Green Chemistry

PERSPECTIVE

Cite this: *Green Chem.*, 2015, **17**, 2679

Can pollutant release and transfer registers (PRTRs) be used to assess implementation and effectiveness of green chemistry practices? A case study involving the Toxics Release Inventory (TRI) and pharmaceutical manufacturers

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Pharmaceutical firms have reported that implementation of green chemistry practices in their manufacturing processes have significantly reduced the quantities of toxic chemicals they use, release to the environment, or otherwise manage as waste. Using the United States Environmental Protection Agency's (EPA's) Toxics Release Inventory (TRI) database and literature publications, we conducted research to assess this claim. Our analyses show that over the 2002 through 2011 timeframe the quantities of toxic chemicals reported annually by pharmaceutical manufacturing facilities to EPA's TRI Program as released to the environment or otherwise managed as waste have declined steadily and by more than 60%. The large reductions in the reported quantities are sector-wide, and it appears that factors such as outsourcing, production levels, regulations, shifts to other waste management practices, or TRI reporting characteristics by the larger pharmaceutical firms are not driving the decline. Our analyses, combined with the extensive evidence in the literature of green chemistry advances within the pharma sector, lead us to conclude that implementation of green chemistry practices is a major contributing factor to the large reductions we report herein. We believe the TRI, an easy-to-use pollution prevention tool used extensively for tracking environmental performance, is uniquely well-suited for assessing the progress made by different industry sectors or specific facilities therein in implementing green chemistry practices and the effectiveness that such practices have in preventing pollution: uses of the TRI that hitherto have not been reported. Moreover, our findings indicate that other pollutant release and transfer registers (PRTRs) may have the potential to be used for these purposes as well.

Received 12th January 2015,
Accepted 24th March 2015

DOI: 10.1039/c5gc00056d

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Introduction

One of the United States (U.S.) Environmental Protection Agency's (EPA's) principal initiatives to facilitate the congressional mandate of preventing pollution has been promotion of green chemistry. For more than a decade many manufacturing firms have increasingly implemented green chemistry practices and, therewith, have claimed significant reductions in the quantities of toxic chemicals they use, release to the environment, recycle, or otherwise manage as waste. This is particularly so for pharmaceutical manufacturing firms. Notable examples apply to the syntheses of the widely used medications sildenafil (Viagra®), pregabalin (Lyrica®), and sitagliptin (Januvia®), to name a few.

While reductions in toxic chemical releases specifically due to implementation of green chemistry efforts is known to the specific facilities or companies that have implemented the efforts, and while these achievements are sometimes publicized at corporate levels for public relations purposes, this information is generally not disclosed as such to the public. Moreover, little information is available on the reductions in toxic chemical uses and waste generation related to green chemistry efforts at the facility or industry sector level, or on the nationwide impacts of green chemistry advances.

The EPA's Toxics Release Inventory (TRI) is a publicly available database that contains information on the quantities of certain toxic chemicals released annually to air, water and land, or otherwise managed as waste by facilities throughout the United States. By July 1st of each year, facilities are required to disclose this and other information regarding toxic chemi-

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cals to EPA, and EPA makes this information available and readily accessible to the public through the TRI. While the TRI has been used for many years as a pollution prevention tool, its use as a practical means to assess and evaluate the overall impact of green chemistry on preventing pollution has not been investigated.

In this paper, we explore the utility of the data collected through the TRI to assess reductions in toxic chemical wastes and the causes of such reductions. Our ultimate goal is to determine whether the TRI can be used to evaluate progress towards sustainability goals through green chemistry advances. As our first step towards this end we set out to determine whether green chemistry practices implemented by facilities or an industry sector do in fact lead to reductions in the quantities of toxic chemicals reported to EPA's TRI Program as released to the environment or otherwise managed as waste, using the pharmaceutical manufacturing sector as a test case. This paper describes the results of our initial research.

Background on the Toxics Release Inventory

The TRI was established by Congress under Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986 (EPCRA), largely as a result of the tragic accidental release of methyl isocyanate that occurred in December, 1984 at a facility in Bhopal, India,[1,2] and another serious accidental chemical release at a chemical manufacturing plant in Institute, West Virginia, in August of 1985.[2]

These incidents underscored growing demands by communities, public interest and environmental organizations for information on the toxic chemicals being used and released by facilities in their communities.[2] In response, EPCRA was enacted in 1986. TRI reporting began for calendar year 1987, with the first reports due by July 1st, 1988. This information was made publicly available by EPA in June of 1989.[3] This annual cycle of facilities reporting to EPA's TRI Program, and EPA compiling and making the information available to the public has continued ever since. Since implementation of the TRI, more than forty countries have implemented their own pollutant release and transfer registers (PRTRs), and many of these PRTR systems were modelled from the TRI.

TRI data and information are used by many people and organizations, and for many diverse purposes.[4,5] In addition to its use by the public, TRI data are used by the federal, state and local governments, for example, for prioritization purposes. EPA makes TRI data available shortly after it is submitted through a variety of means that include online query tools, complete data downloads, location-specific analyses, and data summary documents.[6] The U.S.' National Library of Medicine makes TRI data available through its ToxMap tool.[7]

Over the years the TRI list of toxic chemicals and some of the TRI reporting requirements for facilities have been modified by EPA to reflect the concerns and needs of society and in response to petitions submitted to EPA to make changes to the TRI list of toxic chemicals. Examples of some of the more major changes are available.[8–12] Currently, there are well over 600 discrete chemicals included on the TRI list of toxic chemicals, as well as chemicals classified in 30 chemical categories. Facilities in the manufacturing and other sectors (*e.g.*, electric utilities, metal mining, hazardous waste management) are subject to the TRI reporting requirements.

The collection of TRI data is achieved by requiring facilities subject to TRI reporting that have ten or more full-time employees and that within a calendar year manufacture, process, or otherwise use a TRI-listed chemical in a quantity that exceeds a threshold amount to report to the EPA, and state and tribal governments.

For a given chemical, facilities are required to report the quantities they: released onsite to air, land or water; recycled

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onsite; burned for energy recovery or treated onsite; or transferred offsite to other facilities or locations for treatment, recycling, storage or disposal during the calendar year for which the reporting threshold was exceeded. Releases to air include stack and fugitive emissions. Releases to land include, for example, disposal in landfills and injection into underground wells. Releases to water include discharges into rivers, streams or other bodies of water.

Facilities are required to submit their information by July 1st of the following year on the TRI reporting Form R: one Form R for each chemical for which an applicable reporting threshold was exceeded. Each year EPA's TRI Program receives approximately 70 000 Form R reports from approximately 20 000 facilities.

Tracking pollution prevention progress through TRI

When the TRI was originally implemented the only quantities of toxic chemicals that had to be reported were those released directly to the environment or transferred to offsite locations for treatment or disposal. Also, facilities had the option to report activities that reduced their waste generation and the effect these activities had on the quantities they released to the environment or transferred offsite.

A major change in the types of information required to be reported under TRI regulations occurred in 1990, with passage of the Pollution Prevention Act (PPA).[13] In recognizing the potential of the TRI to be a powerful pollution prevention tool, the authors of the PPA expanded the information required to be reported by facilities under EPCRA Section 313 to include information specific to source reduction and preferred waste management techniques. As described under Section 6607 of the PPA, for a given chemical this additional information includes the quantities of the chemical that were recycled, used for energy recovery, or treated at the facility or elsewhere. The PPA also requires reporting of any source reduction practices (*e.g.*, process modifications, substitution of raw materials) implemented at a facility during the reporting year. Data fields were added to the TRI reporting Form R for these additional required data elements.

Facilities may voluntarily disclose specific details on their source reduction practices, in the form of text, in Section 8.11 of their Form R submissions. Disclosure of information in Section 8.11 of the TRI Form R provides facilities with a unique opportunity to showcase their achievements in preventing pollution to the public and other users of TRI data and information. EPA has recently established an online tool where this pollution prevention data can be easily obtained and readily analyzed.[14]

Despite the wealth of publications detailing green chemistry advances, to the best of our knowledge none have quantified the environmental impacts of green chemistry initiatives throughout a given industry sector. Pollutant release and transfer registers (PRTRs) such as the TRI (the United States' PRTR) are the only means that we are aware of by which the public, researchers, local, state and federal government officials, and interested parties may be able to track implementation of green chemistry practices and its resultant impact on the prevention of pollution.

Method

Facilities that manufacture pharmaceuticals are subject to the TRI reporting requirements, and file Form R reports on chemicals included on the TRI list of toxic chemicals and used in their manufacturing processes. We conducted an analysis of information reported to EPA's TRI Program to determine whether implementation of green chemistry practices by the pharmaceutical industry are reflected in the TRI data. In this analysis, the pharmaceutical industry was defined based on North American Industry Classification System (NAICS) code 325411 (Medicinal and Botanical Manufacturing) and 325412 (Pharmaceutical Preparation Manufacturing). In comparing the pharmaceutical industry to the manufacturing sector as a whole, we define the manufacturing industry to include facilities classified in NAICS codes 31–33, except for those in NAICS 325411 and 325412.

To ensure that our analyses would encompass years of TRI reporting in which green chemistry practices were implemented by the pharmaceutical manufacturing sector and progressively reflected throughout, we compiled TRI data for reporting years 2002 through 2011, using EPA's TRI.NET tool for accessing and analyzing TRI data.[15] Green chemistry research began to emerge in the early 1990s,[16,17] and implementation of green chemistry approaches followed in the late 1990s and continue today. Therefore, it is likely that reductions in toxic chemical releases due to green chemistry approaches would have begun just prior to our selected timeframe. Also, throughout the chosen timeframe the TRI chemical list and reporting requirements remained largely static, and analyses would therefore not be confounded by regulatory changes to TRI reporting.

This research uses information reported to EPA's TRI Program annually by facilities regarding total releases and production-related waste managed. Total releases include onsite and offsite disposal or other releases, including releases to air, surface water, and land (includes underground injection wells). Production-related waste management quantities include the total release quantities as well as the quantities used for energy recovery, recycled, and treated both onsite and offsite.

Results

A total of 266 pharmaceutical facilities submitted 6543 Form R reports for 148 chemicals to EPA's TRI Program for reporting (calendar) years 2002 through 2011. Fig. 1 shows that the total release quantities of all toxic chemicals reported by these facilities to EPA's TRI Program decreased by 67% from 2002 to 2011. In Fig. 1 the acute increase in 2006 is primarily due to unusually large increases in reporting for that year from two

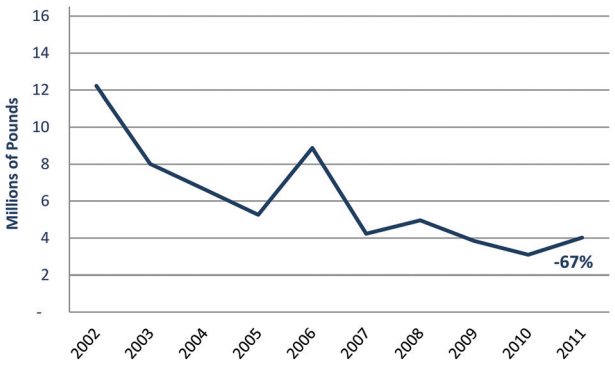

Fig. 1 Quantities of toxic (TRI) chemical releases reported by the pharmaceutical industry.

facilities. One of these facilities reported releases of 3 416 000 pounds of methanol *via* underground injection in 2006. The following year, the same facility reported releases of 159 680 pounds of methanol to underground injection. The second facility reported approximately 29 000 pounds of releases during 2005, 827 000 pounds during 2006, and 26 000 pounds during 2007.

While it is tempting to conclude at the outset that this substantial decline is due to green chemistry advances, it could also be driven by other factors such as production levels, implementation of more stringent regulations, an increase in outsourcing, or general environmental improvements such as equipment replacement or repair, changes in production schedule to minimize equipment and feedstock changeovers, and installation of filters, to name a few.

We examined these other potential causes of this 67% decline to determine if green chemistry advances or these other factors explain the decline observed. With the variability in the data, we wanted to confirm the statistical significance of the trend observed. We conducted a two-tailed *t*-test with equal variances as a conservative approach to test the null hypotheses that releases were the same during the 2002 to 2006 period and the 2007 to 2011 period. The resulting probability is less than 1%, therefore we can reject the null hypothesis, and conclude the releases declined over this period.

Are reductions due to decreased production?

It is possible that a decline in reported toxic chemical releases could be associated with decreased production at facilities that file TRI Form R reports. If the pharmaceutical industry's production declined from 2002 through 2011, it is likely that facilities in the sector would have used fewer quantities of toxic chemicals. This is expected to result in reporting of lower quantities of toxic chemicals, or even submission of fewer Form R reports to EPA's TRI Program, and could explain the decline in reported releases from the sector. To assess the impact of changes in production levels, ideally one would want to use a facility-level annual production metric for all facilities in the sector reporting to TRI. Unfortunately, these data are not included in TRI Form R submissions and are not available from any public source at the facility-level.

To assess trends in the pharmaceutical sector's production levels we used the annual "value added" from the U.S. Census Annual Survey of Manufactures (ASM) as proxy to facility-level annual production output data.[18] Value added is a measure of the contribution of each sector to the Nation's Gross Domestic Product (GDP) and is published annually by the U.S. Census Bureau. Census derives the value added by subtracting the cost of materials, supplies, containers, fuel, purchased electricity, and contract work from the value of products manufactured plus receipts for services rendered.[19] As the Census Bureau reports value added in current year dollars, we adjusted for inflation using the GDP implicit price deflator published by the U.S. Department of Commerce.[20]

While value added serves as a robust proxy for production in many sectors, using this metric as an indication of production trends in the pharmaceutical sector has limitations. It does not account for some of the factors specific to the pharmaceutical sector. These include changes over time in the value of a dose, number of doses, number of patients being treated, number of new drugs manufactured, number of steps in manufacturing processes, and drug prices. These are complex, interconnected factors that cannot be quantified in a single metric for the sector as a whole. Therefore, we used the value added metric as a rough proxy for overall trends in the sector over time, acknowledging that it may be oversimplifying this sector's actual production trends during the 2002–2011 timeframe.

Fig. 2 compares the quantities of releases of TRI-listed chemicals reported by the pharmaceutical industry to the sector's value added during the 2002 through 2011 timeframe. The value added for the pharmaceutical industry decreased by 2% between 2002 and 2011, while over the same time interval releases of toxic chemicals as reported to EPA's TRI Program decreased by 67%. This indicates that toxic chemical releases reported by the pharmaceutical industry decreased considerably more than can be accounted for by a change in production levels over the same period of time. If the changes in

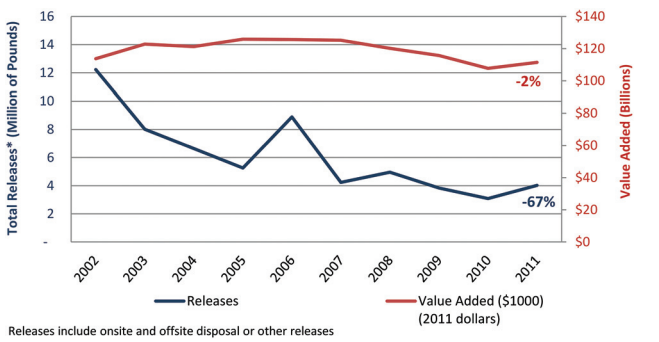

Fig. 2 Quantities of toxic (TRI) chemicals released by the pharmaceutical industry *vs.* value added. Releases include onsite and offsite disposal or other releases.

reported toxic chemical releases were largely associated with changes in production in the pharmaceutical sector, a much smaller decline in reported toxic chemical releases over the time period examined would be expected, rather than a 67% decrease. Therefore, production levels in the pharmaceutical sector do not appear to be a significant factor in the observed reduction in reported releases.

For the more recent years of 2008 through 2011, release trends follow the same direction as value added trends, although there is no correlation in the magnitude of the change. For 2008 to 2009, value added was down 4% while releases were down 23%. When comparing the change from 2009 to 2010, value added for the pharmaceutical sector was down even more, by 7%, and releases were also down, by 19%. For 2010 to 2011, both releases and value added started to increase, although the percent increase was greater for releases than the 3% increase in value added. This recent trend further indicates that while economic factors may influence release trends in the sector, production itself is not likely to be a major factor.

Does the trend observed in the pharmaceutical sector reflect general environmental improvements seen across other manufacturing sectors?

Over the past decade or more, there has been a general decline in release quantities reported to EPA's TRI Program across all industry sectors. There are several plausible reasons for this reduction. These include: implementation of green chemistry practices; adoption of other pollution prevention practices that obviate release of a chemical into the environment; shifts to other waste management methods that reduce the release quantities (*e.g.*, shifts to recycling or treatment of chemicals); a change in the composition of raw materials; or a gradual decrease in the number of facilities that report to EPA's TRI Program.

To determine how the reduction in releases reported by the pharmaceutical sector compares to other manufacturing sectors, we examined the releases reported by the manufacturing sectors as a whole from 2002 through 2011. We looked only at the manufacturing sectors, as opposed to all industry sectors that are subject to the TRI reporting requirements, because the pharmaceutical sector is a subset of the manufacturing sector. Excluded sectors, such as the metal mining sector (NAICS 21) or electric utilities (NAICS 22), report significant releases of toxic chemicals to EPA's TRI Program, and trends in reported quantities with these sectors may be influenced by factors that would not pertain to manufacturing sectors, such as the natural variability in chemical compositions of mined ores, or fossil fuels combusted for power generation.

The release quantities of toxic chemicals reported by the manufacturing sector as a whole for reporting years 2002 through 2011 decreased by 29%, whereas releases quantities decreased by 67% for the pharmaceutical sector (Fig. 3). Given the widespread application of green chemistry practices across the chemical manufacturing sector as a whole, we believe it is reasonable to assume that some of the 29% decrease in toxic chemical releases is due to green chemistry. However we were unable to disaggregate the extent to which green chemistry and other factors contribute to the decrease.

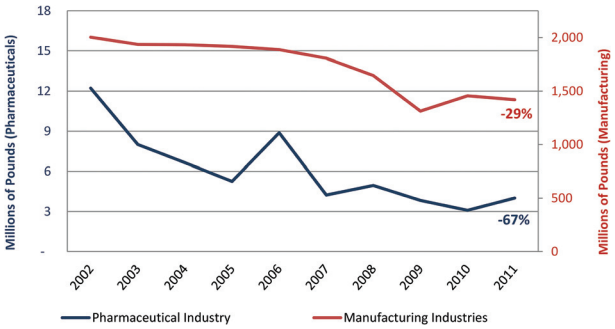

Fig. 3 Quantities of toxic (TRI) chemicals released by the pharmaceutical industry *vs.* all manufacturing industries.

Nonetheless, if the same forces driving the reduction in release quantities of toxic chemicals reported from the pharmaceutical sector were also similarly occurring in the same relative proportions throughout the manufacturing sector as a whole, on a percentage basis the magnitude of the reduction in total releases between the pharmaceutical sector and the other manufacturing sectors would be expected to be similar. That they are not (Fig. 3) indicates that a more pronounced reason is driving the steady, much larger decline in the quantities of toxic chemicals released into the environment by the pharmaceutical industry.

Are reductions a result of outsourcing?

During the time period examined, we assumed that outsourcing of manufacturing operations (or portions thereof) to foreign locations took place across many manufacturing sectors, including the pharmaceutical sector. An increase in outsourcing processes to facilities in other countries could contribute to the reduction in releases occurring in the U.S., as reported to EPA's TRI Program. That is, reported releases from U.S. facilities are expected to decrease as manufacturing activities shift to sites outside the U.S., since these non-U.S. facilities are not required to report to EPA's TRI Program. New drugs that are entirely outsourced rather than manufactured in the U.S. do not influence the trend since they were never represented in the TRI data in the first place. Ideally, to assess the impact of this factor, facility-level data are needed on the chemical or chemicals that were historically used in a U.S. pharmaceutical manufacturing operation but are no longer used because the process using the chemical(s) is now conducted at a facility outside the U.S. Unfortunately, these data are not available at the facility and chemical level.

We used TRI data as a proxy to provide an indication of the impacts of outsourcing. We looked at only those pharmaceutical manufacturing facilities which filed TRI reports to EPA's TRI Program every year from 2002 through 2011. By doing so, the influence from facilities that may have closed due to outsourcing, and therefore stopped reporting to TRI, are eliminated from the trend analysis. Next, for each facility

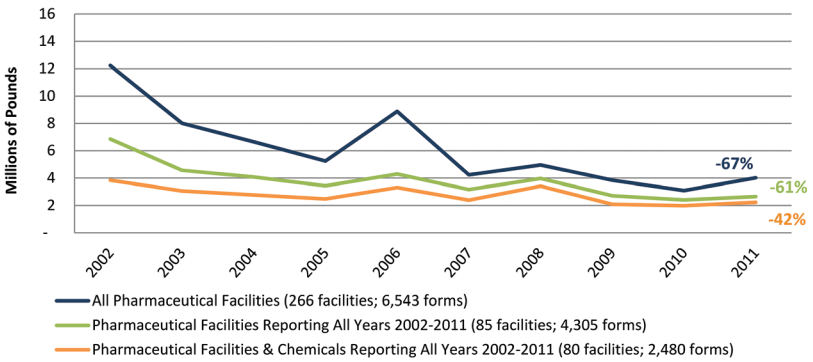

Fig. 4 Quantities of toxic (TRI) chemicals released by the pharmaceutical facilities. Releases include onsite and offsite disposal or other releases.

that reported every year, we only included those chemicals that the facility reported each year. In doing so, the influence of processes within the facility that were outsourced over the time period examined is minimized.

Fig. 4 depicts the results of three trend analyses: (1) total release quantities of all TRI-listed chemicals reported by the 266 pharmaceutical facilities that reported at least once during the 2002–2011 reporting timeframe; (2) total release quantities of any TRI-listed chemicals reported by only those pharmaceutical facilities that reported for each year throughout the 2002–2011 timeframe; and (3) total release quantities of those TRI-listed chemicals that were reported by the same facilities for each year of the 2002–2011 timeframe. Of the 266 pharmaceutical manufacturing facilities that reported to EPA's TRI Program at least once from 2002 to 2011, 85 facilities filed Form R reports for each of these 10 years. Amongst these 85 facilities, the reported total release quantities decreased by 61%. If the sample is further limited to only forms filed by facilities for the same chemical or chemicals every year from 2002 to 2011 (2480 forms filed by 80 facilities), the total releases decreased by 42%. Therefore, the decrease in the releases of the chemicals for which TRI Form R reports were filed for every year over the 10-year period is still considerable. This indicates that while outsourcing may be a contributing factor, it is not the driving force in the reduction of releases reported by the pharmaceutical sector as a whole to EPA's TRI Program.

We further examined the 181 facilities that did not report every year over the time period to assess possible reasons for non-continuous reporting. When facilities stop reporting to EPA's TRI Program, they do not submit any specific information to EPA describing why they are no longer reporting. We therefore further analyzed TRI data to identify possible reasons for non-continuous reporting. Possible reasons and related findings include:

• *The facility manufactures, processes, or otherwise uses TRI-reportable chemicals near or below threshold quantities*. If a facility annually manufactures, processes, or otherwise uses a TRI chemical in a quantity that is near the threshold for TRI reporting, in some years they may exceed the threshold and report, while in other years they are below the threshold and no reporting is required. The facility would then move in and out of TRI reporting for this chemical. In addition, facilities reporting on only one TRI chemical are more likely to drop out of reporting than facilities reporting multiple chemicals. This is because the manufacture, processing or use of the single chemical in a quantity less than the annual threshold quantity for reporting would mean that the facility is not required to report at all. The non-continuous facilities reported fewer TRI forms and lower waste quantities than the continuous reporters, indicating they are more likely to be close to reporting thresholds.

• *The facility is no longer in operation.* A number of the non-continuous facilities appear to have shut down over the time period examined. Additional research is required to quantify the count of closed facilities. Of the 181 facilities that did not report every year over the time period examined, most (118 facilities or 65% of the non-continuous reporters) did not report to TRI in recent years (2010 or 2011) indicating that they may no longer be in operation.

• *Through implementation of green chemistry activities, the facility no longer manufactures, processes, or otherwise uses TRI-reportable chemicals.* The continuous and non-continuous facilities have similar rates (8% and 10%, respectively) of reporting in Section 8.10 (Source Reduction Activities) of the Form R, suggesting that source reduction activities may have been a factor in decreasing chemical quantities below the reporting threshold. Furthermore, initial research confirmed that some of the non-continuous facilities that no longer report to TRI are still active manufacturers, and in some cases, are expanding operations. These facilities may well have implemented green chemistry activities to the extent that they are no longer required to file TRI Form R reports, although further research would be required to confirm this.

Are reduced quantities of toxic (TRI) chemicals released into the environment because of implementation of other waste management practices, such as treatment?

Next we considered the possibility that the reduction in releases of toxic chemicals reported by facilities in the pharmaceutical industry could be due to a shift from releasing to the

environment to other waste management methods. Waste management techniques such as recycling, energy recovery, and treatment are generally preferred to release to the environment. Therefore, the reduction in releases reported by the pharmaceutical sector could be due to the adoption of alternative waste management techniques, and not a true decrease in the generation of the waste itself.

Under the PPA, facilities subject to TRI reporting are required to submit information on the quantities of toxic chemicals that are recycled, used for energy recovery or treated, in addition to the quantities released to the environment as required under Section 313 of EPCRA. To evaluate whether a shift to other waste management methods is a reason for the declining environmental releases of toxic chemicals, we aggregated the quantities of toxic chemicals reported by pharmaceutical facilities as recycled, burned for energy recovery or treated, and compared these quantities to the quantities reported as released during the same period.

The total quantities of waste managed through recycling, energy recovery or treatment decreased by 63%, whereas the quantities released to the environment decreased by 67% (Fig. 5). This indicates that the reduction in the releases reported by pharmaceutical manufacturers is not due a shift towards other waste management methods, at least not to the extent that it is driving the declining trend in releases. If a shift from releases to other waste management methods were occurring, one would expect, at a minimum, the trend line for other waste management methods to decline considerably less than the trend line for releases.

Disaggregation of the total releases and other production-related waste quantities reported by the 80 facilities that filed TRI reporting Form R reports for the same chemical or chemicals for each year of the 2002 through 2011 period further indicates that the reduction in the releases reported by pharmaceutical manufacturers as a whole is not due to a shift in other waste management methods. Fig. 6 provides further detail by showing the contribution of the different waste management methods to the trend presented in Fig. 5. Specifically, Fig. 6 shows the quantities the 80 facilities reported as: released on- and off-site; used for energy recovery on- and off-site; recycled on- and off-site; and treated on- and off-site from 2002 through 2011.

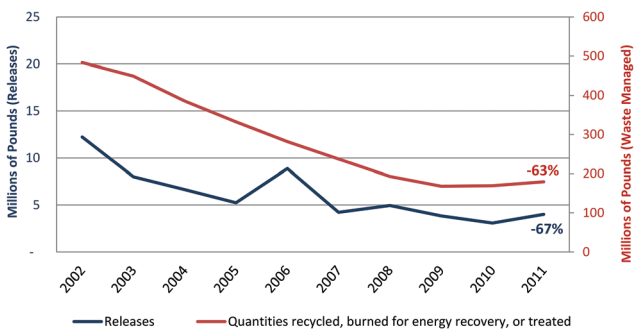

Fig. 5 Quantities of toxic (TRI) chemicals released *vs.* quantities recycled, burned for energy recovery or treated. Releases include onsite and offsite disposal or other releases.

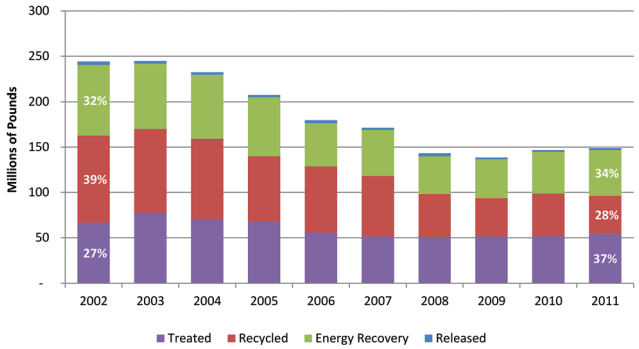

Fig. 6 Waste management methods for pharmaceutical facilities. Includes only facilities and chemicals reported all years 2002–2011 (80 facilities, 2480 forms).

As shown in Fig. 6, while the overall quantity of waste managed declined steadily, the relative proportion of waste managed through energy recovery, recycling, and treatment remained roughly the same during the ten-year period analyzed. This observation further supports the hypothesis that the reduction in the releases reported by pharmaceutical manufacturers is not due a shift towards other waste management methods, as there was little change in the relative proportion of waste managed through recycling, energy recovery, and treatment from 2002 to 2011.

Are the reductions in releases of toxic (TRI) chemicals reported by the pharmaceutical manufacturing sector occurring sector-wide or are the reductions driven by a few companies?

We sought to determine whether the observed reductions are being driven by a few companies or are a sector-wide phenomenon. We wanted to rule-out the possibility that only a few pharmaceutical firms account for the majority of the decrease observed in total release quantities. We aggregated the total releases to the parent company of each facility in the pharmaceutical sector that reported to EPA's TRI Program. We then ranked the parent companies based on the magnitude of their reported releases for the 2002 through 2011 reporting years and compared the trends for the companies with the largest releases to the rest of the sector.

As can be seen in Fig. 7, compared to the sector-wide reduction of 67% in total releases from 2002 to 2011, the three pharmaceutical companies with the largest reported releases experienced a reduction of 73%, and the rest of the sector reduced releases by 61%. Although the percentage reduction in total releases is greatest amongst the top three parent companies (where "top" is defined as those that reported the greatest releases), a substantial reduction was also reported by facilities in other companies throughout the sector. This indicates that the trend in the reduction in toxic chemical releases is evident throughout the pharmaceutical manufacturing

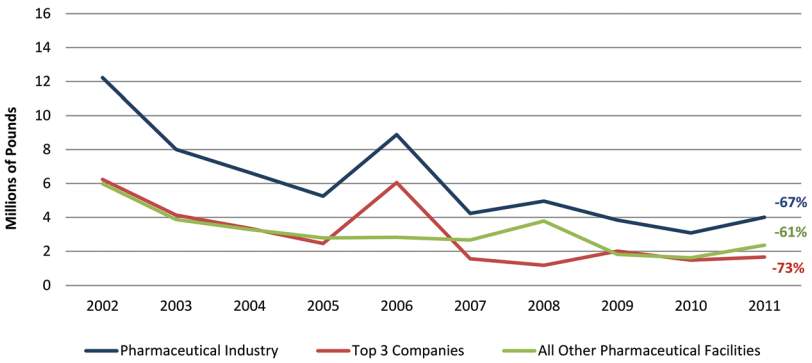

Fig. 7 Release quantities reported by top three releasing pharmaceutical companies *vs.* pharmaceutical sector as a whole.

sector, and is not driven by a particular parent company or companies.

Are the trends consistent with green chemistry implementation?

In the analysis thus far, factors such as outsourcing, changes in production levels, implementation of regulations, shifts to other waste management practices, or TRI reporting characteristics by larger pharmaceutical firms do not appear to be driving the trends observed in this study, although they may have contributed to varying degrees. Pollution prevention appears to be a major contributor to the downward trend observed in toxic chemical releases. While green chemistry is one means to prevent pollution, there are numerous other pollution prevention approaches that do not involve chemistry, such as leak reduction, spill prevention, and improved inventory controls.

To determine whether green chemistry implementation had a role in causing the reductions in the quantities of toxic (TRI) chemicals released to the environment or otherwise managed as waste, we first examined the types of chemicals that are driving the trend. A look at the specific chemicals reported by pharmaceutical manufacturing facilities to EPA's TRI Program shows that the downward trends are largely driven by reductions in the quantities reported for organic solvents.

Five of these solvents: methanol, dichloromethane, toluene, dimethylformamide, and acetonitrile, account for three-quarters of the declining trend from 2002 through 2011 in the overall quantities of the production-related waste (including environmental releases) managed annually, as shown in Fig. 8. While other chemicals also declined at a similar rate, these five solvents are clearly driving the sector's downward trend. A reduction in solvents is consistent with what we would expect to see based on implementation of green chemistry in that the published research on green chemistry advances in pharmaceutical manufacturing indicates the advances have focused on reducing the quantities of organic solvents used in the manufacturing processes.[22–24]

We also considered the possibility that the declines in the quantities of these chemicals reported as waste could be due

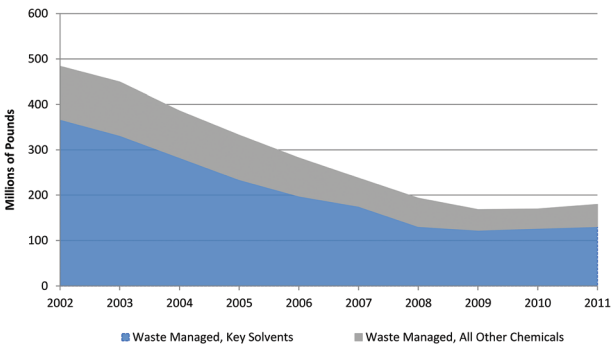

Fig. 8 Quantities of key solvents managed as waste *vs.* quantities of all other chemicals managed as waste by the pharmaceutical industry. The "key solvents" included in this figure are: methanol, dichloromethane, toluene, dimethylformamide, and acetonitrile. Waste managed includes quantities released, used for energy recovery, recycled, and treated.

to implementation of more stringent regulations imposed for these or other chemicals included on the TRI-list and reported on by pharmaceutical manufacturing facilities. We did not identify, nor are we aware, of any regulations that account for the trend depicted in Fig. 8.

Do the source reduction practices reported to EPA's TRI program detail green chemistry advances?

Over the time period examined, there was no explicit green chemistry information required to be disclosed by facilities on the TRI reporting Form R. While the solvent reductions observed in the sector are consistent with what we would expect from the implementation of green chemistry, other pollution prevention practices could be contributing to the declining trend. To look more closely at the potential contributions of green chemistry in the observed trend we examined the types of activities and information reported in Sections 8.10 and 8.11 of the Form R. Facilities are required to report any newly-implemented source reduction activities in Section 8.10 of the TRI Form R, using predefined codes that correspond to activities in any of the following eight general categories: "Good Operating Practices", "Inventory Control", "Spill and

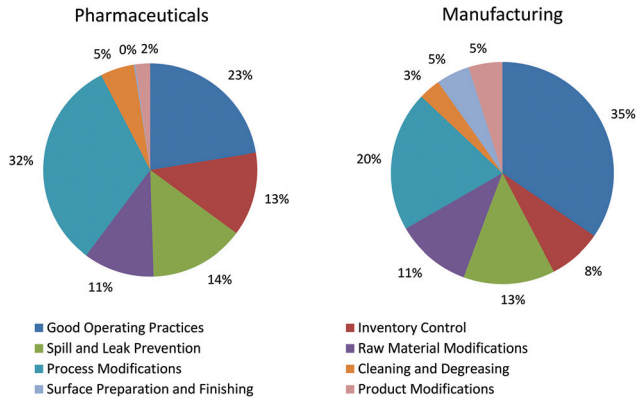

Fig. 9 Newly implemented source reduction activities.

Leak Prevention", "Raw Material Modifications", "Process Modifications", "Cleaning and Degreasing", "Surface Preparation and Finishing", and "Product Modifications".[21] The facility selects the code or codes within any of these categories that most closely represent the implemented source reduction activity or activities.

Throughout the 2002–2011 timeframe there were no green chemistry-specific codes in existence. Therefore, it is not possible from the TRI data for this period to delineate implementation of green chemistry practices from other pollution prevention activities. Facilities that implemented green chemistry activities that increased synthesis efficiency or reduced the use of an organic solvent in a synthesis pathway during the 2002–2011 timeframe would most likely have reported these activities using a code or codes under the Process Modifications category, since it is the category that most closely encompassed green chemistry practices.

The percent of pharmaceutical manufacturing facilities reporting in Section 8.10 from 2002 to 2011 was 36%, which is higher than the 31% reporting rate by the rest of the manufacturing sector. As shown in Fig. 9, the most common source reduction category chosen by the pharmaceutical manufacturing facilities was Process Modifications (32%), whereas other facilities in the manufacturing sector reported Process Modifications to a lesser extent (20%).

In addition, facilities in the pharmaceutical manufacturing sector reported optional pollution-prevention related free text entries (Section 8.11 of Form R) at a higher percentage than the overall manufacturing sector (6.6% compared to 5.0%) over the 2005 through 2011 timeframe. Some of these entries describe green chemistry practices recently implemented at pharmaceutical facilities. Several examples are provided in Fig. 10. Greater optional reporting of newly implemented pollution-prevention practices to EPA's TRI Program by the pharmaceutical sector suggests that the facilities therein are implementing more green chemistry activities than facilities in other parts of the manufacturing sector.

Discussion

Historically, the commercial-scale manufacture of many pharmaceutical substances has generated large quantities of production-related chemical wastes. A major contributor to the production-related waste emanates from the large quantities of organic solvents often used in the manufacture of pharmaceutical products.[22–24] Over the past 15 years or so many pharmaceutical manufacturing firms have increasingly identified and implemented green chemistry practices in their commercial syntheses to reduce the creation of chemical wastes associated with the manufacture of pharmaceuticals and, therewith, the costs incurred with the management of the wastes.[22,25–28]

Based on the published research on green chemistry advances in pharmaceutical manufacturing, it appears that many of the advances focus on reducing the quantities of organic solvents used in the manufacture of pharmaceuticals.[22–24] The Pfizer Pharmaceutical Company, for example, has identified a greener synthesis of its product sildenafil citrate (Viagra®). Implementation of this newer synthesis has led to large reductions in the use and emissions of toxic chemicals, particularly organic solvents, when compared to the synthesis used originally.[29]

The pharmaceutical industry has been recognized by the U.S. EPA and other organizations for its green chemistry developments, and there are numerous examples of green chemistry applications by pharmaceutical firms in the literature. In 2010, EPA's Presidential Green Chemistry Challenge award was presented to Merck and Codexis for their collaborative identification and implementation of a green synthesis used to

"The two major contributions to lessen the purchase of acetonitrile were: (1) the installation of vent condensers on storage tanks, and the re-use of acetonitrile within a same manufacturing process."
"Reused a portion of the methanol/water mixture directly in the new process."
"We now have automated high pressure chromatography systems which replace open column chromatography and decreases the amount of solvent needed to purify product."
"Our process development lab has instituted a new precipitation technique, eliminating reverse phase purification, and reducing solvent waste (potentially dichloromethane waste) by 270 pounds per year."

Fig. 10 Optional green chemistry open-text examples taken from Section 8.11 of TRI form Rs submitted by pharmaceutical manufacturing facilities.

manufacture sitagliptin (Januvia®), a medication used in the treatment of Type-II diabetes. The synthesis resulted in improvements in productivity, increased yield, and reduced waste generation.[30] The Pfizer Pharmaceutical Company also submitted an entry to the EPA's Presidential Green Chemistry Challenge award in 2010 for its green process for manufacturing pregabalin (the active ingredient in Lyrica®), which reduces the amount of solvent used, and also uses less energy when compared to an alternative route.

Our analyses show that over the 2002 through 2011 timeframe the quantities of toxic chemicals reported annually by pharmaceutical manufacturing facilities to EPA's TRI Program as released to the environment or otherwise managed as waste have declined steadily and by more than 60%. Moreover, the large reductions in the reported quantities are sector-wide. The downward trends are largely driven by reductions in the quantities reported for organic solvents. Five of these solvents: methanol, dichloromethane, toluene, dimethylformamide, and acetonitrile, account for three-quarters of the declining trend from 2002 through 2011 in the overall quantities of the production-related waste (including environmental releases) managed annually, as shown in Fig. 8.

It is common knowledge that many U.S.-based firms have moved portions of their manufacturing operations to other countries. Such outsourcing would have an impact on any analyses attempting to characterize the impact of green chemistry practices implemented by these firms at their U.S. facilities. We attempted to characterize the degree to which pharmaceutical manufacturing has been outsourced from facilities within the United States to facilities in other countries during the 2002–2011 timeframe. We did not identify, nor are we aware of, any facility-level data on the chemicals that were historically used in U.S. pharmaceutical manufacturing operations but are no longer used because the process using the chemical is now conducted at facilities located outside of the U.S. Moreover, we did not identify any quantitative or semi-quantitative data or information on the extent of outsourcing of pharmaceutical manufacturing from the United States to other countries.

To address the outsourcing variable we analyzed, as a proxy, the toxic chemical release quantities reported by only those pharmaceutical manufacturing facilities which filed TRI reports to EPA's TRI Program every year from 2002–2011. We further refined the analysis to those facilities that reported on the same chemical(s) for each of these years. Dramatic decreases in the quantities of toxic chemicals released to the environment were observed (Fig. 4). We believe that these results are not attributable to outsourcing.

Our belief is supported by the fact that manufacturing of pharmaceuticals still occurs within the United States. Over the 2002–2011 timeframe 266 facilities in the U.S. that categorize themselves as being in NAICS code 325411 ("Medicinal Botanical Manufacturing") or 325412 ("Pharmaceutical Preparation Manufacturing") filed 6543 TRI Form R reports in which they disclosed to the U.S. EPA's TRI Program their release and other waste management quantities of toxic chemicals that are known to be used in the commercial manufacture of pharmaceuticals. Given their NAICS categories, the types of chemicals they report, and the quantities they report (*e.g.*, large volumes of solvents) they undoubtedly are manufacturing pharmaceuticals.

The identities of manufactured pharmaceutical products are not reported in TRI submissions. As such, there is no way to link the observed reductions in the reported quantities of toxic chemicals with a specific green chemistry practice that is known to be used by a pharmaceutical company to manufacture a specific pharmaceutical product. Nonetheless, that green chemistry practices are employed by facilities within the United States that manufacture pharmaceutical, pesticide and other products and that integration of these practices have directly resulted in substantial decreases in the release and other waste management quantities of toxic chemicals these facilities report to the U.S. EPA's TRI Program has recently been expressed by the DuPont Company.[31]

That reductions in the TRI reported quantities of organic solvents are driving the overall downward trend is consistent with what would be anticipated following the implementation of many of the green chemistry practices for the manufacture of pharmaceuticals, as published in the literature.[22–25,29] Factors such as outsourcing, production levels, regulations, shifts to other waste management practices, or TRI reporting characteristics by larger pharmaceutical firms may have contributed to varying degrees to the trends observed in this study, but these factors do not appear to be driving the trends. Given the weight of the evidence, we conclude that implementation of green chemistry practices are a major contributing factor to the large reductions we report herein.

Our results are consistent with those of Slater and co-workers, who compared the onsite waste disposal quantities reported to EPA's TRI Program by the pharmaceutical industry for 1995 and 2006.[24] Sharp declines were observed in the quantities reported as released to air (as fugitive or stack emissions), landfills, or water, whereas quantities injected underground remained about the same during the 1995 and 2006 reporting years. Slater and co-workers also noted sharp declines in the onsite release quantities reported by pharmaceutical facilities for seven commonly used organic solvents for the 1995 and 2006 TRI reporting years. Five of these solvents are methanol, dichloromethane, toluene, dimethylformamide, and acetonitrile. These investigators also observed a large reduction in the quantities of organic solvents reported as treated or used for energy recovery onsite, moderate reductions in the quantities sent offsite for energy recovery or treatment, and moderate increases in the quantities of solvents recycled both onsite and offsite.

Slater and co-workers assumed that the above differences among the respective quantities are due to implementation of green chemistry practices, and did not investigate other plausible causes as done in the present study. Nonetheless, their findings are consistent with the findings of the present study.

Several green chemistry metrics are available to assess and compare the efficiencies of synthesis pathways. These metrics

represent process efficiency, process mass intensity, effective mass yield, or atom economy of a synthesis.[22,32] Process Mass Intensity, and the "environmental factor" or "E" factor are generally the most widely used green chemistry metrics by industry, particularly the pharmaceutical manufacturing sector.[23,26,27]

While these metrics are useful for comparing the "greenness" of different manufacturing processes, few (if any) address any overall trends in reductions of waste management quantities of a toxic chemical or chemicals by a given facility, group of facilities, parent company, or industry sector. Also, the data and information that pharmaceutical and other firms use to derive these metrics, as well as the manufacturing processes themselves, are mostly proprietary and, as such, are unavailable to the general public, researchers, or government organizations. Pollutant Release and Transfer Registers (PRTRs) such as the TRI (the United States' PRTR) are the only means that we are aware of by which the public, researchers, local, state and federal government officials, and interested parties may be able to track implementation of green chemistry practices and its resultant impact on the prevention of pollution.

Despite the wealth of publications detailing green chemistry advances, to the best of our knowledge none have quantified the environmental impacts of green chemistry initiatives in general or the benefits throughout a given industry sector, except perhaps for the publication by Slater *et al.*[24] In regard to the pharmaceutical manufacturing sector, if implementation of green chemistry advances are occurring on a wide-scale across the sector, as indicated by the literature and specifically in pharmaceutical manufacturing facilities located within the United States, the outcome of these advances should be reflected in the information reported by pharmaceutical manufacturing facilities to EPA's TRI Program and accessible through the TRI database, as many chemicals used during the manufacture of pharmaceuticals are included on the TRI toxic chemical list. Our research findings indicate that this is indeed the case.

While to some the results of our study may not be surprising in retrospect, our results indicate that the TRI is a practical, readily accessible tool that can be used to track and observe the extent of reductions in the quantities of toxic chemicals released by facilities into the environment or otherwise managed as waste as a result of implementation of green chemistry practices. It would seem, therefore, that the TRI can be used to evaluate the impact of green chemistry in achieving sustainability goals. Moreover, the TRI can be used to identify facilities, companies or industry sectors that do not appear to be implementing green chemistry or green engineering practices. These are applications of the TRI that are relevant and, to date, have not been identified or explored.

A primary purpose of TRI data is to inform the public of releases and other waste management activities of toxic chemicals in their communities, and enable citizens to make informed decisions regarding the consequences of such activities to human health and the environment. TRI data are also used by the federal, state and local governments for prioritization purposes and to assess pollution prevention activities. Researchers, public interest groups, as well as others use TRI data for a variety of purposes.

As TRI data and information are self-reported, some may question the reliability of the data and information in regard to its intended purposes. The law that requires certain facilities to report release and other waste management quantities of certain toxic chemicals does not require that these quantities be measured or otherwise determined experimentally—although if by coincidence measurement is required under other regulations these "readily available" measured values can also be used for TRI reporting purposes. When measured data are not "readily available", the TRI regulations only require that facilities determine their release and other waste management quantities of TRI-listed chemicals by making "reasonable estimates". Implicit in the allowance of reasonable estimates is that the law recognizes and permits that TRI data need to be reasonably accurate in regard to the intended uses of such data.

The quality of TRI data and related information that is submitted to EPA is solely the responsibility of the facilities that are required to submit such data and information. Nonetheless, given the widespread use and importance of the TRI database as an information source and decision making tool, EPA's TRI Program has for many years been proactive in identifying and implementing activities aimed at optimizing the quality of TRI data. These activities include: development of industry-specific and chemical-specific technical guidance documents; detailed reporting forms and instructions, sponsoring training workshops; establishment of the TRI Information Center; development of the TRI-ME software product (contains many built-in data quality checks); and in-house data quality analyses, to name a few.

Much of the emission and other waste management quantity data that EPA's TRI Program regularly receives are estimated by the facilities that submit such data. Since the true values for these data are seldom (if ever) known, there is no basis from which the accuracy of data estimates can be quantitatively characterized. While there is likely to be some degree of error in the data, we believe the TRI data as made available by EPA are of sufficient quality for purposes of its intended use. Moreover, data quality is likely to be less of a concern in trend analyses such as the research described herein, since the bulk of the data are reported from the same facilities each year and it is likely that the same assumptions and techniques are used in estimation of the reportable quantities. Hence, we consider the TRI data reported by a facility on an annual basis to be of acceptable quality for this type of sector-level trend analysis.

Over the past several years, EPA has transformed the way the TRI Program collects, analyzes, and disseminates information on toxic chemical waste management and pollution prevention. EPA has emphasized that TRI reporting is not just a legal requirement but also an opportunity for facilities to highlight pollution prevention practices and results, showcase "good neighbor stories," and demonstrate a corporation's com-

mitment to sustainability.[33] Extensive outreach efforts by EPA to facilities, encouraging them to go beyond what is legally required to be disclosed and provide such information in order to publically highlight their environmentally-friendly practices,[14] has yielded a fourfold increase in the number of optional pollution prevention activity descriptions submitted by industry over just two years.

In conjunction with these outreach efforts, EPA has recently increased the prominence and accessibility of the pollution prevention information reported in Sections 8.10 and 8.11 of the TRI reporting Form R.[14,34,35] For example, EPA's 2011 TRI National Analysis highlighted the parent companies that reported the greatest number of source reduction activities.[34] In its 2012 TRI National Analysis, EPA highlighted the pollution prevention practices implemented by some major sectors that contributed to the sharp declines in releases of toxic chemicals over the past decade, including the commonly-reported solvents trichloroethylene, tetrachloroethylene, dichloromethane, and methyl isobutyl ketone.[36] The 2013 National Analysis shows continued increases in newly-implemented pollution prevention activities.[37]

EPA is also looking to feature pollution prevention successes in other forums, such as a recent pollution prevention profile describing the methods used by the fabricated metals sector to lower trichloroethylene releases by almost 80% since 2001.[38]

EPA has developed an online TRI Pollution Prevention Tool that enables data users to easily access the pollution prevention information contained in the TRI database, and conduct pollution prevention-specific analyses.[35] Users can view pollution prevention activities and environmental performance at the facility and parent company levels, as well as by sector. Another feature of the tool is that it allows users to filter data by multiple chemicals, empowering the user with substantially more power to visualize and analyze pollution prevention activities involving various chemicals across many facilities. The tool's user-friendly display also makes it easy to identify facilities and parent companies that have done the most to reduce toxic chemical waste generation, implement preferred waste management techniques that reduce releases, and lower their greenhouse gas emissions. Facilities and parent companies can easily see how their environmental performance compares with other facilities or parent companies.

EPA has enhanced reporting mechanisms to allow facilities to disclose and share information about green chemistry and engineering practices, identify barriers to pollution prevention, and estimate the relative effectiveness of different waste reduction measures, thus ensuring that TRI will be an even richer pollution prevention information resource for industry and the public in years to come. Beginning with the 2012 reporting year, for example, EPA implemented six new source reduction codes for completing Section 8.10 of the TRI Form R report that are more closely aligned with actual green chemistry practices. Facilities subject to the TRI reporting requirements that have implemented new green chemistry practices can select from these codes when they complete Section 8.10 of their Form R report(s).[21] These new codes are:

- Introduced in-line product quality monitoring or other process analysis system;
- Substituted a feedstock or reagent chemical with a different chemical;
- Optimized reaction conditions or otherwise increased efficiency of synthesis;
- Reduced or eliminated use of an organic solvent;
- Used biotechnology in manufacturing process;
- Developed a new chemical product to replace a previous chemical product.

The use of these codes is increasing. Of the 10 439 total source reduction codes that were disclosed for the 2012 reporting year, 382 (3.7%) were green chemistry codes. For the 2013 reporting year, 508 (4.8%) of the 10 623 total source reduction codes that were reported were green chemistry codes. Use of the TRI to track implementation of green chemistry and other pollution prevention practices and characterize the outcome of these practices on reducing production-related toxic chemical wastes is expected to increase in the near future.

In conclusion, our research shows that the pharmaceutical industry reduced its production-related waste quantities of toxic chemicals included on the TRI chemical list by more than 60% during the 2002 through 2011 timeframe. Factors such as production levels, outsourcing, regulations, the overall decline in TRI reporting, a shift to other waste management methods, or a disproportionate influence of larger parent pharmaceutical companies may have contributed to the observed reductions, but they do not account for the majority of the reductions. Our analyses, combined with the extensive evidence in the literature of green chemistry advances, lead us to conclude that implementation of green chemistry practices has been a significant factor.

We believe the TRI can serve as a useful tool for measuring the contribution of green chemistry in progress towards sustainability goals. Moreover, we find the TRI to be uniquely well-suited for assessing the progress made by different industry sectors or specific facilities therein in implementing green chemistry practices: a use of the TRI that hitherto has not been reported. We are currently continuing our research on other types of manufacturing facilities that are subject to the TRI reporting requirements.

Disclaimer

The views, conclusions, and opinions expressed in this paper are entirely those of the authors, and do not necessarily reflect those of the United States Environmental Protection Agency, nor does mention of any chemical substance or commercial product constitute Agency endorsement or recommendation for use.

Conflict of interest

The authors declare no competing financial interest.

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