amazonaws.com/agrian-cg-fs1-production/pdfs/Fipronil_0.0143G_Label1.pdf) (accessed 07-29-2020).
- (83) Hall, J. K.; Pawlus, M.; Higgins, E. R. Losses of atrazine in runoff water and soil sediment. *J. Environ. Qual.* **1972**, *1* (2), 172–176.
- (84) U.S. Geological Survey. *Estimated annual pesticide use*; [https://water.usgs.gov/nawqa/pnsp/usage/maps/compound\\_listing.php](https://water.usgs.gov/nawqa/pnsp/usage/maps/compound_listing.php) (accessed 07-06-2020).
- (85) Carpenter, K. D.; Kuivila, K. M.; Hladik, M. L.; Haluska, T.; Cole, M. B. Storm-event transport of urban-use pesticides to streams likely impairs invertebrate assemblages. *Environ. Monit. Assess.* **2016**, *188*, 345.
- (86) University of Florida's IFAS Extension. *Pests in and around the Southern Home (SP486)*; [https://edis.ifas.ufl.edu/topic\\_book\\_piash](https://edis.ifas.ufl.edu/topic_book_piash) (accessed 07-24-2020).
- (87) University of Hertfordshire. *PPDB: Pesticide Properties Data-Base*; <https://sitem.herts.ac.uk/aeru/ppdb/en/index.htm> (accessed 07-06-2020).
- (88) Connelly, P. *Environmental fate of fipronil*; Environmental Monitoring Branch, Dept of Pesticide Regulation, California EPA: Sacramento, CA, 2001; p 17; <http://www.cdpr.ca.gov/docs/emon/pubs/fatememo/fipronil.pdf>.
- (89) Ryberg, K. R.; Stone, W. W.; Baker, N. T. Causal factors for pesticide trends in streams of the United States: Atrazine and deethylatrazine. *J. Environ. Qual.* **2020**, *49* (1), 152–162.
- (90) Wackett, L.; Sadowsky, M.; Martinez, B.; Shapir, N. Biodegradation of atrazine and related s-triazine compounds: from enzymes to field studies. *Appl. Microbiol. Biotechnol.* **2002**, *58*, 39–45.
- (91) Udiković-Kolić, N.; Scott, C.; Martin-Laurent, F. Evolution of atrazine-degrading capabilities in the environment. *Appl. Microbiol. Biotechnol.* **2012**, *96* (5), 1175–89.
- (92) GIE Media Inc. Golf Course Industry. <https://www.golfcourseindustry.com/article/upi-disease-management/> (accessed 07-23-2020).
- (93) Pesticide Action Network (PAN). *Pesticide Use on Ornamental Turf in 2016*; <http://www.pesticideinfo.org/DS.jsp?sk=33008>.
- (94) Armbrust, K. L. Chlorothalonil and chlorpyrifos degradation products in golf course leachate. *Pest Manage. Sci.* **2001**, *57* (9), 797–802.
- (95) Thurman, E. M.; Goolsby, D. A.; Meyer, M. T.; Kolpin, D. W. Herbicides in surface waters of the midwestern United States: the effect of spring flush. *Environ. Sci. Technol.* **1991**, *25* (10), 1794–1796.
- (96) Battaglin, W. A.; Sandstrom, M. W.; Kuivila, K. M.; Kolpin, D. W.; Meyer, M. T. Occurrence of azoxystrobin, propiconazole, and selected other fungicides in US streams, 2005–2006. *Water, Air, Soil Pollut.* **2011**, *218* (1), 307–322.
- (97) Barber, L. B.; Keefe, S. H.; Brown, G. K.; Furlong, E. T.; Gray, J. L.; Kolpin, D. W.; Meyer, M. T.; Sandstrom, M. W.; Zaugg, S. D. Persistence and potential effects of complex organic contaminant mixtures in wastewater-impacted streams. *Environ. Sci. Technol.* **2013**, *47* (5), 2177–2188.
- (98) Müller, M. E.; Werneburg, M.; Glaser, C.; Schwientek, M.; Zarfl, C.; Escher, B. I.; Zwiener, C. Influence of emission sources and tributaries on the spatial and temporal patterns of micropollutant mixtures and associated effects in a small river. *Environ. Toxicol. Chem.* **2020**, *39* (7), 1382–1391.
- (99) Majewski, M. S.; Foreman, W. T.; Coupe, R. H.; Goolsby, D. A.; Wiebe, F. W. *Pesticides in Air and Rain in the Midcontinental United States*; U.S. Geological Survey Open-File Report 2005-1397, 2002; <http://pubs.er.usgs.gov/publication/ofr20051307>.
- (100) Bexfield, L. M.; Belitz, K.; Lindsey, B. D.; Toccalino, P. L.; Nowell, L. H. Pesticides and pesticide degradates in groundwater used for public supply across the United States: Occurrence and human-health context. *Environ. Sci. Technol.* **2021**, *55* (1), 362–372.
- (101) Bexfield, L. M.; Sandstrom, M. W.; Beaty, D. *Field, Laboratory, and Third-Party Data for Assessment of the Quality of Pesticide Results Reported by the National Water Quality Laboratory for Groundwater Samples Collected by the National Water-Quality Assessment Project*, 2013–18; U.S. Geological Survey Data Release, 2020; DOI: 10.5066/P90BFKA4.
- (102) Domagalski, J. L.; Ator, S.; Coupe, R.; McCarthy, K.; Lampe, D.; Sandstrom, M.; Baker, N. Comparative study of transport processes of nitrogen, phosphorus, and herbicides to streams in five agricultural basins, USA. *J. Environ. Qual.* **2008**, *37* (3), 1158–1169.
- (103) Ator, S. W.; Denver, J. M. Estimating contributions of nitrate and herbicides from groundwater to headwater streams, Northern Atlantic Coastal Plain, United States. *J. Am. Water Resour. Assoc.* **2012**, *48* (6), 1075–1090.
- (104) McCarty, G. W.; Hapeman, C. J.; Rice, C. P.; Hively, W. D.; McConnell, L. L.; Sadeghi, A. M.; Lang, M. W.; Whitall, D. R.; Bialek, K.; Downey, P. Metolachlor metabolite (MESA) reveals agricultural nitrate-N fate and transport in Choptank River watershed. *Sci. Total Environ.* **2014**, *473*–474, 473–482.
- (105) McKnight, U. S.; Rasmussen, J. J.; Kronvang, B.; Binning, P. J.; Bjerg, P. L. Sources, occurrence and predicted aquatic impact of legacy and contemporary pesticides in streams. *Environ. Pollut.* **2015**, *200*, 64–76.
- (106) Welch, E. M.; Dulai, H.; El-Kadi, A.; Shuler, C. K. Submarine groundwater discharge and stream baseflow sustain pesticide and nutrient fluxes in Faga'alu Bay, American Samoa. *Front. Environ. Sci.* **2019**, *7*, 162.
- (107) Rice, C.; Hively, W. D.; McCarty, G. W.; Hapeman, C. J. Fluxes of agricultural nitrogen and metolachlor metabolites are highly correlated in a first order stream in Maryland, USA. *Sci. Total Environ.* **2020**, *716*, 136590.
- (108) Winter, T. C.; Harvey, J. W.; Franke, O. L.; Alley, W. M. *Ground Water and Surface Water: A single resource*; U.S. Geological Survey Circular 1139, 1998; <http://pubs.er.usgs.gov/publication/cir1139>.
- (109) Fisher, I. J.; Phillips, P. J.; Bayraktar, B. N.; Chen, S.; McCarthy, B. A.; Sandstrom, M. W. Pesticides and their degradates in groundwater reflect past use and current management strategies, Long Island, New York, USA. *Sci. Total Environ.* **2021**, *752*, 141895.
- (110) Romanok, K. M.; Bradley, P. M.; Mahler, B. J. *Pesticide and Transformation Product Concentrations and Risk Quotients in U.S. Headwater Streams*; U.S. Geological Survey Data Release, 2021; DOI: 10.5066/P9PSU28Y.
- (111) Diamond, M. L. Surprising degradation products from an under-fire insecticide. *ACS Cent. Sci.* **2017**, *3* (2), 97–98.
- (112) Miller, J. L.; Schmidt, T. S.; Van Metre, P. C.; Mahler, B. J.; Sandstrom, M. W.; Nowell, L. H.; Carlisle, D. M.; Moran, P. W. Common insecticide disrupts aquatic communities: A mesocosm to field ecological risk assessment of fipronil and its degradates in U.S. streams. *Sci. Adv.* **2020**, *6*, eabc1299.
- (113) Norman, J. E.; Mahler, B. J.; Nowell, L. H.; Van Metre, P. C.; Sandstrom, M. W.; Corbin, M. A.; Qian, Y.; Pankow, J. F.; Luo, W.; Fitzgerald, N. B.; Asher, W. E.; McWhirter, K. J. Daily stream samples reveal highly complex pesticide occurrence and potential toxicity to aquatic life. *Sci. Total Environ.* **2020**, *715*, 136795.